DOCTOR OF PHILOSOPHY

Sleep/wake patterns and key predictors for sleep impairment in patient-caregiver dyads:
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Kotronoulas, Grigorios

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Sleep/Wake Patterns and Key Predictors for Sleep Impairment in Patient-Caregiver Dyads: A Longitudinal Observational Study among Women with Early Stage Breast Cancer and their Informal Caregivers during Chemotherapy Treatment

Thesis submitted for the Degree of Doctor of Philosophy

Grigorios Kotronoulas

BSN (Distinction), MSc (Distinction)

"Alexander S. Onassis" Public Benefit Foundation Scholar

School of Nursing and Midwifery

College of Medicine, Dentistry and Nursing

University of Dundee

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List of Abbreviations and Nomenclature

AASM	American Academy of Sleep Medicine
AC	Doxorubicin (Adriamycin), Cyclophosphamide
AGEPT/CG	Age covariate (patient/caregiver)
AIDS	Acquired Immunodeficiency Syndrome
ALCHLPT/CG	Alcohol Consumption covariate (patient/caregiver)
ANOVA	Analysis of Variance
AR (1)	Autoregressive of order 1
BC	Breast Cancer
BCOS	Bakas' Caregiving Outcomes Scale
BCSTAGE	Breast Cancer Stage covariate (patient)
BEDTM	Bedtime
BMI	Body Mass Index
BMIPT	Body Mass Index covariate (patient/caregiver)
BTE	Behavioural Therapy augmented by Education
CAF	Cyclophosphamide, Doxorubicin (Adriamycin), Fluorouracil
CAM	Complementary/Alternative Medicine
CBT	Cognitive Behavioural Therapy
CCF-C	Clinical Characteristics Form-Caregiver
CCF-P	Clinical Characteristics Form-Patient
CES-D	Center for Epidemiologic Studies-Depression
CI	Confidence Interval
CMF	Cyclophosphamide, Methotrexate, Fluorouracil
CMRBDTPT/CG	Number of comorbidities covariate (patient/caregiver)
COPNEGPT/CG	Negative Coping predictor variable (patient/caregiver)
CPAP	Continuous Positive Airway Pressure
CRACBCG	Caregiving Burden predictor variable (caregiver)
CRAS	Caregiver Reaction Assessment Scale
CRF	Case Report Form
CRP	C-Reactive Protein
CTh	Chemotherapy
CThC	Chemotherapy cycle
DCF-C	Demographic Characteristics Form-Caregiver
DCF-P	Demographic Characteristics Form-Patient
DDISTf	PSQI Factor 3 indicating Daily Disturbance
df	Degrees of freedom
DIAGNTM	Time elapsed since cancer diagnosis covariate (patient)
DOHNSF	Department of Health National Service Framework
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders
E-CMF	Epirubicin, Cyclophosphamide, Methotrexate, Fluorouracil
EARLAW	Early Morning Awakenings
EC	Epirubicin, Cyclophosphamide
ECOG	Eastern Cooperative Oncology Group
EDUCPT/CG	Educational Background covariate (patient/caregiver)

EEG	Electroencephalogram
EMG	Electromyogram
EMPLOYPT/CG	Employment Status covariate (patient/caregiver)
EOG	Electrooculogram
FEC	Fluorouracil, Epirubicin, Cyclophosphamide
FML	Full Maximum Likelihood estimation
GP	General Practitioner
GSQI	Global Sleep Quality Index (overall sleep/wake impairment score)
HADS	Hospital Anxiety and Depression Scale
HIV	Human Immunodeficiency Virus
HSE	Habitual Sleep Efficiency
ICC	Intraclass Correlation Coefficient
IL-1	Interleukin-1
IL-6	Interleukin-6
IQR	Interquartile Range
ISI	Insomnia Severity Index
KPS	Karnofsky Performance Status
MAR	Missing at Random
MDASI	M. D. Anderson Symptom Inventory
MENOPPT	Menopausal Status covariate (patient)
MHLM	Multivariate Hierarchical Linear Model
MLM	Multilevel Modelling
MORNFEEL	Feelings of Restfulness upon Morning Awakening
MOS-SS	Medical Outcomes Study-Sleep Scale
MSAS	Memorial Symptom Assessment Scale
MVA	Missing Values Analysis
NAPNEED	Need for Daytime Napping
NAPTIME	Average Daytime Napping Duration
NHS	National Health Service
NOCAW	Nocturnal Awakenings
NREMS	Non-Rapid Eye Movement Sleep
OLS	Ordinary Least Squares
OSA	Obstructive Sleep Apnoea
OTC	Over-the-Counter
PAPT/CG	Physical Activity covariate (patient/caregiver)
PHYSPT	Physical Burden predictor variable (patient)
PIS-C	Participant Information Sheet-Caregiver
PIS-P	Participant Information Sheet-Patient
PS	Performance Status
PSQf	PSQI Factor 1 indicating Perceived Sleep Quality
PSQI	Pittsburgh Sleep Quality Index
PSPT/CG	Performance Status covariate (patient/caregiver)
PSYCHPT/CG	Psychological Burden predictor variable (patient/caregiver)
R & D	Research and Development
REC	Research Ethics Committee
REGIMTYP	Type of chemotherapy protocol covariate (patient)
RELDUR	Duration of Dyad Relationship
RELTYPE	Type of Dyad Relationship

REM	Rapid Eye Movements
REML	Restricted Maximum Likelihood estimation
REMS	Rapid Eye Movement Sleep
r_{ES}	Effect size *r*
RM-ANOVA	Repeated Measures Analysis of Variance
RSCL	Rotterdam Symptom Checklist
RSTLSSLG	Restless Legs
SAU	Sleep aid use
SD	Standard Deviation
SE	Standard Error
SEf	PSQI Factor 2 indicating Sleep Efficiency
SEM	Structural Equation Modelling
SEXCG	Caregiver Gender covariate (caregiver)
SDSTRBPT/CG	Nocturnal Sleep Disturbances predictor variable (patient/caregiver)
SHI	Sleep Hygiene Index
SHPT/CG	Sleep Hygiene predictor variable (patient/caregiver)
SL	Sleep (onset) Latency
SLCA	Sleep affected by cancer diagnosis covariate (patient/caregiver)
SLPAST	Past history of sleep problems covariate (patient/caregiver)
SLPNSS	Daytime sleepiness
SLSHOUS	Dyad sharing the same house
SLSROOM	Dyad sharing the same bedroom
SMKNGPT/CG	Smoking Status covariate (patient/caregiver)
STAI	State-Trait Anxiety Inventory
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
SURGTM	Time elapsed since breast surgery covariate (patient)
SURGTYP	Type of breast surgery covariate (patient)
SWS	Slow Wave Sleep
TC	Paclitaxel, Cyclophosphamide
TNF-α	Tumour Necrosis Factor alpha
TNM	Tumour, Node metastasis, distant Metastasis cancer staging system
TST	Total Sleep Time
UICC	Union Internacional Contra la Cancrum
VC	Variance Component
WAKETM	Wake time
WASO	Wakefulness after Sleep Onset

Acknowledgments

Some say that working on your PhD is a long and lonely journey… others claim this to be a fierce battle of you against your own self… Well, I have been fighting my self for quite a long time now, and I can assure everyone that he has suffered (and will keep suffering) enough by my non-negotiable demand to learn more and more. But I also know for sure that I wasn't alone in this. …The PhD journey, I mean.

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The love and support of my parents have always been invaluable to me, but especially during these four years that we are apart. I am unsure whether they would ever imagine it, but they have actually mastered Skype to make their soothing presence available (as they have ever done) regardless of distance. My brother has been my best friend for so many years – thank you for doing everything one possibly could to make it seem like we never were away. …And I know that somewhere up above my grandmother will be smiling proudly for me.

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Declaration

Candidate's Declaration

(i) I, Grigorios Kotronoulas, hereby certify that I am the author of the present thesis; that, unless otherwise stated, all references stated have been consulted by me; that the work of which the thesis is a record has been done by me; and that the thesis has not been submitted in any previous applications for a higher degree.

Date…… Candidate's Signature……

Supervisors' Declaration

(ii) We hereby certify that the candidate has fulfilled the conditions of the relevant Ordinance, and Regulations of the University of Dundee, and that as such the candidate is eligible to submit the following thesis in application for the degree of Doctor of Philosophy.

Date…… Supervisor's Signature……

Date…… Supervisor's Signature……

Abstract

Background and Objectives: Alterations in the habitual sleep/wake patterns of women with breast cancer and their informal caregivers may be concurrently exacerbated and co-vary during the patient's treatment. The current study set out to longitudinally explore sleep-wake patterns of patient-caregiver dyads in the context of adjuvant chemotherapy (CTh) for breast cancer. Taking into consideration the complexity of mechanisms interfering with a care dyad's sleep, diverse sleep-impairing factors were also investigated.

Design and Methods: Descriptive, observational, repeated-measures dyadic study. Forty eight newly diagnosed women receiving outpatient adjuvant CTh for early stage breast cancer (stage I-IIIA) and their nominated primary informal caregiver completed self-reported sleep measures at pre-treatment (week prior to CTh), post-CTh cycle 1, post-CThC4, and approximately 30 days after the end of CTh (total of ≥6 cycles received). Additional data on the dyads' sleep hygiene practices (SH), patient physical burden, caregiving burden (CRACB), psychological burden (PSYCH), nocturnal sleep disturbances (SDSTRB), and maladaptive coping strategies were collected at each assessment point.

Results: Prior to CTh, 65% of dyads consisted of at least one poor sleeper, a rate further increasing to approximately 88% at CThC4. Multivariate hierarchical linear modelling revealed curvilinear trajectories for most dyads' sleep/wake parameters that nevertheless reached significance ($p<.05$) for patients only. In both groups, sleep/wake impairment reached its peak at mid-treatment (CThC4); yet, patients consistently reported significantly more sleep problems than their carers. Partial convergence also emerged as suggested by positive correlations and no between-groups differences in daily disturbance, daytime napping duration, total sleep time, and overall sleep/wake impairment at pre-treatment. At CThC4, rates of change in sleep latency and daytime napping duration were also similar. In exploratory analyses, increased CRACB, poor SH, and SDSTRB consistently predicted poorer outcomes in the dyad members' own sleep-wake patterns. Cross-partner effects most frequently emerged with regard to the dyads' PSYCH, as well as for CRACB. Among the most interesting findings, increased patient PSYCH adversely affected caregiver perceived sleep quality and daytime napping. Reversely, increased CRACB was related to worse patient sleep quality, reduced sleep time, and difficulty to fall asleep. Some links might be suggested for own poor sleep hygiene and worse partner outcomes on daytime functioning, sleep efficiency, or wake after sleep onset.

Conclusions and Future Implications: This is one of the first studies to show that a dyadic approach in the assessment of sleep/wake patterns in patients with breast cancer and their informal carers is a promising method to enhance exploration of potentially concurrent sleep/wake-impairment and associations with sleep-impairing factors that may co-vary in dyad members. Replication of the current findings in future dyadic sleep research is warranted. Meanwhile, clinicians will need to engage in concurrent systematic and ongoing sleep assessments that synthesise and contrast data to establish a care dyad's level of sleep quality.

PART I

PREFACE.

Rationale for Thesis and Overview of Chapters

Background

A diagnosis of cancer severely disturbs a person's continuum of life. As far as women with breast cancer are concerned, sudden and abrupt changes may be posed post-diagnosis and during anti-cancer treatment, which, when combined with a permanent body disfigurement indicating that the threat may still be present, can be profoundly disrupting. Several sources of discomfort can be identified along the continuum of illness, and sleep/wake impairment is one of them [1]. Sleep is a vital human process known to be essential for health, well-being, and optimal physical and psychological functioning [2], thus making it reasonable to argue that any severe and/or long-term disruption may have serious consequences on the equilibrium of life [3, 4]. Admittedly, throughout the period of diagnosis and treatment, women with breast cancer are also in great need of support [5]. To a considerable extent, support is expected to be provided by their significant others, family members and/or friends, who are frequently recognised as patients' informal caregivers. However, caregiving can be so demanding and stressful that the burden posed to these persons may lead to alterations in their own sleep, too [6].

At the early stages of breast cancer, women and their primary informal caregivers are faced with a host of challenges; not only do they have to go through intense curative treatment modalities, but also they must effectively cope with illness, both as individuals and as members of a close relationship. With regard to adjuvant chemotherapy, patients and caregivers are most frequently required to deal with unknown procedures, toxic agents, and the experience of multiple symptoms, the intensity of which can disproportionately increase the physical and psychological burden posed [6]. As they share closely their everyday concerns, these care dyads may be faced with similar challenges and most of their needs may manifest at the same time.

Sleep/wake problems may be prominent for both the patient and their caregiver, even at the same time, possibly for a considerable time period and, in other cases, long after treatment is completed, thus posing an additional short-, mid- or long-term burden on their lives. All

women with breast cancer and their informal caregivers need initial and ongoing screening for debilitating symptoms such as sleep/wake impairments throughout anti-cancer treatment. When nocturnal disturbance and/or daytime dysfunction are evident or suspected, further tailored assessment and treatment is required. The present study attempts to add to the body of knowledge in the emerging field of sleep research in cancer care by suggesting a more comprehensive approach to the assessment of sleep-related issues in people affected by cancer: this more detailed assessment recognises the dyadic nature of sleep, acknowledges the potential for interdependence in sleep/wake patterns, and includes additional sleep-impairing factors that arise at the dyadic level.

Research interest

The present study derives from the researcher's interest in how the experience and challenges of cancer affect quality-of-life issues in patients and their informal caregivers, who are seen as a unit instead of merely as individual parts when receiving care. Sleep is one such issue. It can be postulated that when altered sleep/wake patterns occur at the same time (or period) in two closely interacting individuals, as in the patient-caregiver relationship, the related adverse effects can be even more disturbing for both of them. By mapping changes in sleep/wake patterns over time, exploring inter-relationships between these changing patterns, as well as identifying influential and reciprocal sleep-impairing factors, care can become more responsive and tailored, not only to each individual's but also to the care dyad's combined (sleep) needs.

Importance for Cancer Care

The current thesis proposes that sleep assessment protocols should aim to simultaneously address sleep/wake impairment in both patients and their caregivers. Neither the patient nor the caregiver goes through the experience of cancer independently, but rather as a pair. That being said, individualistic assessments may fall short when sleep/wake patterns of the care dyad are the focus. Instead, a dyadic approach to sleep assessment takes into consideration the concurrent situation of dyad members, acknowledges the potential for interdependence

that affects and is affected by close relationships, and examines the possibility for nocturnal and daytime interactions. It is evident that in order for the multidisciplinary team to complete comprehensive sleep assessments, not only do they need to possess the knowledge required but they also need to know where to look to gather as much relevant information as possible.

This study draws upon previous successful longitudinal sleep studies in women with early stage breast cancer receiving chemotherapy treatment [7-9]. However, it goes one step further by also including informal caregivers and it does so by targeting care dyads (i.e. paired patients and carers) rather than two arbitrary groups. Given the scarcity of longitudinal research data [10], information till now unknown will be also gathered regarding changes in informal caregivers' sleep/wake patterns in order to promote targeted multidisciplinary sleep assessments. Most importantly, the advantages of repeated sleep measurements will be reflected in the analysis of dyadic sleep data, the results of which are expected to shed light on similarities, differences and interrelations in the dyads' sleep/wake patterns, and will begin to clarify how changes in one member's sleep/wake parameters may (or may not) be related to changes in the other's.

It is also anticipated that dyadic longitudinal sleep assessment will shed light on the impact that already known and still unexplored factors have on patients' and caregivers' sleep. Although for now inferences will only refer to the fast-moving period of uncertainty and new challenges that are associated with adjuvant chemotherapy for breast cancer, this dyadic approach can be well applied to investigate relationships in other cancer contexts, too. With the dyadic methodology implemented here, not only own but also cross-partner effects of key sleep-impairing factors will be explored, thus promoting a more thorough investigation of the multiple individualistic and dyadic sources of sleep disturbance. What is more, being able to anticipate the time points where sleep/wake disruption/deprivation reaches a peak for both members of the care dyad and what the main causes for them may be, will allow for interventions to support the patient-caregiver dyad and enhance their well-being.

It is hoped that the present study will stimulate further dyadic sleep research that will eventually inform the development of sleep intervention protocols for the comprehensive management of sleep disorders in people affected by cancer throughout their illness experience. These interventions will ensure that sleep/wake patterns are assessed in depth and are managed in a concurrent manner to achieve concurrently increased levels of well-being for patients and their caregivers.

Thesis Content Guide

The thesis is presented in two Parts. Part I will attempt to provide an overview of the state-of-the-art literature pertinent to sleep-related issues in the context of cancer and health care. Part I comprises the following four chapters:

- Chapter 1 introduces the basic knowledge about sleep physiology and sleep-related issues in the context of cancer care. The concept of nine key parameters for the assessment of sleep in cancer populations is introduced along with terminology for sleep-wake disturbances. In addition, a general approach to sleep-impairing factors is presented, drawing upon the principles of three theoretical models.

- Chapter 2 begins with providing facts and figures about breast cancer focusing mainly on the early stages of diagnosis. A brief discussion of the experience of living with early stage breast cancer follows, culminating with a discussion about the experience of impaired sleep/wake patterns. Findings from two systematic literature reviews conducted for the purposes of this project are discussed in detail. The first section provides evidence with regard to the extent that habitual sleep/wake patterns are compromised in women receiving neo-/adjuvant chemotherapy for breast cancer. The second section brings together evidence with regard to six categories of sleep-impairing factors in this population. The Chapter concludes with a discussion pertinent to the limitations of the current body of evidence.

- In Chapter 3, the role of supportive systems for patients with (breast) cancer is reviewed, in particular the role and competencies of significant others as informal caregivers. The extent of burden placed on persons assuming caregiving roles is then analysed, which, when combined with physiologic and emotional effects, can lead to interruptions in habitual sleep. As part of this Chapter, a systematic review of studies investigating caregiver sleep and correlates in the context of cancer and other major chronic illnesses was conducted, and its findings are presented here. Limitations and research gaps in the existing knowledge are thoroughly discussed in the last section.

- Chapter 4 introduces the novel concept of exploring sleep/wake patterns in dyads of persons in close relationships, such as the patient-caregiver relationship. The Chapter starts off with a discussion of the added value of concurrent assessments of health outcomes in patient-caregiver dyads based on findings of a scoping review of dyadic studies irrespective of health care context. Next, the theoretical underpinnings of dyadic sleep assessment are taken into consideration, where it is recognised that, despite

its hypothesised advantages, to date, sleep assessment is viewed and conducted in a confined individualistic way. This observation is evident in the findings of a systematic review conducted for the purposes of this thesis, where sleep assessment in patient-caregiver dyads is still an under-researched area. Current research gaps are addressed towards the end of this Chapter.

Part II is dedicated to the research project conducted as part of the present thesis. It consists of the following five chapters:

- Chapter 5 (Methodology) summarises the evidence analysed in the previous four chapters and introduces the specific research problem to be addressed. A detailed discussion follows with regard to the selection of research design and methods, and outcome and predictor variables to be examined. Next, an account of the screening procedures to select the most appropriate outcome measures is provided. The final section refers to information pertinent to the analysis of dyadic data, according to basic dyadic principles and via the use of sophisticated statistical techniques.

- Chapter 6 (Study Aims and Methods) explicitly details the aims, hypotheses and research questions that have driven the current project, and then moves on to describe all of the procedural steps taken. This section includes an account of population and sample eligibility criteria, data collection schematics and procedures, ethical considerations, instrumentation, and data analytic strategy. Preliminary findings of the project's feasibility phase are discussed prior to proceeding to the next Chapter.

- Chapter 7 (Results) is divided into four sections to provide a clear account of results. The first section discusses accrual rates, attrition rates and patterns of missingness, and gives an overview of the dyads' demographic and clinical characteristics. The second section attempts a descriptive analysis of dyadic outcome and predictor variables, followed by preliminary bivariate correlation analyses. The third and fourth sections are dedicated to the main data analysis, providing findings with regard to overtime changes in the sleep/wake patterns of care dyads, and modelling the effects of sleep-impairing factors, respectively.

- Finally, Chapter 8 (Discussion and Future Implications) attempts a critical discussion of important findings and implications of the current study. This Chapter is also divided into four sections. The first section concentrates on the essence of the previously stated results, provides an overall appraisal of findings, and links these with previous

research and/or past hypotheses. The strengths and limitations of the current project are explicitly analysed in the next section. The Chapter concludes with a detailed account of implications for future research and clinical practice, and a brief recapitulation of all important concepts, findings and suggestions derived from the current study, whilst the requirement for replication in future research is re-stressed.

CHAPTER 1.

Overview of Sleep-Related Research and Clinical Issues in the Context of Cancer

1.1. Introduction

Sleep difficulties have been reported as a frequent complication of, and are associated with, various clinical conditions [11]. Over the past fifteen years, the attention of the scientific community has shifted towards systematic investigation of sleep/wake impairments during the experience of cancer as an important aspect of care in this population.

Changes in habitual sleep are among the most remarkable and important concerns of patients with cancer [12], and most prominent and debilitating symptoms of their caregivers [10]. Patients and caregivers identify sleep-related issues as vital aspects of the experience of cancer. If sleep/wake impairments persist, physical and psychosocial function, mood, symptom distress, quality of life, or even survival may well be affected [13]. Importantly, while for healthy people sleep provides a needed refuge from the demands of animate and inanimate environment, for those facing the threat of cancer it constitutes a form of respite from the jumble of physical discomfort and psychological distress, and may allow them to meet the next day with renewed energy and motivation [11].

The fact that disordered sleep constitutes a major problem during the cancer experience is evident by the extent of relevant literature, and verified by the importance attributed to quality of sleep by both patients and caregivers (through personal, subjective experiencing), and clinicians (through systematic, objective investigation) in several aspects of life during the experience of cancer [13-16]. The subjective importance patients with cancer and their caregivers attribute to sleep/wake problems has potential consequences for behaviours associated with self-care and the identification of symptoms, help-seeking strategies and reporting of disturbances to the health care team, as well as acceptance and compliance with recommended therapeutic interventions [17, 18]. Alternatively, objective significance of fragmaneted/restricted sleep includes its potential to adversely affect clinical and care-related outcomes in patients with cancer [13], including fatigue [19-23], performance status [24,

25], mood [26-30], immune function [31], quality of life [30, 32, 33], and survival [34-36]. This reported significance dictates the need for continuing intervention and the provision of relief to patients and carers in times of distress.

1.2. Overview of Sleep Physiology

Sleep is a fundamental and omnipresent biological phenomenon, a homeostatically regulated process that is necessary for the body to restore energy and revitalise, in which there is minimal processing of sensory information and no interaction with the environment [2]. However, human sleep also is a complex and dynamic physiologic process [11]. In order for clinicians and researchers to better interpret the varying aspects of impaired sleep, it is important to have a clear understanding of the basic physiologic mechanisms that rule its functions.

One difficulty in understanding sleep is that it is not a unitary state, but a combination of two sub-states of distinct brain activity actively generated in specific brain regions [37]. Therefore, sleep definition requires the combined input from an electroencephalogram (EEG), an electrooculogram (EOG), and an electromyogram (EMG). The resulting polysomnogram identifies the sleep state and stages [38]. Each stage of sleep has a characteristic EEG frequency and waveform (**Figure 1-A1**, Appendix 1) [38]. One state is characterised by Rapid Eye Movements (REM) and is usually termed REM Sleep (REMS); the other, in which no rapid eye movements occur, is known as non-REM Sleep (NREMS).

In humans, NREMS is usually subdivided into stages 1-4, which correspond roughly to increasing depth of sleep, decreasing muscle tone and cognitive quiescence [11, 37]. Stages 3 and 4 are often grouped together under the label 'slow wave sleep' (SWS) [38]. Interestingly, in NREMS the metabolic rate is increased above resting waking levels [38]. REMS is a completely different sleep stage, characterised by a virtual absence of muscle tone in antigravity muscles, a largely awake brain, and dreaming. In the normal sequence (called 'sleep architecture'), waking is followed by NREMS's lighter stages (1 and 2) and then within 10 to 20 minutes by SWS. These stages of deeper sleep are maintained for nearly one hour in normal young individuals but are much shorter (5-10 min), if present at all, in older individuals. Lighter stages of NREMS then re-appear and the first REM period is initiated [37, 39]. This cycle is repeated three to four times during the night but with decreasing amounts of SWS and increasing amounts of REMS [38]. It can be said that the deepest stag-

es of sleep occur predominantly during the first half of sleep, whereas the significantly longer and more intense REM periods occur during the second half of the night [11].

The sleep/wake cycle is a component of the body's overall circadian rhythm [11]. The timing, duration, and depth, or intensity, of sleep is regulated by two interacting processes, the relationship of which has been formalised in the *Two-Process Model of Sleep Regulation* [40-42]. This model provides an understanding of the physiological mechanisms that drive sleep and wakefulness [40, 41]. Visually, the model is a wave-like structure that shows the relationship between the two physiological processes of sleep regulation **(Figure 2-A1)**. The homeostatic/somnostat component (Process S) increases during the awake state (i.e. drives the need for sleep) and decreases during sleep (i.e. decreases the need for sleep). Process S reflects the physiologic need for sleep, which builds across the day and dissipates through the night [42]. If there is a deficit in nocturnal sleep, a compensatory mechanism boosts the need for sleep, which can be translated into a sleepy feeling in the daytime and need for napping. The circadian process (process C) determines alterations of high and low sleep propensity that are independent of prior levels of sleep/wakefulness or the wake-like process S, which determines the onset and end of sleep [40, 41]. Conversely, process C is the mechanism that helps the body stay asleep. It is directed by a clocklike mechanism that resides in the hypothalamus; this 'pacemaker' works in conjunction with neurotransmitters that facilitate sleep (such as melatonin) and thermoregulatory processes (rhythm of core body temperature) [43]. The coordination between the two dynamic processes modulates the onset and offset of sleep as well as the rhythms of sleep propensity, wake propensity and the degree of daytime alertness. Importantly, onset and maintenance of normal sleep patterns are dependent on the satisfaction of a number of conditions, including:

- Appropriate timing of sleep within the 24-hour circadian rhythm;
- Adequate level of physical comfort;
- Acceptable sleeping environment;
- Intact central nervous system function; and
- Relative absence of psychological distress and psycho-physiologic arousal [11].

That said, the restorative functions of sleep are dependent on a reasonably uninterrupted sleep architecture, which, in many medical conditions, is adversely affected. Hence, factors that oppose or enhance the aforementioned processes can have significant effects on the timing, duration and structure of sleep, and daytime wakefulness (see Section 1.5) [4, 43].

1.3. Classification and Terminology of Sleep/Wake Disorders

Alterations in normal or habitual sleep (the one a person is used to consider as normal and 'functions' as normal for them) mark the onset of sleep/wake disorders, which may be short-term or persist for long periods of time. Sleep/wake disorders include a wide array of problems characterised by the symptoms of insomnia, excessive daytime sleepiness, or abnormal movements, behaviours, or sensations during sleep [4, 43]. Traditionally, sleep/wake disorders have been classified according to the American Academy of Sleep Medicine (AASM) in the *International Classification of Sleep Disorders* [44] into three primary groups: (i) dyssomnias, (ii) parasomnias, and (iii) sleep disorders secondary to medical or psychiatric conditions. Dyssomnias are those disorders that result in disturbance in quality, quantity, or timing of nocturnal sleep, or produce excessive daytime sleepiness. Dyssomnias may be related to intrinsic factors (e.g., idiopathic insomnia, obstructive sleep apnoea, periodic limb movements), extrinsic factors (e.g., medications, environmental conditions), or circadian rhythm factors. (e.g., shift work, irregular sleep/wake pattern, advanced or delayed sleep phase). Parasomnias include abnormal behaviours or sensations during sleep, such as nightmares, sleep walking, and bruxism. The third category includes sleep disorders associated with medical or psychiatric disorders, such as Parkinson's disease, sleep-related epilepsy, and mood disorders. However, a recent revision of sleep/wake disorders suggested their categorisation into the following eight groups [45]:

- **Insomnias:** Primary disorders that lead to repeated difficulty with sleep initiation, duration, consolidation, or quality; this difficulty occurs despite adequate time and opportunity for sleep and results in daytime impairment;

- **Sleep-related breathing disorders:** They are characterised by disordered respiration during sleep;

- **Hypersomnias of central origin:** Disorders characterised by the primary complaint of daytime sleepiness. This is unrelated to circadian rhythm sleep disorders, sleep-related breathing disorders, or other disorders;

- **Circadian rhythm sleep disorders:** Recurrent or chronic patterns of sleep impairment resulting from alterations to the circadian system or misalignment between circadian rhythms and the 24-hour social and physical environments (e.g., shift work, irregular sleep/wake patterns, advanced or delayed sleep phase);

- **Parasomnias:** Undesirable physical events or experiences that occur at sleep onset, during sleep, or during arousal from sleep (e.g., nightmares, sleep terrors, sleep walking, or enuresis);

- **Sleep-related movement disorders:** Conditions primarily characterised by relatively simple, stereotyped movements that disturb sleep (e.g., periodic limb movements);

- **Isolated symptoms and unresolved issues:** Symptoms that either lie at the borderline between normal and abnormal sleep or that exist on a continuum of normal to abnormal events in sleep (e.g., snoring);

- **Other sleep disorders:** Disorders not otherwise classified (e.g., other physiologic/organic sleep disorders) [11, 43, 45].

Numerous additional sleep-related terms can help characterise sleep/wake disorders and are outlined in **Table 1-A2** (Appendix 2).

Two of the most common complaints or symptoms, also defined in the *International Classification of Sleep Disorders*, are insomnia and excessive daytime sleepiness. Insomnia may be a primary sleep disorder (see above) or a symptom of one of many other sleep/wake disorders, such as sleep-related breathing disorders [43]. Sateia and Santulli [11] argue that in clinical practice, insomnia can be defined as a subjective complaint of poor sleep, and in that sense insomnia is a symptom rather than a diagnosis. This definition encompasses complaints of insufficient sleep, difficulty initiating or maintaining sleep, interrupted sleep, poor quality or 'non-restorative' sleep, or sleep which occurs at the wrong time in the day-night cycle [11]. A comprehensive description should include clarification of the nature of the complaint and consideration of potential aetiologies, or contributing factors (see Section 1.5). In most cases, sleep deprivation in the form of insomnia results in a broad spectrum of psycho-physiological changes, depending on the degree, type and duration of deprivation, and most frequently includes progressive fatigue, sleepiness, impairment of concentration, and irritability [11, 45].

Daytime sleepiness is defined as the inability to stay awake and alert during the major waking episodes of the day, resulting in unintended lapses into drowsiness or sleep; it also may be seen in a wide range of sleep/wake disorders as their most common consequence [4]. Interestingly, because of its often vague and non-specific presentation, the condition is fre-

quently overlooked [11, 46]. The sleepy individual is inactive and poorly motivated [11], and may have little insight into the nature and severity of the problem or the negative effects that daytime sleepiness has on his/her life. In milder forms, daytime sleepiness may cause only minor decrements in social and occupational functioning [45]. When severe or excessive, however, the condition can be debilitating, causing a broad range of neuropsychological deficits that affect daytime functioning and quality of life [4]. Daytime sleepiness can be life-threatening because of associated alterations in alertness and reactivity [47]. What is more, while poor sleep can cause excessive daytime sleepiness, abnormal daytime sleep patterns can also adversely affect nocturnal sleep.

In contrast to the above-mentioned congruent terms, more general terms, such as sleep/wake disturbances, sleep problems, sleep disruption/fragmentation, sleep deprivation, alterations in sleep or impaired sleep, are also frequently reported in an attempt to describe complaints, symptoms, or groups of symptoms experienced by individuals. They are not diagnostic entities as defined by the AASM; yet, they are often implemented when a specific diagnosis has not or cannot be made [43]. The lack of standardisation in the definition of these terms has led to them being used interchangeably. In order to facilitate interpretation of findings in this study, use of such terms throughout the thesis will be employed to indicate the following concepts:

- **Sleep/wake alterations/impairments:** Adverse changes in habitual sleep/wake patterns that may lead to perceptions of ‘a problem’ with sleep.
- **Sleep deprivation/restriction:** Diminished duration of nocturnal sleep that may lead to ‘sleep debt’.
- **Sleep disruption:** Interruptions in nocturnal sleep that may lead to sleep fragmentation and perceptions of diminished sleep quality and restfulness.
- **Nocturnal sleep disturbances:** Actual triggers occurring during the night such as feelings of hot/cold or nightmares that may lead to sleep impairments.

1.4. Key Parameters for the Assessment of Sleep in Cancer Populations

The empirical observation of impaired sleep in people affected by cancer has been supported and boosted by systematic research. Two major assessment methods have been used in sleep

research in the context of cancer; most frequently these employ subjective measures, but also, increasingly, objective. Subjective sleep measures range from single-item scales (e.g. visual analogue scales) to multi-item, multidimensional assessment tools (e.g. sleep-specific questionnaires, sleep diaries/logs, diagnostic interviews) [4, 43] that evaluate a variety of aspects of sleep [13]: sleep quality, number of awakenings, depth and length of sleep, feelings on arising, satisfaction with sleep, and soundness of sleep [4, 48]. Such features reflect an individual's perceptions; thus, measuring these perceptions has been argued to be utterly important in nursing research [49]. Conversely, the gold standard for the objective measurement of sleep is laboratory or in-home ambulatory polysomnography. It entails the simultaneous recording via EEG, EOG and EMG [50] of multiple variables, which allows for detecting specific sleep and wake states [43] through the provision of in-depth information about stages of sleep. An alternative method, (wrist) actigraphy can be used to record movement over time in the form of activity and rest counts, thereby providing an indirect objective measurement of sleep [43, 51]. Compared to subjective sleep measures, objective measures have the advantage of providing highly reliable data on several sleep and wake variables, as well as on circadian rhythms.

Current evidence indicates that sleep/wake impairment in the cancer continuum is a multifaceted experience, including total sleep time of less than 50 hours per week [52]; fewer than usual hours of sleep [53]; multiple awakenings in the middle of the night; difficulty falling asleep [53, 54]; decreased sleep duration and efficiency [55]; early morning awakenings, leg restlessness or interruptions of breathing during sleep [54]; drowsiness [56], daytime sleepiness [12] and the need to nap at unusual hours during the day [53]; frequent and/or unpleasant dreams [12, 14]; feelings of inadequate restfulness the next day[55]; and the need for the use of hypnotics or sedatives [55, 57, 58]. Despite current advances, knowledge gained so far is still fragmentary, mainly because of methodological inconsistencies that limit comparability of assessment evidence. First, whereas it has become evident that a thorough description of sleep/wake patterns requires comprehensive evaluation of several key features, sleep studies in the context of cancer have only rarely or sporadically included all or most of them. Second, whereas prevalence rates for sleep deficits have been consistently reported, data pertinent to severity are lacking. Third, inadequate research measures, inconsistencies in the phase of treatment or cancer experience, as well as a lack of consensus regarding which sleep parameters to measure and report, have all played an important role in contributing to these inconsistencies within the knowledge. Due mainly to these issues, assessment has been identified as one of the major challenges that researchers face when examining the sleep/wake patterns of patients with cancer and/or their caregivers [43].

In light of an evident lack of standardisation of variables required for a comprehensive assessment of sleep and wakefulness, in 2005, a panel of expert clinicians and researchers proposed the use of a core of nine sleep/wake parameters to provide a common language for the quantification of the problem in patients with cancer and their caregivers [43, 49]. The systematic use of these variables was anticipated to increase consistency in terminology that could allow studies to be easily compared and contrasted [4, 43, 49]. These *key sleep parameters* include total sleep time; sleep latency; nocturnal awakenings; wake time after sleep onset; napping during the day; excessive daytime sleepiness; quality of perceived sleep; stability of circadian rhythms; and sleep efficiency. Definitions of these terms are outlined in **Tables 2-A2** and **3-A2**. Because of the complex nature of the problem, no single parameter is recommended to screen for sleep/wake impairment in patients with cancer and their caregivers [49]. Instead, all nine parameters collectively describe the nature/characteristics of impaired sleep.

1.5. Aetiology of Sleep/Wake Impairment: Theoretical Background

The aetiology of sleep/wake impairments in patients with cancer and their caregivers is multidimensional, given that numerous factors are likely to alter the normal regulatory processes of sleep [4, 59]. As described earlier, onset and maintenance of normal or habitual sleep is dependent on a host of person- and environment-related prerequisites (see Section 1.2). Yet, additional sleep-impairing factors can exert adverse effects. Knowledge of the underlying reasons for sleep impairment is essential for a comprehensive assessment and targeted management of sleep/wake disorders [60]. Given that care is specifically rather than vaguely focused on the potential source of the problem, the latter can be resolved even if no actual hypnotic treatment is administered.

One method of identification and classification of sleep-impairing factors is the use of certain theories, models or frameworks as a structured way to better understand pertinent definitions and assessment/measurement of specific sleep variables [61]; thus, familiarity with this body of knowledge is regarded to be paramount [49]. In spite of their importance, a recent literature review revealed that only three out of ten identified sleep studies in patients with cancer included a description of a sleep-related theory, model or framework that provided conceptual guidance [61]. Three conceptual models were found to focus on sleep/wake disturbances as a primary variable of interest, whereas eight additional mod-

el/theories tended to include sleep/wake disturbances as a secondary variable or as one variable within a cluster of several symptoms [61]. Two of the most influential models related to sleep/wake disturbances are the *Conceptual Framework for Understanding Impaired Sleep* and *Spielman's Three-Factor Insomnia Model*, which can be used in conjunction to offer various approaches to the examination of sleep-impairing factors in people with cancer and their caregivers.

1.5.1. Conceptual Framework for Understanding Impaired Sleep

According to the Conceptual Framework for Understanding Impaired Sleep [62], sleep loss can be conceptualised to result from sleep deprivation/restriction (i.e. inadequate amount of sleep) and/or sleep disruption (i.e. fragmentation of sleep). As outlined in **Figure 1-1**, sleep deprivation can be the consequence of self-imposed sleep restriction such as poor sleep hygiene or multiple responsibilities, and/or of noxious stimuli in the sleeping environment. The resulting 'sleep debt' can increase daytime sleepiness and dysfunction. Alternatively, sleep fragmentation can result from a host of sleep-impairing factors, including health conditions, physical and/or psychological distress, alcohol/caffeine intake, nicotine use, relationships and situations in the home, restless bed partners, or own disturbances such as disordered breathing or parasomnias. Sleep disruption may affect an individual's perception of sleep quality and restfulness gained. Regardless of the underlying mechanism, sleep loss may place an individual at risk for adverse health outcomes and diminished well-being.

1.5.2. Spielman's Three-Factor Insomnia Model

Spielman's Three-Factor Insomnia Model (also known as the 3P model) proposes interactions among predisposing, precipitating, and perpetuating factors of insomnia symptoms (**Figure 1-2**) [63, 64]. The model includes both stress and behavioural factors to explain the evolution of insomnia symptoms and describes how individual differences cause initiation of acute disturbances in sleep that become chronic. The model can be used for the classification of explanatory factors into three comprehensive groups:

- **Predisposing:** Highly subjective traits that increase a person's overall risk and vulnerability to develop sleep disorders. Factors that predispose the development of insomnia symptoms may include advancing age, female gender, arousability, past patient and family history of sleep disorders and medical illnesses, and disruptive sleep behaviours (in other words, sleep hygiene) [60, 63-65].

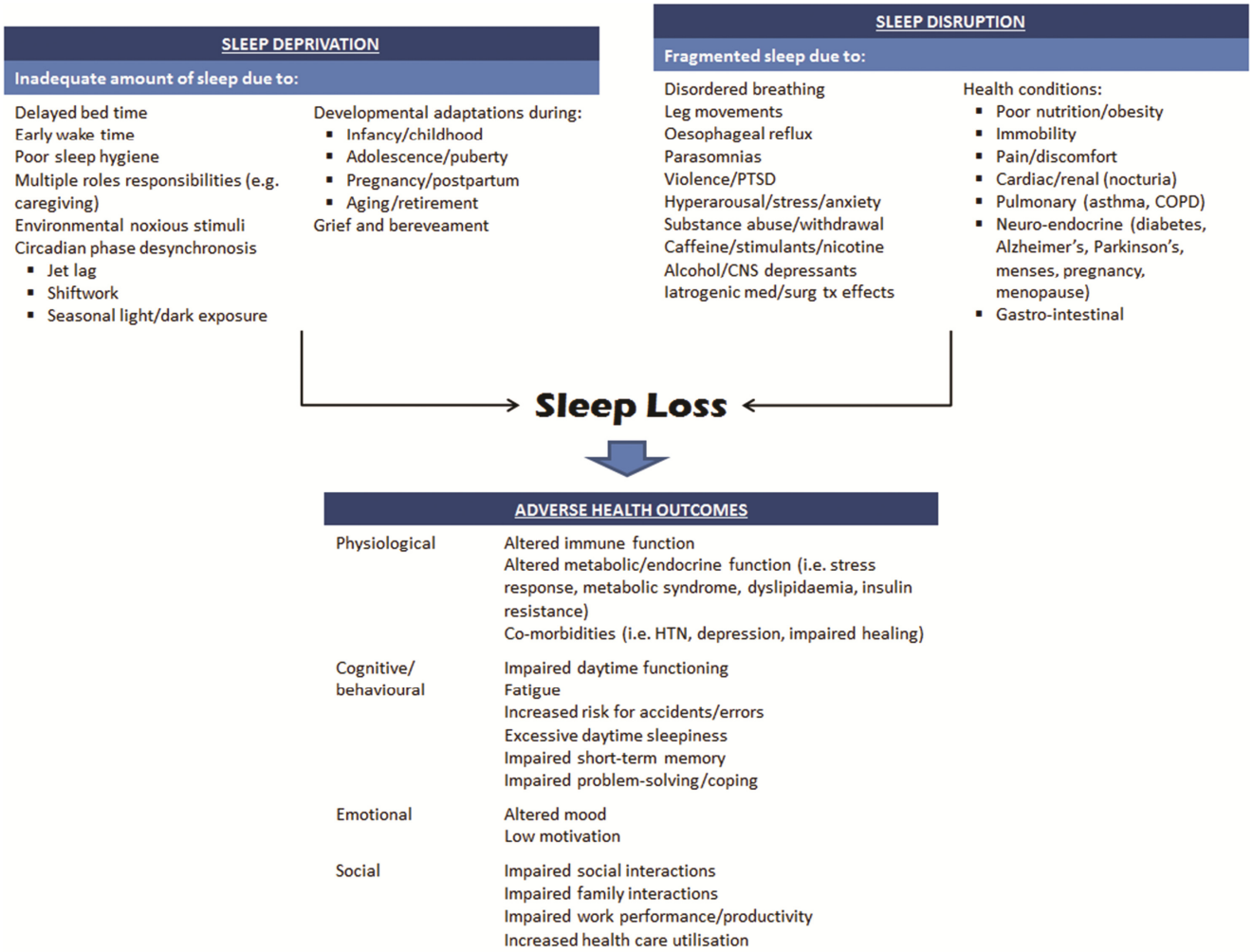

Figure 1-1. Lee Conceptual Model of Impaired Sleep. *Source:* Lee et al. 2004 [62]

- **Precipitating:** Situations and conditions that, albeit temporary, are actual triggers of insomnia symptoms. Diseases such as cancer constitute possible contributors to sleep problems, since they are not single events but a succession of major stressful factors, each of which can act by itself and detrimentally on sleep [60]. Factors likely to promote sleep problems in people with cancer and their caregivers include disease-related, treatment-related and psychosocial factors.

- **Perpetuating:** Variables involved in the reinforcement of insomnia symptoms over longer periods of time. In many cases, sleep problems are simply opportunistic and normal rhythms can be restored after precipitating factors have abated or after an individual's adjustment to their prolonged occurrence. However, insomnia symptoms can become chronic, especially among the more susceptible individuals. Perpetuating factors exert their negative effects by increasing alertness (physical, cognitive, behavioural) and causing anxiety (the inherent 'pressure' to sleep) [64]. Several of these variables (e.g., maladaptive sleep behaviours or faulty beliefs and attitudes about sleep) are difficult to change and require training and consultation [59].

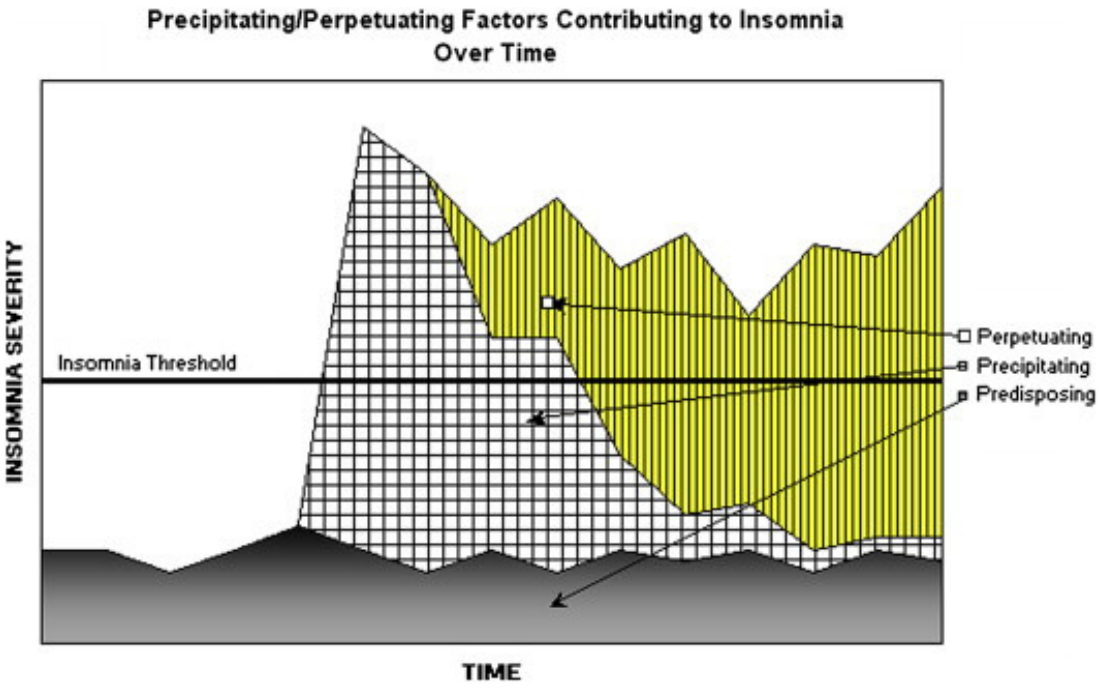

Figure 1-2. Spielman's Three-Factor Insomnia Model. *Source*: Glovinsky et al. 2008 [66]

Collectively seen, the models suggest that a host of internal (person-related) and external (environment-related or circumstantial) factors can interfere with habitual sleep/wake processes at different levels and through different mechanisms. A group of factors can alter the homeostatic/somnostat process of sleep, heighten arousal and increase the likelihood for sleep deprivation. Another group can interfere with the circadian process of sleep and cause disruption/fragmentation. The ways that these factors act can be direct (precipitating and/or perpetuating effects) or indirect (predisposing effects). In addition, depending on their nature, some of these factors contribute only in acute and transitory episodes of sleep/wake disruption (precipitating), whereas others potentially result in prolongation and chronicity of sleep deprivation (predisposing and/or perpetuating). In general, patients with cancer and their caregivers are considered to be at high risk for disruption in their sleep/wake patterns because of a number of such factors that may alter normal sleep regulatory processes. A detailed description of sleep-impairing factors in women with early stage breast cancer and their caregivers is provided in Chapters 2 and 3, respectively.

1.6. Summary

Impaired sleep/wake patterns can be frequent complaints among people affected by cancer that pose significant consequences on their daytime functioning and general well-being. Eight groups of sleep/wake disorders have been suggested; however, symptoms of insomnia and excessive daytime sleepiness are those most commonly reported. Assessment of sleep/wake patterns is paramount to the effective management of these potentially debilitating problems. Nine parameters of sleep/wake disturbance have been proposed to provide a common language in studies assessing patients with cancer and/or informal caregivers. These parameters can serve as key outcomes in both exploratory and experimental studies. Underpinned by theoretical models, this research will be able to investigate how these variables are affected by a host of factors that may predispose individuals to alterations in sleep architecture, as well as precipitate and/or perpetuate sleep deprivation and disruption.

CHAPTER 2.

Breast Cancer and the Experience of Impaired Sleep/Wake Patterns

2.1. Breast Cancer Epidemiology, Clinical Evaluation and Management

Worldwide, breast cancer is the most frequently diagnosed life-threatening cancer in women [67]. Current data reveal that 425,147 new cases of invasive breast cancer occurred in Europe in 2008 [68]. The lowest European rates are seen in eastern and southern Europe and the highest in northern and western Europe [69, 70]. In the UK, breast cancer is the most common cancer in women: 46,458 women were diagnosed in 2008 [68, 70] accounting for 31% of all cancers [71], while around 126 new cases of breast cancer are diagnosed each day [72].

Over the past 35 years, breast cancer incidence rates have risen (and still rise) globally, with the highest rates occurring in the westernised countries. Reasons for this trend include changes in reproductive patterns, increased screening, dietary changes, and decreased activity. Although breast cancer incidence is on the rise, breast cancer mortality has been decreasing, especially in industrialised countries [71, 73]. Increased public awareness and improved screening have led to earlier diagnosis at stages amenable to complete surgical resection and curative therapies [74]. Consequently, survival rates for breast cancer have improved significantly, particularly in younger women [67]. Almost 2 out of 3 women with breast cancer now survive their disease beyond 20 years. The most recent estimate (2008) suggests that around 550,000 women are alive in the UK, who have had a diagnosis of breast cancer [75]. Nevertheless, supportive care needs of women living with and beyond breast cancer still exist, thus urging for comprehensive assessment and management services.

Breast cancer is diagnosed by taking a biopsy, or sample of breast tissue, and examining it under the microscope [72]. Subsequent treatment decisions are based on the extent of the disease and characteristics of the cancer, menopausal status and general health of the patient. Breast cancers are derived from the epithelial cells that line the terminal duct lobular unit, and are usually subdivided into non-invasive (in situ) and invasive cancer [71, 76]. Cancer

cells that remain within the basement membrane of the elements of the terminal duct lobular unit and the draining duct are classified as in situ. Conversely, an invasive breast cancer is one in which there is dissemination of cancer cells outside the basement membrane of the ducts and lobules into the surrounding adjacent normal tissue [76].

When an invasive breast cancer is diagnosed the extent of the disease should be assessed and the tumour staged. Prognosis in breast cancer relates to the stage of the disease at presentation [76]. The American Joint Committee on Cancer staging system groups patients according to extent of the primary tumour (T); absence or presence of lymph node metastasis (N); and absence or presence of distant metastasis (M). This classification system is widely known as the TNM system [76]. It is often used in combination with the International Union Against Cancer (Union Internacional Contra la Cancrum, UICC) staging system, which classifies breast tumours into five stages [71] **(**see **Table 4-A2)**. The earlier the cancer is diagnosed, the more favourable survival rates are. Around 9 out of 10 women diagnosed with stage I breast cancer survive their disease beyond five years. However, this drops to around 1 out of 10 if diagnosed with stage IV disease [72]. The term *early stage breast cancer* refers to those patients whose cancer has not spread outside the breast and the axillary lymph glands under the arm on the same side as the tumour (stages I-IIIA). Selection of patients for the present study was based on the afore-mentioned definition.

The treatment of early stage breast cancer is usually multimodality, requiring careful coordination and planning among all members of the multidisciplinary team. Treatment at this stage of the disease is given with curative intent [72]. Surgery is considered to be the primary treatment for breast cancer, and many patients with an early-stage disease are managed with surgery alone [67]. This may consist of either breast conservation (e.g., wide local excision, central excision, quadrantectomy) or mastectomy, which may be followed by immediate or delayed breast reconstruction and adjuvant treatment [67, 72, 77].

Adjuvant therapy is given to reduce the risk of cancer recurrence from the microscopic spread of cancer cells to the axillary lymph nodes that is known or suspected, and cannot be detected at the time of diagnosis. Among the different modalities of adjuvant treatment in breast cancer, chemotherapy has become firmly established as one of the major therapeutic modalities as it reduces the risk of recurrence and death by about 30%-50% and 20%, respectively [72, 78-80]; however, its benefits in women over 70 are not well established. Because of its side-effects, adjuvant chemotherapy is usually given to women at significant risk of recurrence (i.e., lymph node metastasis), or if their cancers are oestrogen-receptor negative [72]. Nevertheless, there has been an increasing trend to give chemotherapy to almost all young patients with operable breast cancers regardless of lymph node status as there is

evidence of real benefit in their disease-free survival [79]. Regimens based on anthracyclines such as doxorubicin and epirubicin are the current standards of care [81]. Other commonly used drugs in the treatment of early stage breast cancer include alkylating agents (e.g., cyclophosphamide) and anti-metabolites (e.g., methotrexate, 5-fluorouracil). Examples of some widely used combination regimens include the following:

- CMF = cyclophosphamide, methotrexate, fluorouracil
- AC = doxorubicin, cyclophosphamide
- EC = epirubicin, cyclophosphamide
- FEC = fluorouracil, epirubicin, cyclophosphamide
- CAF = cyclophosphamide, doxorubicin, fluorouracil
- E-CMF = combination of epirubicin with the CMF regimen [79].

The addition of a taxane (paclitaxel or docetaxel) is usually recommended in sub-groups of women with higher risk disease, including those with increasing size of the primary cancer, higher histological grade and presence of tumour in the axillary nodes [72, 82].

2.2. Experiencing Early Stage Breast Cancer

The experience of living with breast cancer, even at an early stage, can have a multilevel impact on a woman (physical, psychological/emotional, social) and may affect her over a trajectory that is extended over (at least) three distinct, yet interrelated, phases: pre-diagnosis/diagnosis phase; pre-/treatment phase; and recovery and follow-up phase. This 'treatment' pathway is not always as straightforward as described; rather, it may represent a particularly demanding and difficult 'roller-coaster'-like experience (**Figure 3-A1**), which deserves the attention of the multidisciplinary team throughout its trajectory [83].

A diagnosis of breast cancer can be numbing, not just for its immediate impact, but because it represents the loss of present familiarity and the loss of a sense of control and future [83-85]. Women display numerous different reactions to their diagnosis of breast cancer. Shock, feelings of anger, anxiety, sadness and despondency are entirely appropriate responses to a life-threatening situation. However, when they become persistent and overwhelming, these

feelings can be profoundly damaging [84]. Among other related areas of functioning, sleep may also become affected.

Obtaining a treatment plan and relevant information can afford some relief from anxiety. Yet, the emotional 'roller-coaster' keeps on going, and anxiety occurs as the woman waits for treatment to commence. Fears with regard to side effects and their impact, as well as the likelihood of treatment failure may be prominent [83]. During treatment, then, the woman has to deal not only with the ongoing emotional and psychosocial impact of the diagnosis, but also the burdens and costs of disfiguring, toxic and lengthy treatment [84]. In most cases, treatment begins with surgery. The physical removal of breast cancer can be reassuring but leads to some kind of disfigurement (partial or total removal of the breast), which induces a profound sense of loss and threatens a woman's sexual identity and ability for social interactions [77, 84]. However, it is chemotherapy that has been traditionally associated with the most debilitating side effects and the highest emotional burden [85, 86]. Although, nowadays, symptom management shows considerable progress, most women with breast cancer will experience at least some chemotherapy-related symptoms, such as nausea and vomiting, fatigue, and hot flashes and/or night sweats [84], in most cases accompanied by disturbed sleep and daytime sleepiness [87-93]. The daily disruption and cumulative effect of having chemotherapy may be significant [94]. Even the treatments used to counteract the side effects of chemotherapy can cause side effects of their own; for instance, steroids as part of the anti-emetic regime may increase appetite resulting in weight gain and feelings of an altered body image and decreased attractiveness [85]. Aside from its emotional and physical impact, chemotherapy can result in increased psychological manifestations. The incidence of anxiety and depression has been described as significantly higher in women receiving chemotherapy after mastectomy, directly related to the degree of toxicity experienced [95, 96].

The period following treatment can be particularly difficult. In addition to side effects continuing to be experienced, the loss of contact with the health care team can trigger considerable fear and uncertainty [83, 84]. Women struggle to re-enter their world and regain their life; some of them will seek to return to work or previous engagements. Having lived with cancer during the intensive period of treatment might be followed by changes, including physical discomfort, sleep disturbances, difficulty in emotional relationships, empowerment or regret, and fragility, which will influence the extent of and time for a woman's adjustment [84, 97, 98] during rehabilitation and survivorship.

2.3. Sleep/Wake Patterns of Women Receiving Chemotherapy for Early Stage Breast Cancer

Sleep has been suggested as an area of functioning that is frequently and largely impaired in women who go through the lived experience of breast cancer [99]. Of note, regardless of disease stage, post-diagnosis cases of insomnia reach 33% [100], while post-treatment incidence of impaired sleep/wake patterns widely ranges between 57% and 99% [87, 101-103].

These facts have given rise to an impressive number of sleep studies, which have invariably explored sleep/wake disturbances as a result of both the disease itself and the treatment [33, 88, 100, 102, 104-110]. A significant part of this research has specifically focused on women diagnosed with breast cancer at an early stage (I-IIIA), especially in the context of chemotherapy treatment. It can be argued that research in this area has been legitimised as highly significant due to the increased vulnerability of this specific population [99]. As described earlier, the cumulative effect of toxic agents on bodily functions, the physical impact of concurrent, frequent, severe and/or distressing symptoms, the emotional burden of daily disruptions in life, together with a host of anxieties and depressed mood, may well be responsible for, or pave the way towards, alteration of habitual sleep/wake patterns. Such body and life changes become especially important for women already susceptible to sleep alterations given the unseen or evidenced impact of breast cancer diagnosis and of primary breast surgery on their sleep. By interfering with the onset and maintenance of normal sleep, and depending on their very nature, these triggers can contribute to a spectrum of experienced sleep impairment even before, but mainly during and after chemotherapy for early-stage breast cancer.

A systematic search for publications that evaluated the sleep/wake patterns of women with early-stage breast cancer across chemotherapy treatment was conducted. This systematic review aimed to answer two questions:

a. What do research findings report about key sleep/wake parameters of women receiving neo-/adjuvant chemotherapy for breast cancer?

b. What are the methodological and research gaps in this body of evidence?

The systematic search aimed to identify original research studies conducted in the context of early-stage breast cancer, specifically focussing on examination of women's sleep/wake patterns during neo-/adjuvant chemotherapy. Studies were identified by systematically searching three research and evidence electronic databases, namely Medline (1948-2011 May week 02), CINAHL (Beginning-2011), and EMBASE (1980-2011 Week 18). An initial search

strategy was devised and subsequently revised through an iterative process (Appendix 3). Using a snowballing strategy, the reference lists of retrieved studies were also examined for any studies that may have been overlooked. Reference lists of key topical research reviews also were examined [12, 13, 43, 49, 59, 60, 99, 111-115]. Additional literature was sought through use of the search engine Google Scholar to locate relevant publications using the aforementioned key words.

Studies were eligible in this review if they were written in the English language; were conducted with adult (>18 years of age) women diagnosed with early-stage (I-IIIA) breast cancer [71]; examined sleep/wake patterns as a primary or secondary variable via use of sleep-specific measures (objective and/or self-reported); examined sleep/wake patterns prior to, during and after adjuvant/neo-adjuvant chemotherapy treatment, in chemotherapy naïve patients; and were published as original articles in peer-reviewed journals from January 1980 to July 2011 representing the period in which sleep-specific instruments were developed, and studies of sleep within different clinical populations emerged. Exploratory studies, both quantitative and qualitative, were included, although intervention studies were also considered if they provided baseline and/or control arm sleep data.

Studies were excluded on the basis of the following criteria: (a) studies with mixed samples with regard to type of disease or treatment, except if data for patients with early-stage breast cancer were reported separately; (b) studies using generic quality of life measures or single item tools to elicit information about sleep patterns; (c) studies conducted with patients pre-selected for insomnia or impaired sleep; (d) studies where the stage of disease or the type of chemotherapy were not explicitly described; and (e) unpublished studies, dissertation studies, or conference presentations.

A shortlist of papers was initially compiled, where titles and abstracts were screened to assess relevance to the review. Potentially eligible papers were retrieved in full and checked for adherence using the afore-mentioned inclusion and exclusion criteria. Study characteristics of the finally selected studies were extracted using a systematic scheme. Due to heterogeneity of the studies retrieved, findings were only integrated in a narrative synthesis. In order to summarise findings with regard to specific sleep/wake parameters, weighted grand means ($\bar{X}$) and standard deviations were calculated based on information from different studies, and adjusting for different sample sizes. The weighted mean is similar to the common arithmetic mean, where instead of each of the data contributing equally to the final average, some data contribute more than others, namely those deriving from bigger sample sizes. The weighted mean's mathematical definition is given in **Figure 4-A1**.

The evidence categories employed by the Department of Health in the National Service Frameworks (DOHNSF, 2001) [116] were used for levelling evidence, and aiding appraisal of quality of the papers reviewed. This framework was used because it has been piloted for use with both peer-reviewed and non-peer-reviewed research [117]. **Table 5-A2** outlines the levels of evidence as established using the DOHNSF validated grading hierarchy. No studies were excluded on the grounds of quality, given the lack of agreement in the application and interpretation of quality criteria [118].

The selected studies were analysed, summarised and synthesised to provide evidence regarding alteration in key sleep/wake parameters in this population. Additional sleep/wake parameters, including perceived sources of sleep disturbance, use of sleep aids, insomnia syndrome, feelings upon waking, and total rest time, also were appropriately summarised or clustered into respective categories. A brief description of the characteristics of the included studies can be found in Appendix 3. Findings presented below and in Appendix 3 were published in a peer-reviewed journal and can be found in Kotronoulas et al. [119] (see Appendix 7).

2.3.1. Overall Incidence of Sleep/Wake Impairment

Evidence suggests that sleep in women with early-stage breast cancer may already be disturbed *before* chemotherapy commences [120, 121]. Data show deficits in almost all key sleep parameters before the first cycle of adjuvant/neo-adjuvant chemotherapy, mainly in the last 48-72 hours before treatment [9, 121-124], although wider assessment time frames ranging from 1 week to 1 month have also been used [8, 120, 125]. However, impairment of sleep/wake patterns is maximised *during* adjuvant chemotherapy [90]. A focus on the first (CThC1) [7-9, 49, 104, 123, 126-128], third (CThC3) [122, 124, 129] and fourth (CThC4) [8, 9, 122, 123, 130] chemotherapy cycles was noted in the relevant studies. Purposeful assessment of women's sleep/wake patterns soon after (mainly within the following 30 to 60 days) the last chemotherapy cycle was infrequently included as an important clinical endpoint within the studies reviewed [49, 104, 122, 123, 131]. Nevertheless, the on-going sleep problems evidenced suggest that sleep alterations initially occurring during treatment can become chronic in nature [111].

2.3.2. Subjective Sleep Quality

Subjective sleep quality – the perception of sleep as restorative and sufficient for function [113] – was reported to be generally and consistently poor throughout the course of chemotherapy [7, 8, 121-125, 129, 130, 132, 133]. Despite inconsistencies or limited available data, it can be inferred that initially poor perceived sleep quality might reach a peak during treatment, with a tendency for a slight improvement close to the end of treatment. However, only partial or no significant over-time relationships between distinct time-points exist [122, 130, 131], which could suggest that fluctuations in poor sleep quality are subtle rather than marked, and ratings of greater sleep disruption may be associated with temporal adverse events during a period of consistently poor quality of sleep. Among women reporting lower pre-treatment sleep disruptions, adverse effects on their sleep patterns might be more evident during treatment [8]. Moreover, greater sleep disturbance at baseline might anticipate the maintenance of poor sleep quality during treatment [8], but more research is needed to implicitly confirm this hypothesis.

2.3.3. Sleep Efficiency

Despite progressive decline, sleep efficiency remained within normal range for the majority of women and across all phases of chemotherapy. Predominantly within the first week prior to chemotherapy initiation, sleep efficiency was found to be at or above the normal cut-off value of 80%, with a weighted grand mean of 85.2% (range of means 75.9%-89.1%) based on actigraphic recordings [120-123, 125], and 89% based on daily sleep diaries [122]. Over the course of treatment, sleep efficiency presented with no major changes compared to baseline as reported for the week following CThC1; however, during the first week after CThC4, objective sleep efficiency was found to average at 81.8% [122, 123, 125]. Kuo et al. [129] observed a similarly decreased sleep efficiency (79.9%-82.1%) during the active (week 1) and recovery (week 3) phases following administration of CThC3. Four weeks following four to eight cycles of adjuvant chemotherapy treatment, sleep efficiency was restored close to baseline based on actigraphic findings [104, 122, 123].

2.3.4. Nocturnal Total Sleep Time

One to three days prior to chemotherapy treatment, total sleep time averaged at 392.4 minutes (6.54 hours) based on actigraphic data [120-123, 125, 128, 134]. Similarly, a weighted grand mean of 0.89 (range 0.75-0.99) on the respective Pittsburgh Sleep Quality

Index (PSQI) component indicated duration of sleep of seven hours or less for the previous month [7, 120, 125, 130]. A trend towards somewhat longer sleep at night seemed to be maintained during chemotherapy treatment with actigraphic measures yielding weighted grand means of slightly more than seven hours of sleep in the first three days post-treatment initiation [7, 122, 128], and one week (7-10 days) after CThC3 [122, 129], whereas a drop to approximately 7 hours per night on average was evident following CThC4 [122, 123, 125, 128]. Control data from a randomised clinical trial (RCT) suggested that at different time points following adjuvant treatment women's nocturnal sleep time was slightly below 7 hours per night [122, 123].

2.3.5. Sleep-Onset Latency

Within the month prior to chemotherapy initiation, subjective sleep latency may well exceed the normal value of 20 minutes as evidenced by a weighted grand mean of 1.15 (range .92-1.49) on the PSQI sleep latency component, implying that sleep latency may fluctuate between 16 to 30 minutes per night [7, 120, 121, 125, 130]. After initial chemotherapy administration [130] and over treatment continuation [130], a trend of consistent increases in subjective sleep latency is evidenced, with perceived time to fall asleep possibly averaging 35 minutes the week after CThC3 [129], and objective latency for all three weeks over-reaching 20 minutes [104, 129]. Three weeks after CThC4, perceived sleep latency might approximate baseline levels [125], although actigraphic data may suggest that difficulty falling asleep still is prominent exceeding 25 minutes on average [104].

2.3.6. Nocturnal Awakenings

Actigraphically-recorded episodes of awakening during the week prior to chemotherapy initiation may be particularly elevated ($\overline{X}$=19.8/night) [120-123, 125]. During the first few nights (days 1-7) after CThC1, nocturnal awakenings may further increase in frequency [7, 122, 126] with the first night's sleep after treatment described as the most fragmented [7]. Over treatment continuation, awakenings seem to become stabilised at this high level. Despite a decline in their frequency, awakenings may still be prominent approximately 4, 8, and 12 weeks after the end of chemotherapy [104, 122, 123], although it is unclear to what extent this might be the result of other treatment modalities commencing at this particular period of time. Interestingly, self-reports may not corroborate objective findings, with per-

ceived awakening episodes not exceeding an average of 3/night, irrespective of chemotherapy phase [122, 129].

2.3.7. Wakefulness after Sleep Onset (WASO)

The nights before chemotherapy initiation women may spend approximately 18% of their total rest time in wakefulness [120, 121]. During this period, WASO may be as high as 77.4 minutes/night [120-122, 125], very similar to the week after initial treatment [7, 122]. Manifestation of multiple nocturnal awakenings during the course of chemotherapy may result in increased night-time restlessness and prolonged time in sleeplessness post-sleep onset, possibly exceeding one hour per night [104, 122, 123, 125, 129]. Using a 7-day sleep diary, Berger et al. [122] showed that WASO fluctuated during the course of treatment with greater increases occurring the week after CThC1 and CThC4, and a moderate decline 30 days or more after the end of treatment. Yet, self-reported WASO was considerably lower (approximately 23-33 minutes lower) than the objectively recorded.

2.3.8. Daytime Napping

At pre-treatment, total daytime nap time may be increased, exceeding 1 hour per day ($\overline{X}$=64.8 minutes) [120, 121]. During treatment continuation, the overall need for rest may be further increased, and women who may be less active during the day may take more naps and spend more time resting [127, 129]. Disappointingly, evidence with regard to daytime napping during the course of chemotherapy is near to zero. In a small feasibility study, Berger et al. [124] described a trend towards increased objectively measured napping time in the first three days after CThC3 as compared to the days before chemotherapy administration, and days 5-7 post-treatment, which might have been related to concurrently increased levels of fatigue.

2.3.9. Daytime Sleepiness/Dysfunction

Daytime sleepiness per se has not been systematically examined in women receiving chemotherapy for early stage breast cancer. Instead, the broader term of daytime dysfunction as measured by the PSQI has received greater attention, but mainly during the pre-treatment period. Daytime dysfunction may be prevalent the week prior to chemotherapy initiation ($\overline{X}$

PSQI daytime dysfunction=.82) [7, 120, 121, 125, 130, 134], and further deteriorates during the first week post-initial treatment, and remain relatively increased over treatment continuation (i.e., CThC3 and CThC4) [125, 129, 130]. In this period, daytime sleepiness might be more prominent immediately (first week) after chemotherapy rather than during the recovery phase, that is, the following two weeks in a three-weekly administered regimen [129]. Following treatment, levels of daytime dysfunction associated with sleepiness remain unknown.

2.3.10. Circadian Rhythms

Pre-treatment circadian rhythms in women with early stage breast cancer were described as robust and synchronised in the studies reviewed [9, 120, 121] with acrophases, mesors and amplitudes within normal limits. Nevertheless, progressively impaired circadian activity and rest cycles such as low activity, less consolidation of higher daytime, and lower night-time activity were recorded after initial chemotherapy administration [9, 49, 104, 126, 127, 134]. Similarly dampened circadian rhythms were prevalent over treatment continuation, especially after CThC3 and CThC4, where mesor, amplitude, up-mesor, down-mesor and rhythmicity remained impaired [9, 49, 104, 126, 134]. After the end of treatment, sleep architecture was still altered with less SWS sleep and less REM sleep compared to normative data [135]. Yet, despite these deficits, circadian rhythms of women may be significantly closer to normal at this point compared to CThC1 and CThC3 [49].

2.3.11. Use of Sleep Aids

Moore et al. [136] reported that 17%-20% of women were using a sleep aid two days prior to chemotherapy initiation, which slightly increased to 23% the first night post-treatment with a decline to 14% seven days later. This pattern was similar during cycles two through four, whereas an over-time decrease in sleep aid use was noted up to one year later. Prescription sedative/hypnotics were the most frequent (46%) sleep aids in use, followed by over-the- counter analgesics (24%), whereas use of alcohol or herbs was rather infrequent. Costantini et al. [137] concluded with similar findings; nearly 14% of the women were making use of a sleep aid prior to the treatment, whereas approximately 32% were prescribed a sleep aid during chemotherapy. Benzodiazepines (39.2%) and non-benzodiazepines (37.3%) were the most frequently prescribed sleep aids in this sample.

2.4. Sleep-Impairing Factors in Women Receiving Chemotherapy for Early Stage Breast Cancer

Within the scope of a broader meta-analytic review of the literature looking at sleep-impairing factors in women diagnosed with breast cancer, a systematic search was undertaken to locate studies where potential triggers for sleep/wake impairment had been examined in the context of neo-/adjuvant chemotherapy treatment. Studies were identified by systematically searching three research and evidence electronic databases, namely Ovid (Medline 1988 – 2012), EMBASE (1980 – 2012), and CINAHL (Inception – 2012). The reference lists of included studies were searched by hand for any studies that may have been overlooked.

Studies were eligible to this review if they were published in English; employed any research design (cross-sectional/longitudinal surveys, case-control studies, intervention controlled/non-controlled trials etc.); studied adult (≥ 18 years of age) female patients with histologically confirmed diagnosis of breast cancer, irrespective of tumour stage or type of treatment; examined sleep as a primary or secondary variable via use of sleep-specific measures, namely polysomnography or actigraphy (objective) and/or validated sleep scales/instruments (subjective); studied patients with no other medical co-morbidities; provided measures of statistical associations between sleep patterns and sleep-impairing factors in the target population; were published in the period between January 1990 and March 2012.

Studies were excluded if they utilised generic quality of life measures or symptom scales, or single item sleep scales to elicit information about sleep patterns; reported on mixed cancer samples, except if separate analyses and associations were reported for groups of patients with breast cancer; were unpublished studies, conference papers, or dissertation abstracts.

Methodological quality of each study was evaluated through use of an adapted version of the 14-item standardised checklist of pre-defined criteria introduced by Mols and colleagues [138]. Adaptation was based on information from previous similar reviews [139, 140]. Areas of concern included a study's research design, sampling and bias, and data collection and measurement. Clarification of the different methodological components will be aided through use of the STROBE statement checklist for reports of observational studies (**Table 7-A2**) [141, 142]. To promote an evidence-type approach, a validated grading hierarchy was also used to assess the level of evidence presented according to the type of research using the evidence categories employed by the DOHNSF (2001) [117] (**Table 6-A2**).

Twenty-six articles reporting on 16 studies were identified (**Table 9-A2**). Relevant findings were critically analysed and clustered into six broad categories. **Figure 2-1** presents an overview of the identified factors, theoretical categorisation of which was performed according to a combination of main points of the Conceptual Framework for Understanding Impaired Sleep [62] and Spielman's Three-Factor Insomnia Model [63, 64]. Effect sizes *r* (r_{ES}) were calculated to estimate clinical significance of the identified relationships between sleep-impairing factors and different sleep/wake parameters (see **Tables 11-A2, 12-A2** and **13-A2**). Research and clinical limitations of the current body of evidence also were discussed. A brief account of the characteristics of the included studies can be found in Appendix 4.

		Conceptual Framework for Understanding Impaired Sleep	
		Sleep deprivation due to:	**Sleep disruption due to:**
Spielman's Three-Factor Insomnia Model	**Predisposing factors**	Age Race/ethnicity Educational attainment Socio-economic status Children at home Marital status Comorbidity Performance status Disease stage Daytime activity Overweight Sleep hygiene	Age Race/ethnicity Educational attainment Children at home Past sleep history Past sleep aid use Inflammatory biomarkers Comorbidity Menopausal status Breast cancer diagnosis Breast cancer surgery Sleep hygiene
	Precipitating factors	Physical burden (fatigue, hot flashes, nausea/vomiting)	Comorbidity Chemotherapy treatment Physical burden (fatigue, hot flashes, nausea/vomiting) Psychosocial distress Maladaptive coping
	Perpetuating factors	Daytime activity Sleep hygiene Physical burden (fatigue, hot flashes)	Age Comorbidity Menopausal status Sleep hygiene Physical burden (hot flashes) Psychosocial distress Maladaptive coping

Figure 2-1. Classification of identified triggers of sleep/wake impairment in women receiving chemotherapy for early stage breast cancer according to two theoretical sleep models.

2.4.1. Demographic Factors

In only six studies was age examined as a potential covariate of sleep/wake impairment [7, 8, 121, 123, 125, 131, 132, 136, 143-148], hence evidence is inconclusive. At different points during chemotherapy treatment, Roscoe et al. [147] found no significant relationships between age and sleep/wake circadian parameters. Despite a similar overall absence of significant associations, a few partial and/or weak correlations were reported in women after administration of CThC1. Specifically, actigraphic data showed that older women had greater ratios spent in WASO (r_{ES}=.17 to .28) [7], less total sleep time (r_{ES}=–.22 to –.35) [7, 8, 121, 123, 125, 131, 132, 136, 143, 145, 146], and percentages spent asleep at night (r_{ES}=–.17 to –.28) [7, 121, 123, 131, 136, 143]. Perceived sleep difficulty was also greater, yet of limited significance (r_{ES}=–.07), for older women 3 to 4 months post-surgery [144]. However, a secondary RCT data analysis showed that it was the younger rather than the older women who made greater use of sleep aids during CThC6 and 90 days after the end of adjuvant chemotherapy; clinical significance of this finding was nevertheless negligent (r_{ES}=–.05) [136].

Limited and inconsistent findings exist with regard to the role of race/ethnicity in increasing susceptibility of women with early stage breast cancer to sleep loss. Whereas Colagiuri et al. [144] concluded with no significant associations between subjective sleep difficulty and ethnicity, Liu et al. [146] reported a few associations of non-Caucasian race and greater overall sleep/wake impairment (r_{ES}=–.21), and more time in WASO (r_{ES}=–.22); yet, no differences were found for total sleep time, total wake time, or daytime napping duration [146, 148]. The sleep-impairing effects of educational attainment are also questionable as evidenced by the consistent absence of significant links to objective sleep data [7, 8, 121, 123, 125, 131, 132, 136, 143, 145, 146]. In terms of subjective complaints, two studies provided only inconsistent findings (r_{ES}=.04 [144] and r_{ES}=.22 [148]), yet women with a higher educational background seemed to be more susceptible to poorer sleep quality. In addition, education seems not to influence actual use of sleep aids during adjuvant chemotherapy [136]. The overall socio-economic status rather than education itself has been proposed as a more robust predictor of sleep quality among women [149]. In the context examined here, though, such a link is yet to be established. Similarly, the studies reviewed revealed no significant links between either employment status or personal income, and sleep [144, 146, 148]. The presence of a (sleep) partner/roommate and/or children at home could represent an additional source of sleep disturbance. Yet again, limited current evidence has failed to indicate sleep-impairing effects for marital status [144, 146, 148] or presence of children at home [144].

2.4.2. Medical and Cancer-Related Clinical Factors

A host of medical and cancer-related clinical factors can, in theory at least, predispose women receiving adjuvant chemotherapy for breast cancer to sleep/wake impairments. Research evidence, however, only partially supports this hypothesis. For instance, only scarcely has sleep history of women been evaluated in the chemotherapy treatment context [7, 136, 137]. Yet, positive associations have been yielded, with past history of poor sleep quality (r_{ES}=.14) [136] or past sleep aid use (r_{ES}=.35) [137] associated with more frequent use of sleep aids during chemotherapy. Similarly under-researched, coexistence of medical illnesses or psychiatric disorders can increase the risk for deregulation of sleep/wake patterns [60, 150], however the magnitude of these relationships might be small (r_{ES}=.06 and .08, respectively) [144]. A retrospective chart review also reported trends towards increased sleep aid use during chemotherapy for women with a psychiatric disorder (r_{ES}=.16) or past use of psychiatric medications (r_{ES}=.18) [137].

Functional ability can be compromised as a result of primary treatment and can interfere with sleep architecture. At different points during chemotherapy, two research groups concluded with predominantly weak associations (r_{ES}=.07 to .29) between poorer performance status and greater alteration in circadian parameters such as acrophase, peak activity, mesor and amplitude [7, 121, 123, 131, 136, 143, 147], but no link with daytime sleep [147]. Pre-treatment menopausal status can also predispose women with breast cancer to sleep/wake deregulation, especially as natural menopause is frequently accompanied by complaints of poor sleep [151, 152]. Rissling et al. [125] found only a modest relationship between menopausal status and actigraphically measured duration of nocturnal awakenings, so that prior to chemotherapy post-menopausal women had longer awakenings at night than the pre-/peri-menopausal ones (r_{ES}=.33). A similar in direction, but not in magnitude, relationship was also reported for self-reported data (r_{ES}=.08) [144]. A notable absence of any other significant findings became apparent when menopausal status was examined as a potential covariate for objective [7, 8, 121, 123, 125, 131, 132, 136, 143, 145, 146] and/or subjective [7, 8, 121, 123, 125, 131, 132, 136, 137, 143, 145, 146] sleep deficits. Yet, trends indicated that it was the pre-menopausal women who seemed to be more susceptible to manifesting poor sleep.

Having been diagnosed with early stage breast cancer can represent an independent trigger to sleep/wake impairment; two studies compared women receiving chemotherapy with healthy controls [128] or men with prostate cancer [153] and concluded with particularly mixed findings with regard to all different sleep parameters. Primary breast cancer surgery can be seen as an additional trigger to increase the likelihood for sleep/wake impairment

during chemotherapy treatment [154, 155]. However, in the studies reviewed, neither time since surgery [126, 127] nor type of surgery (mastectomy v. lumpectomy) [144, 146] was associated with either recorded or self-reported sleep deficits. Extent of disease is of predictive value to breast cancer prognosis, but can also trigger worrying thoughts about survival which can subsequently interfere with sleep [156]. Yet again, in all but one study [7, 121, 123, 131, 136, 143], tests fell short of statistical significance. Specifically, during CThC1, only weak relationships between higher stage breast cancer and more dampened circadian rhythms were found (r_{ES}=–.04) [143].

2.4.3. Lifestyle and Behavioural Factors

Long-term poor sleep/wake behaviours and lifestyle habits may trigger, preserve and perpetuate an individual's trouble sleeping, especially in the wake of a life-threatening disease such as cancer [4]. The term 'sleep hygiene' characterises an array of sleep-related activities that expose persons to numerous, complex and interrelated cues that, when favourable, prepare them for an appropriately timed and effective sleep [65, 157]. Conversely, when used inappropriately or abused, they can act more as stimuli to wakefulness and alertness than as sleep promoters, and hence disrupt sleep. Poor sleep hygiene can be seen as disruptive behaviour with regard to (a) scheduling (e.g., irregular sleep/wake schedule); (b) sleep practices (e.g., inadequate bedtime routine; prolonged daytime napping); (c) environmental factors (e.g., inadequate room temperature; loud noises; intense light level); and (d) physiologic factors (e.g., excessive exercise close to bedtime; timing/consistency of meals; smoking, alcohol or caffeine consumption close to bedtime) [157]. Interestingly, while it has been tested as a potential intervention to improve sleep quality of women with breast cancer [122, 124, 158-161], no study was found that specifically examined sleep hygiene as a long-term predictor of poor or good quality of sleep during active adjuvant chemotherapy. Yet, among women 3-4 months post-breast cancer surgery (44% during active chemotherapy), alcohol (r_{ES}=.02) and nicotine intake (r_{ES}=.08) were weak covariates of poor sleep quality [144].

Reduced daytime activity and a sedentary lifestyle have been suggested as possible antecedents to sleep/wake deficits in patients with cancer [150, 162]. Moderate physical activity can positively influence depth of subsequent sleep through either altered plasma concentrations of biologic sleep mediators [163] or increases in body temperature. Whilst converging evidence (a) describes daytime circadian activity as reduced and correlated with increased levels of fatigue across adjuvant chemotherapy for breast cancer [9, 49, 126, 127], and (b) supports physical exercise of moderate intensity to improve sleep quality during treatment [163,

164], it is unclear whether reduced physical activity predisposes women with breast cancer to sleep/wake impairment during chemotherapy as only one of the studies reviewed found a weak to modest relationship in favour (r_{ES}=.12) [144]. In addition, three studies evaluated body mass index (BMI) as a proxy measure of physical activity. Findings suggest that throughout adjuvant chemotherapy women with higher BMI experienced greater objective sleep impairments (r_{ES}=.24 to .26) [8, 125, 132, 145, 146] and circadian rhythm alterations (r_{ES}=–.22) [7, 121, 123, 131, 136, 143], but not greater daytime dysfunction [146], than those with lower BMI. Interestingly, only a weak positive relationship of self-reported sleep problems with higher BMI was found [144].

2.4.4. Psychological, Emotional and Social Factors

Multiple sources of anxiety and worry can be recognised for women with breast cancer throughout chemotherapy. These include intrusive thoughts; nocturnal anxiety attacks; fear of relapse; uncertainty regarding treatment effectiveness [100]; unfamiliarity with forthcoming procedures; anticipatory worry about possibly debilitating symptoms; and concerns about family or daily living matters. Actigraphic data yielded only a few sporadic significant relationships between circadian activity rhythm parameters and perceived anxiety distress following CThC1 and CThC3, and 30 days after adjuvant chemotherapy [7, 121, 123, 131, 136, 143]. Overall, magnitude of associations was rather weak, with r_{ES} ranging from .01 to .08. However, when the more qualitative aspects of sleep/wake impairment were taken into consideration, two studies concluded with modest effect sizes (r_{ES}=.28 to .44) for the relationship between anxiety and self-reported sleep quality [144, 165], thus supporting its subjective nature.

Compared to anxiety, depressed mood was identified as one of the most consistent correlates of sleep/wake impairment in the studies reviewed. Prior to chemotherapy initiation, at a period where fatigue also was high, depressive symptoms were strongly correlated to poor subjective sleep quality (r_{ES}=.52) [8, 132]. What is more, as part of a cluster of interrelated symptoms, pre-treatment higher depressive symptoms could contribute to worse sleep during chemotherapy treatment [8]. Between cycles one and four of adjuvant chemotherapy, a slight trend of increase in depression was also documented [128], which theoretically can be related to consolidation of altered sleep/wake patterns. Converging evidence gives partial support to this hypothesis. Despite some moderate associations between more depressive mood and poorer self-reported sleep at different points during treatment (r_{ES}=.36 to .38) [144, 165], evidence regarding further impact on circadian activity parameters (e.g., circadi-

an consistency, strength of circadian rhythms, amplitude) over chemotherapy continuation was rather weak [132, 143, 147]. However, between CThC2 and CThC4, Roscoe et al. [147] reported a significant increase in daytime napping duration (possibly suggesting more daytime dysfunction) as women's depressive mood became worse (r_{ES}=.36). Even after the end of chemotherapy, depressive symptoms were found to perpetuate sleep loss further in the treatment continuum [166].

Additional psychosocial factors may play a role in determining who is at greatest risk for impaired sleep in response to cancer experience [110]. For instance, coping processes and social support can possibly orientate towards psychological adjustment to cancer diagnosis and treatment [110, 167]. Unfortunately, only one cross-sectional study was found that examined the effects of coping and perceived social support on sleep in the context of adjuvant chemotherapy. Hanprasitkam et al. [165] reported that among 159 women during active chemotherapy, perceived greater support from the family or friends was moderately correlated to more favourable outcomes in self-reported sleep/wake parameters. Albeit indirectly measured, positive coping (as perceived through the use of religious practices) also was related to better sleep outcomes (r_{ES}=–.16) [165].

2.4.5. Biological Factors

Several hormones and neuropeptides such as cortisol, melatonin and serotonin have the capacity to affect sleep [2]. That said, alterations in circadian activity evidenced in women undergoing treatment for non-metastatic breast cancer are considered to contribute to altered hormone secretion and cytokine production that could independently or collectively affect sleep and wakefulness [4]. In a small sample (n=11) of women during adjuvant chemotherapy for breast cancer, mean serum serotonin levels were significantly lower the day before and after CThC4 compared to CThC1 [128]. Conversely, no significant between-treatments fluctuations in melatonin were recorded, whereas cortisol levels decreased significantly the day after chemotherapy in the breast cancer group, possibly due to the effects of pre-chemotherapy corticosteroid administration [128]. Although no direct tests between serotonin and sleep variables were performed, the significant positive associations between serotonin levels and fatigue, and between serotonin levels and depression, as well as between night-time melatonin levels and depression, propose the potential for an indirect link to disturbed sleep.

Several cytokines including interleukin-1 (IL-1), interleukin-6 (IL-6), C-reactive protein (CRP), and tumour necrosis factor alpha (TNF-α) are also thought to play a key role in the

circadian process of thermoregulation that is related to sleep regulation [168]. Of note, cancer cells produce, or stimulate the production of such biomarkers [169]. In the studies reviewed, two research groups explored associations between these biomarkers and sleep/wake parameters in women during chemotherapy, providing, however, mixed findings [145, 166]. Throughout treatment (pre-treatment, post-CThC1, post-CThC4), Liu et al. [145] found only a few significant relationships, whereby changes in objective recordings of WASO were negatively associated with changes in CRP levels (r_{ES}=–.40), and increases in IL-1 (r_{ES}=.32) and IL-6 levels (r_{ES}=.35) predicted increases in negative sleep quality reports. Conversely, close to the end of chemotherapy, cross-sectional associations of self-reported sleep with either IL-1 or TNF or CRP fell short of significance [166]. What is more, whereas anaemia or a decreased haemoglobin level is a considered factor that contributes to fatigue (see below), the indirect relationship between reduced haemoglobin levels and more sleep disturbance remained too unverified [165].

2.4.6. Chemotherapy-Related Factors

Cytotoxic systemic therapy can increase the risk for disordered sleep [60]. Indeed, converging evidence suggests that women who had received adjuvant chemotherapy rather than radiotherapy or hormone therapy were more likely to report persistent sleep/wake impairment after treatment was over [100, 102, 166]. The reason for this is twofold. Chemotherapy administration logistics, such as chemotherapy protocol/regimen, chemotherapy cycle length, or active versus recovery period in a chemotherapy cycle, can exert adverse effects on women's sleep/wake patterns as their intensity increases. Three of the selected studies examined these potential triggers of sleep/wake impairment [126, 127, 129, 136]. Given doxorubicin's known high toxicity profile [170], women receiving doxorubicin-based regimens (CAF, AC) were found to experience greater fatigue, more dampened circadian rhythms (e.g. mean mesor values of 65%-75% of norms), and greater sleep disturbance from CThC1 to CThC3 than women on other chemotherapy protocols (CMF) [126, 127]. Yet, Berger [126] reported that nocturnal awakenings were similarly elevated irrespective of treatment group. Effect sizes for these relationships were small to large (r_{ES}=–.10 to –.45).

In terms of cycle length, women on the more intense 21-day protocols had more disrupted mesor and amplitude values than those on 28-day protocols [126]. Within the same CThC, three studies examined differences in sleep/wake patterns of women between the active (i.e. the first two weeks post-chemotherapy administration) and recovery period (i.e. weeks 3/4 before administration of the next CThC) [126, 127, 129, 146]. Although the magnitude of

associated effects could not be estimated based on the available data, there was a general clinical trend towards greater circadian rhythm alterations (dampened mesor and amplitude), more difficulty in sleep onset and maintenance (prolonged sleep latency, WASO, nocturnal awakenings; decreased total sleep time), poorer sleep quality and more daytime dysfunction (more daytime sleepiness, prolonged naptime) in the first two weeks of each CThC compared to later time points [126, 127, 129, 146].

The toxic effects of chemotherapeutic agents are widely known. High chemotherapy toxicity means more frequent, severe and distressful physical symptomatology as well as sleep-disruptive events (e.g. the need to use the bathroom at night due to nocturia, nightmares), which independently or collectively have the potential of interfering with habitual sleep/wake patterns [160]. In general, sleep disturbances including pain, hot flashes, cold, coughing and/or snoring, and difficulty breathing were described in the selected studies as highly prevalent irrespective of chemotherapy phase for early stage breast cancer [119]. The greatest part of available data relate to the pre-treatment period, where sleep disturbances may occur at least once or twice a week [7, 121, 125, 132]. Consistently high levels of sleep disturbances post-CThC1, and over chemotherapy continuation (CThC3 and CThC4) were also reported [125, 146], without, however, evidence of significant over time variations. Payne et al. [128] concluded with no significant within-cycles time effects, suggesting that sleep disturbances were equally prevalent both the night before and the night after CThC1 and CThC4.

In the studies reviewed, fatigue, hot flashes, and nausea/vomiting were specifically examined as potential covariates of sleep/wake impairment during chemotherapy for early stage breast cancer [7, 8, 104, 121, 123, 125-127, 131-133, 143, 145-147, 165, 166, 171]. Not surprisingly, the studies mainly focused on chemotherapy-induced fatigue as a primary and consistent covariate of poor sleep in this context. Over the course of chemotherapy, women who self-reported greater overall sleep/wake impairment (r_{ES}=.12 to .56) [7, 8, 121, 123, 131-133, 143, 145, 146, 165, 166, 171], prolonged sleep latency (r_{ES}=.25 to .30) [7, 104, 121, 123, 131, 136, 143], more frequent use of sleep aids (r_{ES}=.21 to .25) [121, 123, 131, 132, 136, 143], and poorer sleep quality (r_{ES}=.21 to .31) [121, 123, 132, 133, 143] were found to experience increased levels of fatigue. Conversely, daytime fatigue was not found to consistently increase time in rest and napping during the day [7, 121, 131, 132, 143, 146, 147], but was related to greater daytime dysfunction (r_{ES}=.21 to .42) [120, 121] during this period. What is more, robustness of circadian activity rhythms (peak activity, mesor, 24h auto-correlation, amplitude) was adversely affected in fatigued women [7, 104, 121, 123, 126, 127, 131, 143, 147]. Indeed, by prospectively assessing fatigue, circadian activity and

rest during chemotherapy, Berger and Farr [127] reported that increased fatigue during CThC3 was associated with severe reduction in daily activity. The relationship between fatigue and subjective/objective measures of total sleep time, sleep efficiency, WASO, and nocturnal awakenings is nevertheless shrouded in ambiguity.

Berger et al. [123] examined the perceived impact of hot flashes on sleep of women during chemotherapy, and concluded with significant over time increases from baseline to follow-up for the pre- and peri-menopausal rather than the post-menopausal individuals [123]. Despite the absence of specific measures of frequency or severity of menopausal symptoms, control of menopausal status after treatment, and explicit inferential statistics to test associations, these results possibly suggest greater influence of climacteric symptoms on the sleep of women with regular or irregular menses during chemotherapy. This notion was partially supported by longitudinal data describing several objectively recorded sleep deficits following treatment among women with regular menses both before and after treatment, possibly due to increases in depression related to climacteric symptoms [125]. Nevertheless, the significant increase in vasomotor symptoms after treatment in the peri-menopausal group was not followed by similar disruption in objective and subjective sleep parameters. Two studies specifically explored the impact of hot flashes on overall sleep/wake impairment close to post-treatment and concluded with weak to modest effect sizes (r_{ES}=.17 to .19) [148, 172], suggesting a positive relationship where increase in hot flashes was accompanied by greater disruption in sleep/wake patterns.

A significant positive, yet moderate, relationship between nausea/vomiting-related distress and sleep/wake impairment was also found over chemotherapy continuation (at least two CThC received), thus supporting hypotheses regarding the sleep-disruptive effects of nausea on nocturnal sleep [165]. Lastly, between CThC3 and CThC4, overall physical symptom distress was strongly correlated with daytime dysfunction [129], a finding that generates new hypotheses about whether overall symptom burden could act as a more robust predictor for nocturnal and daytime sleep-related impairments.

2.5. Summary and Critique

Admittedly, varying deficits in sleep/wake parameters may be evident in a significant part of this population. Regardless of whether objectively or subjectively measured, nocturnal sleep patterns of women can already be affected prior to chemotherapy initiation, deteriorate over

treatment continuation and be accompanied by daytime dysfunction, and impairments can persist even after the last CThC. Interestingly, whereas sleep quality and restfulness may become compromised, the actual use of sleep aids may be particularly low, thus revealing a discrepancy between how sleep/wake problems are assessed and how they are subsequently managed. Yet, research data are not equally distributed among the different sleep components/parameters, or across all major time points throughout chemotherapy. Especially with regard to women's circadian rhythms, daytime rest patterns, and use of sleep aids, more focused investigation is warranted. Other variables, such as night-time dreaming and feelings of restfulness upon arising, have been only superficially reported, with strange dreams being infrequent at least before treatment initiation [104], and only moderate levels of energy after a night's sleep, possibly throughout treatment [134, 143]. However, the potential links between circadian rhythm parameters and feelings of restfulness upon arising [143] is worth further examination in future studies to identify patients at risk for non-restorative nocturnal sleep.

One should be careful in evaluating the quality of the existent data. In all but two studies [87, 133], time after surgery was not reported, making it unclear whether evidenced sleep deficits could be attributed to the known effects of surgical procedures because patients might have been assessed too close to the time – within 2-3 weeks – after surgery. What is more, no study evaluated women's past sleep history, sleep habits or concurrent use of medications possibly affecting sleep, while only one study evaluated the influence of menopause on sleep before initiation of adjuvant chemotherapy, among those which reported data pertinent to participants' menopausal status. In this study, Berger et al. [123] found that compared to pre- and peri-menopausal women, post-menopausal women had lower total sleep time, experienced more nocturnal awakenings and spent more time awake after sleep onset. In three studies [8, 9, 120], researchers included a small number of women (15% of the sample sizes) scheduled to receive neo-adjuvant chemotherapy (i.e. chemotherapy given to reduce tumour size prior to surgery), thus leading to results that may actually not reflect sleep patterns of women to receive adjuvant chemotherapy. While unclear, women receiving neo-adjuvant treatment may have been assessed closer to diagnosis, at which time sleep may be profoundly affected by the emotional impact of a diagnosis of a life-threatening disease. Lastly, data regarding subjective sleep quality might reflect slight inaccuracies due mainly to sleep measures' time frames for recall: in some studies [7, 122, 130, 133] women were asked to reflect on their sleep patterns for the previous month, which renders it questionable whether data would reliably reflect the immediate period (last week) prior to treatment initiation.

In appraising data collected through repeated sleep assessments during chemotherapy, one should note the following points: (a) a large part of evidence is derived from multiple secondary analyses to clinical trials based on observations from control groups [49, 122, 123]. The fact that data from the same pools were repeatedly used in further studies, along with the possibility that women's sleep in the control group was affected by their mere participation to a clinical trial to improve sleep, might have impacted on the reproducibility and generalisability of observations; (b) studies exist where the assessment of sleep parameters was conducted in an incomplete fashion, over only specific chemotherapy cycles (CThC1-CThC3 [126], only CThC3 [129], baseline to CThC4 [9]) without baseline and/or post-treatment data available, thus rendering comparisons limited or impossible; (c) while some studies have included a post-treatment assessment with relative consistency [49, 122, 123], they have included patients with varying adjuvant chemotherapy protocols, differing in the chemotherapy agents used but, most importantly, in their duration. Hence, true sleep values might become unclear due to a mix of data from women who might have completed chemotherapy protocols of different duration (≤4 CThC v. 6 or 8 CThC) or different intensity (e.g. anthracycline-based v. anthracycline-based followed by taxanes). For instance, in a study where the post-treatment assessment point was deliberately selected as being the same for the entire sample, the chemotherapy protocol was of a four-cycle duration only [9]. However, several adjuvant chemotherapy regimens (e.g. FEC, CMF) may be given over a span of six CThC, so that the accumulated distress caused by chemotherapy-related symptoms may be greater and associated with more severe sleep problems.

Admittedly, a host of potentially predisposing, precipitating and/or perpetuating factors can contribute to disruption and/or restriction nocturnal sleep and daytime dysfunction in women receiving chemotherapy for early stage breast cancer. Six categories of sleep-impairing factors were identified, namely demographic, medical/clinical, lifestyle/behavioural, psychosocial/emotional, biological, and chemotherapy-related. To date, the most consistent findings relate to the precipitating/perpetuating effects of fatigue, depression and hot flashes, as well as the predisposing/perpetuating effects of performance status and body mass index. Whilst research so far has been able to identify some of these and other underlying links, many questions remain to be answered in future studies.

The contribution of aging to alterations in sleep architecture has been examined in a rather subjective manner, and different age groups have been formed based on different premises as to who those persons may be that can be regarded as 'older'. Unconvincing theories with regard to the role of education and race in poor sleep also have been introduced. This is

mainly due to the lack of evidence, given that these variables still represent two of the most under-represented person-related factors for disturbed sleep. Furthermore, are these relationships truly different in women with breast cancer compared to healthy women from the general population, and do the sleep-disrupting effects of the above-mentioned factors have any additional significance for women with breast cancer? More comparative studies will be required to answer this.

The effects of prior breast surgery as well as those of chemotherapy procedures will need to be continually adjusted in future studies. Type of surgery, time elapsed since the operation, type of chemotherapy protocol, and time in-between CThC administration can all increase the likelihood for sleep/wake impairment. In addition, many other medications co-administered to anti-cancer agents have known effects on nocturnal sleep architecture and daytime functioning [4]; however, they have never been included as covariates in the relevant studies. Insomnia, lethargy and restlessness are well recognised and confirmed side effects of corticosteroids, particularly dexamethasone [173, 174], although prochloroperazine, metoclopramide and granisetrone (a serotonin [5-HT3] antagonist) have also been found to disturb sleep in patients with cancer [175, 176], having a high sedative potential.

A pressing question is also this: How reliable are pre-treatment assessments of sleep patterns in the absence of data regarding sleep quality prior to cancer diagnosis? A history of disturbed sleep may render individuals susceptible to sleep problems even if pre-treatment quality and quantity of sleep are adequate. Whereas for some women disturbed sleep may be a reaction to the experience of cancer, for others this may be the continuation of a pre-existing condition that needs to be identified. The extent to which sleep hygiene practices and behaviours change over time, how such changes might also predict changes in the women's sleep/wake patterns, and whether changes occur in response to experience of poor sleep remains to be established.

Whilst much research has been devoted to the establishment of inter-relationships between fatigue, depression, and sleep, more robust designs such as day-to-day process analyses could allow for directionality to be clarified. Similarly, in order for the indirect effects of factors such as coping styles and social support to be established, comprehensive methodologies and more sophisticated statistical approaches could allow for potential mediators (e.g., psychological symptoms) to be co-examined. Despite the extremely important data on circadian rhythm activity, it is equally important to establish whether deficits in the biological clock can be explicitly depicted on reports of perceived quality of sleep. In addition, contrary to hot flashes, only rarely have night sweats been tested as possible contributing factors to disturbed nocturnal sleep in this population, and these need to be included in future studies

as a potential covariate. In any case, longitudinal sleep studies will need to examine how changes in these and other potential covariates are related to or are predictive of changes in the sleep/wake parameters of women during chemotherapy. This is of paramount importance as it goes beyond the static baseline-only assessment of significant covariates that was introduced in some studies [7, 131], and acknowledges the fact that in an ever-changing situation, fluctuations in sleep/wake patterns are not only affected by baseline characteristics, but even more so by changes in these characteristics.

Last but not least, the clinical, as opposed to the statistical, significance of the relationship between these triggers and sleep/wake patterns has only rarely been examined in relevant studies. The need to understand the magnitude of these relationships calls for the systematic calculation and reporting of effect sizes. Moreover, whereas a number of physical symptoms may independently contribute to sleep/wake impairments, their cumulative effects could provide a better explanation to their link with disrupted/restricted sleep and daytime dysfunction. With the advent of the concept of 'symptom clusters', namely groups of symptoms that are related one another and experienced at the same time [177], this seems to be a valid hypothesis. Consideration of the use of composite scores deriving from assessments of different sleep-impairing physical symptoms could provide a more robust measure of burden and a more consistent predictor of sleep/wake deficits in this population. From a clinical point of view, then, this approach could lead to more comprehensive assessments, which would increase the odds for identification of more 'subtle' symptoms that could nevertheless affect nocturnal sleep.

CHAPTER 3.

Cancer Caregiving and the Experience of Impaired Sleep/Wake Patterns

3.1. Informal Caregiving in the Context of (Breast) Cancer

Women diagnosed with a curable breast cancer are frequently recognised as having pressing needs that emanate from the experience of a host of symptoms and concerns that arise post-diagnosis, peak during treatment and may remain prominent during survivorship [178-180]. Women may have a transitory care requirement, often before, during and immediately after treatment; however, in their majority they will rely – in some cases, heavily – on families and friends for help and support [181], perhaps for an extended period of time. Throughout these major health transitions, families and friends offer, or in other cases are required, to shoulder the burden of often complex care [182-184]. Regardless of its nature, support provided by persons regarded as significant by the woman – often recognised by health professionals as her 'informal caregivers' – has been found to be equal to or more beneficial than support derived from other 'formal' sources [185, 186]. By providing actual and ongoing care for essential daily tasks to be undertaken and for an acceptable quality of life to be achieved [181], significant others in caregiving roles can have an important part in a woman's ability to respond to and cope with the pressure of living with breast cancer [185].

From the health system's perspective, the expectation and prevalence of caregiving in significant others also is high. As social welfare costs rise in many nations and the medical management of cancer becomes more complex, there are increasing obligations placed on individuals close to the ill person to undertake caregiving responsibilities [187] and deal with extensive coordination of care [10]. Moreover, recent changes in health policy [188], such as shifting the balance of care from hospitals to the community, and the shortage of health care providers [184], have further impacted on the roles and responsibilities of these persons in providing primary and ongoing care at home [189, 190]. In fact, the use of outpatient-based cancer treatment means that it is often family members, partners, or friends who provide daily support to the person with cancer, not healthcare professionals [191]. According to Carers UK, and based on the 2001 census, around six million people in the UK (half a million in

Scotland) provide care on an unpaid basis for a relative, friend or neighbour in need of support due to old age, disability, frailty or illness [192-194]. Carers save the UK economy an estimated £87 billion a year, and economic considerations form a key element in government policy to support carers [193].

Informal service providers have always been the primary source of human service care to individuals in need. During the past four decades, the informal provision of care to patients with chronic illnesses such as cancer has become so common that the meaning of the term 'caregiving' is taken for granted; however, the definitions and boundaries of what is included in it are not always clear [187, 195]. Traditionally, the concept of caregiving has been equated with that of the family [196]. The provision of assistance and support by one family member to another is a regular and usual part of family interactions, and is in fact a normal and pervasive activity. Thus, caregiving due to chronic illness represents something that, in principle, is not very different from traditional tasks and activities rendered to family members [187, 195]. The difference, however, is that caregiving in chronic illness often represents an increase in care that *surpasses* the bounds of normal or usual care [187].

Despite the focus of empirical research on a limited inclusion of only blood relatives as informal caregivers, factors such as families' nationality and race/ethnicity, and the sexual orientation of the ill person may dictate broader conceptualisations [197], including individuals "*considered as family* by the patient" (p. 295) [196]. In the context of cancer, Thomas et al. [198] broadly define the caregiver as *someone who shares* the experience of cancer with the patient. Obviously, current approaches to informal caregiving tend to be more inclusive of all persons who may be involved in the care of a patient with cancer, rather than focusing only on spouses, children or other members of the family: partners, close friends, even neighbours may also provide informal care to a person. This recognition of 'significant others' being involved in care explains the current shift illustrated within the literature towards use of the term 'informal caregivers' instead of the narrower one of 'family caregivers' [199-201].

3.2. Roles of Informal Caregivers

What the existing literature signals is that *what caregivers do* as individuals and/or as part of caregiver networks can make an essential contribution to the patient's 'care package' and that patients' well-being can be profoundly affected by the quality of the informal care they

receive [202]. This revelation implies that caregivers can be constructed as the 'co-caregivers' of formal health care providers [202]. However, Thomas & Morris [202] pose a core question: 'what is the informal carer role and how does it contribute to the care of the patient with cancer?' (p. 178). Current knowledge or understanding about what informal caregiving actually involves in cancer contexts, and about the difference that this makes to the overall health care endeavour is based on limited information derived from a few studies. In general, care may be organised into numerous dimensions, each possibly consisting of several specific tasks and processes (**Figure 3-1**) [196, 198, 203-207]. Moreover, it has been suggested that informal caregiving roles and responsibilities may (a) occur in relation to the health transition experienced by the ill person during treatment [203]; (b) be fluid and ever changing [203]; (c) be novel and never before undertaken [206]; (d) be adopted as necessary [196, 208]; and (e) depend on the specific moment, setting or patient need [203].

Figure 3-1. Roles and tasks potentially undertaken by individuals providing informal care for people with cancer. *Source:* Kotronoulas et al. [209].

Nonetheless, evidence regarding caregiving roles is confined in terms of generalizability and consistency with regard to type of cancer, stage of disease, phase in the cancer experience, or setting. For instance, it is unclear whether differences in roles assumed are influenced more by the type or the stage of the disease, or by who the caregiver might be (family versus non-family member; spouse versus child); whether caregiving tasks are driven more by patient need (caregiving 'on demand') or by caregiver attitude towards provision of care; or how (or if) they develop/evolve across time, cultures or socioeconomic status. Whereas caregiving might become more significant during periods when patients are in receipt of medical treatments and/or are at later critical moments in the cancer experience [198], which tasks might be involved in different phases have not been explored. Albeit basically useful, the aforementioned broad role categorisation seems too simplistic to depict the array of caregiving tasks, and might imply that caregiving roles are confined in only those that happen to fall into these specific categories, or should be similar to every individual case. It can be argued that, in the case of patients who might rely more on self-care, caregiving roles might be more limited, or even focused on some areas rather than others. Some findings exist that husbands of women with breast cancer might provide less assistance with more intimate activities such as bathing, toileting, or eating [206]. Still, whether this is a purely gender- or age-related behaviour needs to be confirmed.

Given the diversity of the caregiving demands, it is equally reasonable to claim that caregivers themselves will possess different skills, capabilities and preferences for performing the different caregiving tasks [181], which, to a great extent, are influenced or mediated by several endogenous (individual-related) and exogenous (environment-related) factors. In addition, it should be recognised that not all people assume a supportive role in the event of a diagnosis of cancer among their loved ones. Age, gender, cultural background, ethnicity, socioeconomic status, educational level, type of personality, coping style, personal health, as well as family dynamics, quality of relationships, and over time adjustment to cancer diagnosis and illness stage [167, 187, 195, 201, 210] may work together as integral factors in predicting a person's involvement in caregiving, the extent of associated tasks, and finally, their *reaction* to this demanding role.

3.3. Impact of caregiving on informal caregivers

Nowadays, caregivers are legitimised as persons affected by cancer in profound ways [202]. Key cancer service policy documents reflect this acceptance, acknowledging the presence of these 'significant others' and their interests as service users alongside patients [211, 212]. This is mainly because patient illness experience cannot be understood as an individualised, socially isolated phenomenon [195, 213]. Rather, a serious illness carries with it considerable physical, psychological and social consequences for the family, friends and other close associates [202]; in particular, those individuals who assume the short- or long-term role of the caregiver are impacted the most. When cancer becomes a reality, spouses, partners, other family members and friends may actively participate in shaping the cancer experience, and also *share* in this experience. The practical and emotional involvement of these socially significant others in patients' journeys, however, often affects their own lives, sometimes considerably [214]. Among other factors, caregivers may be forced to make changes in their lives, take on new roles and responsibilities, or give up past activities [206]. These life changes can be viewed as commonalities or *stressors*, which can create burden and strain, especially when extremely high physical and emotional demands are placed on caregivers [190].

It is generally accepted that a conceptualisation of caregiver burden contains both objective and subjective dimensions [187]. *Objective burden* can be defined as the time and effort required for one person to attend to the needs of another. Thus, it may include the amount of time spent in caregiving, the type of caregiving services provided, and financial resources expended on behalf of the 'dependent' person [201, 215]. Alternatively, *subjective burden* usually refers to perceived beliefs and feelings regarding the performance of caregiver tasks and assumptions of the caregiver role. Definitions of subjective burden are more varied than those of objective burden, and studies in the context of cancer care have included such elements as the extent to which caregiving causes strain with regard to work, finances, physical well-being, family relationships and social life, or emotional distress associated with caregiving [187, 195, 199, 216].

Current hypotheses suggest that patients with cancer and their informal caregivers react to cancer as one emotional system [217, 218]. Based on this assumption there may be a significant reciprocal relationship between each person's response to the illness, with caregivers often reporting similar [219, 220] or greater [221] emotional distress, anxiety, or depression than patients do. What is more, some studies report that caregivers' psychological distress reduces over time after diagnosis [222], but others suggest it increases and becomes prolonged [10, 223, 224]. The latter might be the case for caregivers who disregard their own

problems in order to focus exclusively on fulfilling patients' needs; however, this is only one of several possible explanations. Along these lines, caregivers may be less likely than patients to disclose their concerns and worries, and up to only half of those with serious psychological problems may actively seek help [167]. Similarly, caregivers' family and social well-being might become affected, especially in relation to talking about the illness, dealing with deficits in sexual well-being, changing roles and assuming new responsibilities, as well as maintaining support systems [184]. For instance, informal caregivers may experience role overload when they take on a patient's household or family responsibilities in addition to their own [184, 225]. Difficulty communicating their feelings and negotiating their roles can hinder patients' and caregivers' ability to support one another and decrease the dyad's intimacy [226].

More often than not, caregivers of patients with cancer will also experience a decline in their own physical well-being [184, 227]. Although early on in the illness trajectory caregivers' health status is similar to that of the normal population, they often report more problems with fatigue, alterations in habitual sleep/wake patterns, and impaired cognitive function than non-caregivers [219]. Over time, as caregiver burden and strain increase, caregivers' physical well-being might be at stake with possible, yet not the only, reasons including little time to rest, engagement in fewer self-care behaviours (e.g., physical activity), or failure to seek medical care for themselves when sick [184, 223]. A considerable proportion of informal caregivers have chronic health problems of their own, which can be exacerbated by the stress of caregiving [201]. Presence or worsening of pre-existing symptoms, as well as development of new ones may interfere with caregivers' ability to assume roles and fulfil those already assumed. Furthermore, adjustments caregivers may be forced to make in their way of life [228] can result in added strain on their physical well-being. Eventually, both unrelieved symptoms and ongoing demands of caregiving may adversely affect both functional status and quality of life [10].

Excerpts of this discussion on caregiving tasks/roles and caregiving burden were published in a peer-reviewed journal and can be found in Kotronoulas et al. [229] (see Appendix 7).

3.4. Sleep/Wake Patterns of Caregivers of Adults with Cancer

Several evident and latent caregiver stressors can be a threat to individual well-being by specifically affecting the caregiver's habitual sleep/wake patterns [230]. Sleep research in the

context of cancer caregiving has gained some interest in the last 15 years; yet, sleep impairment remains one of the least assessed symptoms in this population [10]. In spite of the absence of a consistent method of assessment, and with evidence mainly deriving from cross-sectional studies with non-homogeneous samples with regard to phase of cancer experience (palliative care, survivorship, active treatment) or duration of caregiving, it is now widely known that sleep of caregivers of patients with cancer can also be adversely affected [10]. Difficulty falling and staying asleep, experience of restless and non-restorative sleep, as well as development of insomnia and chronic sleep loss may be common complaints raised [43, 231]. What is more, inconclusive evidence exists that informal caregivers of patients with cancer might experience restless sleep and daytime dysfunction to a greater extent compared to caregivers of patients with other illnesses such as acquired immunodeficiency syndrome (AIDS) or age-related dementias [232]; yet, studies among caregivers of patients with Parkinson's [233, 234] or Alzheimer's [234, 235] disease point to the direction of general similarities in sleep-related distress. In any case, occurrence, frequency and/or severity of sleep/wake problems may widely vary, mainly but not solely depending on the overall caregiving situation. Existent evidence is indicative of this variability, highlighting the need for a cautious interpretation when more general conclusions are to be drawn upon.

To evaluate the sleep-related distress in caregivers of adults with cancer, a two-part critical review of the empiric literature was conducted. In the first part, a systematic search for publications that evaluated sleep/wake patterns among informal caregivers of adults with cancer was conducted. The purpose of this synthesis of evidence was to answer two questions:

a. What do research findings report about key sleep/wake parameters of informal caregivers of adults with cancer?

b. What are the methodological and research gaps in this body of evidence?

The systematic literature review aimed to identify original research studies conducted in the context of informal caregiving, and specifically focusing on examination of caregivers' sleep/wake patterns and potential correlates of disturbed sleep. The review was conducted in a two-fold manner to address its two objectives. Initially, given the limited sleep research conducted in the context of cancer caregiving, all relevant publications were retrieved irrespective of disease context, study design, or primary or secondary focus on sleep patterns. These studies would form a large pool of evidence, especially with regard to factors affecting sleep in informal caregivers of adults with cancer with findings complemented by evidence deriving from caregivers of people with non-cancer illnesses. From this pool of stud-

ies, original papers were extracted that specifically examined sleep/wake patterns of informal caregivers of adults with cancer.

Studies were identified by systematically searching three electronic databases, namely Medline (1948-2011 May week 02), CINAHL (Beginning-2011), and EMBASE (1988-2011 Week 18). An initial search strategy was devised and subsequently revised through an iterative process (Appendix 5). Using a snowballing strategy, the reference lists of retrieved studies were also examined for any studies that may have been overlooked. Reference lists of two topical research reviews also were examined [10, 236]. Additional literature was sought through use of the search engine Google Scholar to locate relevant publications using the aforementioned key words.

In the first stage, studies were eligible in the review if they (a) were written in the English language; (b) were conducted with adult (>18 years of age) individuals who were self-identified or patient-identified as providing informal care irrespective of their relation to the ill person; (c) examined sleep as a primary or secondary variable; and (d) were published as original articles in peer-reviewed journals from January 1990 to July 2011 representing the period in which sleep-specific instruments were developed, and studies of sleep in informal caregivers emerged. Both quantitative and qualitative studies were included. In the second stage, studies were considered eligible if they specifically examined sleep of informal caregivers of persons diagnosed with cancer irrespective of stage of disease, and through use of sleep-specific subjective and objective measures. Intervention studies also were eligible if they provided baseline and/or control arm sleep data. Studies were excluded from the present review on the basis of the following criteria: (a) studies examining sleep/wake patterns of informal caregivers of individuals with terminal illnesses (cancer or otherwise), or conducted among bereaved caregivers; and (b) unpublished studies, dissertation studies, or conference presentations.

A shortlist of papers was initially compiled, where titles and abstracts were screened to assess relevance to the review. Potentially eligible papers were retrieved in full and checked for adherence using the afore-mentioned inclusion and exclusion criteria, thus forming a pool of papers reporting on sleep patterns of informal caregivers. In a second step, additional criteria were applied to identify studies examining sleep of informal caregivers of patients with cancer. Study characteristics of these latter studies were extracted using a systematic scheme. Due to heterogeneity of the studies retrieved, findings were only integrated in a narrative synthesis.

The evidence categories employed by the Department of Health in the National Service Frameworks (DOHNSF, 2001) [116] were used for levelling evidence, and aiding appraisal of quality of the papers reviewed. This framework was used because it has been piloted for use with both peer-reviewed and non-peer-reviewed research [117]. **Table 5-A2** outlines the levels of evidence as established using the DOHNSF validated grading hierarchy. No studies were excluded on the grounds of quality, given the lack of agreement in the application and interpretation of quality criteria [118].

The selected studies were analysed, summarised and synthesised to provide evidence with regard to the overall incidence of sleep-related problems. Sleep data were further analysed on the grounds of patient disease stage, which was one of the few common points of reference within this diverse sample of studies. A separate analysis was conducted for studies focusing on caregivers of persons with a specific type of cancer, whereas, potentially unique in this population, sleep findings were clustered together separately. A brief description of the characteristics of the included studies can be found in Appendix 5. Findings presented below and in Appendix 5 were published in a peer-reviewed journal and can be found in Kotronoulas et al. [182] (see Appendix 7).

3.4.1. Overall Incidence of Sleep-Related Problems

Between 36% and 95% of caregivers reported altered nocturnal sleep associated with poor sleep quality in the studies reviewed [23, 25, 27-29, 232, 237-241], based on different sleep measures and cut-off scores. When examined under the prism of disease stage, prevalence rates ranged from 36% to 80% during the early phases of cancer [23, 30, 240-243], whereas they reached 95% (42%-95%) when care was provided to patients with advanced disease [25, 27-29, 232, 237, 238]. Such rates are somewhat comparable, but a slight trend of increased frequency seems to exist as disease severity increases. Across active treatment, 36.7% to 59% of caregivers reported sleep problems prior to treatment initiation [25, 242, 243], whereas sleep problems were reported by more than 70% of the respondents during the patient's treatment [23, 28, 30, 241].

3.4.2. Caregiver Sleep/Wake Patterns in the Context of Patients with Advanced Disease

In long-term family caregivers of patients with advanced-stage cancer, particularly disrupted and restricted sleep was reported: perceived sleep duration of 5.9 to 7.8 hours per night; habitual sleep efficiency ratings ranging from 74% to 80%; trouble falling and staying asleep; as well as restless, non-restorative sleep coupled with daytime dysfunction [27-29, 232, 237, 244]. Where actigraphic measurements were implemented, similar trends were revealed: actual sleep time of even less than five hours/night (range 4.8 to 6.2 hours); sleep latency ranging from 11 to 45 minutes; and sleep efficiency ranging from 73% to >90% [28, 29, 244]. Three studies aimed at examining changes in the sleep/wake patterns of caregivers, without, however, these being related to any major events or transitions. In the studies of Carter [28, 29], where observation spanned over 10 [28] and 16 [29] weeks, respectively, all sleep variables varied widely both within (as evidenced by high individual standard deviations) and between time-points (as evidenced by different mean values). Although fluctuations pointed to no specific direction, over time sleep disturbance was evident. Gibbins et al. [244] recorded sleep for a small interval of seven consecutive days, where, despite within time-points variations, caregiver sleep parameters remained relatively stable and somewhat disturbed across time. Of note, generally low daytime activity levels were recorded, with large periods of the day (28%-31% of the day) spent immobile. At this time, caregivers took approximately nine naps a day each lasting 9 minutes on average [244].

3.4.3. Caregiver Sleep/Wake Patterns in the Context of Patient Early Stage Disease

Data on the sleep/wake patterns of this specific caregiver population are generally scant. Nevertheless, two recent and largely heterogeneous, cross-sectional studies using mixed samples of caregivers at various disease stages provided some descriptive general evidence. In the first study [241], 90 family caregivers providing care for an average of five months to patients receiving chemotherapy for different types of cancer were studied. Increased sleep latency and daytime dysfunction, a somewhat diminished sleep duration (6 to 7 hours per night), as well as multiple nocturnal disturbances were self-reported, whereas habitual sleep efficiency remained at a satisfactory level [241]. In a more detailed way, Dhruva et al. [243] reported subjective and objective sleep data of 103 family caregivers at the initiation of patients' primary or adjuvant radiotherapy for prostate, breast, lung, or brain cancer. In this sample of relatively older caregivers (mean age 61.7 years), objective sleep measurements

indicated no major disturbances with regard to sleep onset latency (13 minutes on average), total sleep time (approximately 7 hours on average), sleep efficiency (84.4%), and daytime sleep (close to 6% of wake time). However, the number of nightly awakenings exceeded 17 per night, leading to an increased amount of time being awake after sleep onset (12.7% of total sleep time) [243]. When circadian rhythm parameters were examined, all but one (acrophase) were outside normal values. These results are indicative of low daytime and higher night-time activity; however, this trend was not found to correspond with deficits in subjective and objectives sleep variables.

3.4.4. Caregiver Sleep/Wake Patterns in the Context of Specific Disease Type

Only few studies have targeted caregivers of patients with a specific type of cancer, and their limited exploratory scope should deter from any attempt to generalise findings. Results from two reports indicated only moderate levels of sleep disturbance among female, family caregivers of patients with prostate cancer at the initiation of radiation therapy [25, 240], especially with regard to increased nocturnal awakenings and WASO. Although the majority of participants were above their 60th year of age, patient and caregiver good functional status, as well as low treatment-related burden, might have played a role to the low percentage of reported sleep problems; yet, such relationships were not explored. Conversely, Cho et al. [23] highlighted the presence of poor sleep quality, difficulty with falling asleep and daytime dysfunction after CThC1 for gastric cancer. However, neither caregiving characteristics were reported nor detailed data with regard to key sleep parameters were provided. Whether caregivers were recruited at different time points in the course of chemotherapy also remains unknown. Among 61 family caregivers of newly diagnosed women with early stage breast cancer, eight out of ten caregivers reported poor sleep quality [30]. Sleep latency and duration as well as daytime dysfunction were the areas predominantly affected in this group. However, lack of homogeneity with regard to the duration of caring period and timing of assessment (for some sleep was assessed during chemotherapy, while for others after the treatment had ended) renders these data inconclusive.

3.4.5. Additional Sleep Data Relevant to Persons in Caregiving Roles

Overestimation of self-reported sleep problems compared with objective assessment was suggested in two studies [240, 244]. Conversely, Carter [28] reported that caregivers typically under-rated their sleep disturbance when compared with actigraphic measures. Perhaps

caregivers perceived their sleep problems as less important when compared with the patient's advanced illness [241]. Interestingly, less than 20% of caregivers were found to make actual use of prescribed or over-the-counter sleep medication in the majority of the studies reviewed [23, 27, 30, 241, 243, 244]. Authors explained this trend as reluctance, possibly driven from caregivers' fear of not being alert to provide care to the patient during the night [23, 27, 29, 237], or from cultural beliefs surrounding the use of sleep medication [23]. Such attitudes can well explain why often caregivers refrain from engaging in discussions with clinicians, and consequently do not receive adequate care [241]. While prescription of hypnotics may be common among caregivers of patients with degenerative illnesses such as dementia [245], caregivers in the context of cancer might not receive similar attention. Nonetheless, in a Turkish study among caregivers of patients undergoing chemotherapy [241], seven out of ten participants were using some form of non-pharmacological strategy (e.g. lifestyle or behavioural practices, biological treatments) to help them get through the sleep-deprived days.

3.5. Sleep-Impairing Factors in Caregivers of Adults with Cancer

Admittedly, not all caregivers develop sleep problems, and when these do occur they might not be easily explained or categorised. For instance, while some caregivers may complain about their sleep, objectively assessed sleep patterns may not replicate their complaints or not be significantly worse than those of non-caregivers. Altered sleep patterns in caregivers of adults with cancer are often presumed to be linked to night-time behaviours of the person they care for. Whilst important and still underresearched, this is only one source of sleep-related distress for persons in caregiving roles. Indeed, several additional underlying factors may play a detrimental role to the development of sleep/wake problems, and may have different significance for persons with different characteristics.

The second part of the critical review conducted gathered evidence from studies that evaluated potential factors interfering with nocturnal sleep and/or triggering daytime dysfunction related to poor sleep in informal caregivers of adults with cancer. The purpose of this synthesis of evidence was to answer two questions:

a. What do research findings report about factors affecting sleep/wake parameters of informal caregivers of adults with cancer?

b. What are the methodological and research gaps in this body of evidence?

Forty-four articles were identified through the systematic search undertaken (see Appendix 5). Relevant findings were synthesised, critically analysed and categorised into two broad themes: factors directly relating to the person and his/her lifestyle habits or behaviours, and factors relating to the caregiving experience also including patient-related parameters. This categorisation aims at highlighting that these factors can be independent of the caregiving situation, as well as directly related to it [245]. In agreement with Conceptual Framework for Understanding Impaired Sleep [62] and Spielman's Three-Factor Insomnia Model [63, 64], such factors can predispose caregivers to sleep restriction, and precipitate and perpetuate sleep/wake impairments, acting both interchangeably and in tandem. **Figure 3-2** presents an overview of the identified factors theoretically classified according to the aforementioned models.

		Conceptual Framework for Understanding Impaired Sleep	
		Sleep deprivation due to:	**Sleep disruption due to:**
Spielman's Three-Factor Insomnia Model	**Predisposing factors**	Age Gender Comorbidity Sleep hygiene	Age Personality Past sleep history Biologic/genetic Comorbidity Sleep hygiene
	Precipitating factors	Caregiver burden Fatigue	Comorbidity Caregiver burden Declining health Emotional distress Maladaptive coping Social support
	Perpetuating factors	Sleep hygiene Caregiver burden Fatigue	Age Past sleep history Comorbidity Sleep hygiene Declining health Emotional distress Maladaptive coping Social support

Figure 3-2. Classification of identified triggers for sleep/wake impairments in informal caregivers of adults with cancer according to two theoretical sleep models.

3.5.1. Person- and Lifestyle-Related Factors

A host of person-related characteristics have been proposed as potential triggers for sleep/wake deficits in informal caregivers. Importantly, while the effects of these predisposing risk factors can be seen early on within the caregiving experience, in other cases it is the occurrence of additional precipitating factors – most probably related to caregiving itself – that triggers their manifestation, which in turn can perpetuate already established alterations in sleep patterns.

Age – There is a lack of consistency with regard to the extent of age-related sleep problems in persons assuming caregiving roles. This possibly reflects methodological inadequacies as well as a significant variability in the caregiver samples studied. Lower habitual sleep efficiency was reported among older caregivers of patients with breast cancer during chemotherapy [30]; however, whether this was a true association or mediated by co-existing factors (e.g. sharing the caregiving responsibility with others) remained unexplained. Conversely, other research groups failed to conclude with a significant association [27, 241]. When three caregiver groups were compared (providing care to patients with cancer, AIDS or dementia), Flaskerud et al. [232] attributed sleep restlessness evidenced in caregivers of patients with cancer to their younger age. Although disrupted nocturnal sleep [246, 247] and longer time in bed [248] have been reported in older caregivers of persons with dementia, it is in the younger carers that daytime dysfunction seems to be more prevalent [249]. This is perhaps an indication that daytime dysfunction may be of greater importance to younger, more active and possibly still employed caregivers, whereas the older ones can compensate their sleep loss through increased daytime napping.

Gender – Disrupted sleep in the female caregivers of elderly people [250] or patients with Parkinson's disease [251], and in the male caregivers of spouses with moderate to severe dementia [252] was reported. Nevertheless, clinical or statistical differences in sleep by gender are absent among caregivers of patients with cancer [23, 27, 30, 237, 241]. Potential reasons for this paucity might include potentially equally distressed male and female participants in the studies reviewed; inability of self-reported data to accurately capture salient differences that objective data could reveal; and over-representation of female [23, 27] or male [30] caregivers in these caregiver samples (>77% of participants) that might have prevented associations from reaching statistical significance. For instance, although no differences in perceived sleep quality were reported in two studies, female caregivers did report greater frequency of depressive symptoms and fatigue severity than the males [23]. Alternatively, while Mills et al. [252] concluded with greater sleep disruption in male caregivers of spouses with moderate to severe Alzheimer's disease, they were not able to explain this difference

given that this subgroup did not report disproportionately more stress overload or problem behaviours than all other subgroups.

Personality – Despite some weak to moderate preliminary correlations, Carter & Acton [238] failed to include personality parameters (optimism, mastery or neuroticism) in a predictive model of sleep/wake patterns among caregivers of patients with cancer [238]. Importantly, it remains unclear whether the actual association of type of personality with sleep is an indirect one, with depression and/or coping being the link between the two variables. In several studies among caregivers of people with cancer, dementia or Parkinson's disease, personality traits emerged as a strong predictor of caregiver depression and coping [253-256]. Thus, a more substantial hypothesis would be that personality deficits lead to increased levels of depressive mood and poor coping; these in turn interfere with caregiver sleep architecture.

Past sleep history – Primary sleep disorders diagnosed in the past may be aggravated by a caregiving situation of tension and restlessness, but in other cases they can be fairly new in onset, thus greatly affecting vulnerable individuals. Similarly, a past history of unstable habitual sleep patterns also can increase susceptibility for impaired sleep. Impressively, investigation of these covariates in informal caregivers remains near to zero. Only recently, Gibbins et al. [244] examined the presence of a notable history of disordered sleep in caregivers of patients with advanced cancer; 12% of poor sleepers reported past sleep problems, 36% attributed sleep problems to patient diagnosis, and an additional 36% reported considerable aggravation of past sleep problems after patient diagnosis. However, sleep history was not specifically examined as a potential contributor to caregiver sleep disturbances.

Biological and genetic factors – Until recently, research relevant to the roles of pro-inflammatory cytokines in sleep/wake impairment in caregivers of patients with cancer was scant [257-260]. Findings from a longitudinal, repeated-measures study suggested that certain functional genetic variations in the tumour necrosis factor-alpha (TNF-α) [261] and interleukin-6 (IL-6) genes [262] might act as co-predictors of baseline level and trajectories of sleep disturbances. While effect sizes were indicative of a somewhat meaningful clinical difference between allele homozygotes and carriers of the rare allele, mean levels of sleep disturbance were below cut-off points for clinically significant sleep problems [261, 262]. Thus, there is a requirement for additional research with larger samples and with greater variability in levels of sleep disturbances to replicate such findings.

Comorbid conditions – A number of serious health conditions can adversely impact sleep, including thyroid disease, hypertension, arthritis, and cardiovascular disease [245, 263].

Medications used to treat these conditions may further increase the risk for development and maintenance of sleep problems [235], although in a study of dementia caregivers a significant relationship was not found [264]. Overweight or obese caregivers might be at greater risk for sleep-disordered breathing as well as disordered bed- and wake-times [263], and this also might be age-related or gender-related [245]. Nonetheless, underlying complexity, lack of directionality, and lack of sufficiency in self-rated measures of physical health, may have been responsible for discrepancies in relevant evidence [241]: whereas some studies favour a link between health status and caregiver sleep [248, 265], others have failed to show a statistical association [249, 266]. Regardless, mediators including age, health habits, gender, and level of psychological distress should be taken into account when the relationship between caregiving, health problems and sleep is examined [245].

Sleep hygiene – Habitual sleep routines can play a role in the deregulation of sleep/wake patterns in caregivers of patients with cancer [65, 267-269]. Sleep hygiene recommendations have been almost uniformly included as part of various cognitive-behavioural techniques [65] for caregivers of patients with cancer [29] and dementia [270]. Despite their overall importance, sleep hygiene practices of caregivers of patients with cancer or other chronic illnesses have never been assessed. Similarly, recorded attempts to explore over-time or health transition-related changes in sleep routines of persons in caregiving roles are absent. Therefore, a rather theoretical than evidence-based knowledge exists.

3.5.2. Factors Related to the Caregiving Experience

Subjective caregiver burden – Relevant literature partially confirms caregivers' increased vulnerability to sleep disturbance. Significant differences have been reported in caregivers of patients with cancer [234] or other chronic illnesses [249, 264, 271-273] compared to individuals in non-caregiving roles. There is a possibility, however, that this is a matter of subjectivity, given that objectively evaluated sleep patterns might not differ according to caregiving status [247, 248]. Caregivers' appraisal or personal interpretation of their situation might be more important than their actual caregiving role [274]. Equally, it is reasonable to assume that not all caregivers perceive their caring role as burdensome, and even if it is felt as such, what might be considered to be burdensome may not necessarily be linked to sleep impairments. In fact, only weak to moderate [271, 273] or even absence of associations [248, 275] between subjective caregiver burden and sleep disturbances exist, indicating an increased complexity in underlying mechanisms. That said, stronger triggers such as depression might be responsible, rather than the caregiving experience itself [276]. Even in the

cases where a positive relationship was found, the lack of longitudinal data cannot exclude the possibility that the caregiver sleep problems observed might have preceded and accounted for burden, rather than resulted from caregiving [266, 276].

Objective caregiver burden – As patient needs increase, primary caregivers are expected to provide intensive care, which allows only for minimal periods for rest and sleep [233, 277]. Yet, current limited evidence only moderately supports such a hypothesis [274]. Frequency of engagement in caregiving activities was also associated with poor nocturnal sleep and excessive tiredness in caregivers of persons with Parkinson's disease who provided daily care compared to those only occasionally being involved in patient care [233]. Conversely, the extent of caregiver involvement in patient care, as perhaps implied by the number of activities undertaken, remained unrelated to sleep problems other than merely nocturnal sleep disturbances [265]. However, adaptation of the caregiver's sleep-wake schedule to that of the patient's might provide one of several explanatory links [278], with caregiver narratives providing support to this relationship [277]. The patient's fatigue [275] and own sleeping difficulty [237, 244, 245, 277] might be additional triggers. Despite the inconclusive findings, this seems to apply mainly to co-habiting patient-caregiver dyads, and to bed- or room-sharing caregivers.

Fatigue – The extent to which care influences caregivers' daily schedule might be seen as a contributor to perceptions of fatigue [279, 280]. The interaction between fatigue and nocturnal sleep disruption and/or daytime sleepiness potentially flows both ways, which can lead to a negative feedback loop, where each symptom can be attributed to the manifestation of the other [111, 281]. Yet, only moderate correlations were reported in two widely dissimilar, cross-sectional studies after the first chemotherapy cycle for gastric cancer [23] and before radiotherapy for prostate cancer [25]. A causal link between the two variables was not established. Admittedly, fatigue and sleep disturbances could co-exist and co-vary without otherwise interacting. Indeed, relatives of patients with cancer in palliative care reported moderate levels of fatigue, even though they were sleeping fairly well [279]. Findings from a recent longitudinal study proposed baseline sleep disturbances as a significant predictor of the overall severity of the evening fatigue trajectories among female caregivers of patients with prostate cancer [239].

Health deficits – The caregiving situation itself may be associated with negative health effects [282, 283] that can adversely impact sleep. As a direct consequence of increased objective burden, then, caregivers may exercise less than their non-caregiving peers, a fact that further increases their risk for medical co-morbidity [245]. In a cross-sectional study of predominantly female family caregivers of older adults with memory impairment, objective

increases in total sleep time were positively, whereas increases in WASO were negatively, associated with caregivers' physical functioning after adjusting for caregiver age [284]. In the context of cancer caregiving, female family caregivers of patients with prostate, lung or brain cancer at the initiation of radiotherapy were categorised into active and inactive groups based on physical activity estimates [240]. Increased daytime napping was recorded in the group of lower physical activity. Conversely, only marginal sub-clinical differences were observed in self-reported sleep: on average, women in the active group slept approximately fifty minutes more than the inactive ones, whereas inactive caregivers reported increased sleep latency (mean 23.3 versus 11.7 minutes) compared to the active ones. Even so, adjustments for age, level of depression, or concurrent illnesses were not performed.

Sleep hygiene deficits – In theory at least, caregivers "might fall into iatrogenic sleep routines (…) to compensate for having their nightly rest disturbed" (p. 145) [245]. Such routines may include napping during the daytime, drinking coffee to stay awake or alcohol to help fall asleep with the ultimate result being a further decrement in their nocturnal sleep quality and quantity [245]. However, Aslan et al. [241] reported that a mere 7% of the participants consciously attributed their sleep problems to their poor sleep routines. Due to the absence of systematic research, the extent of sleep hygiene's contribution to poor sleep is still unclear.

Emotional distress – The emotional distress associated with caring for an ill loved one may explain alterations in sleep/wake patterns of informal caregivers [237, 241]. Although superficially examined, some moderate correlations between sleep problems, anger, and anxiety among caregivers of patients with advanced cancer have been reported [232]. A type of "anxiety from exposure to adverse effects of the therapy on the patient" (p. 372) has been identified by caregivers themselves as a potential reason for sleep problems [241, 277]. The emotional distress of illness experience may explain alterations in cancer caregivers' sleep patterns as well [237, 241]. In 164 community-dwelling caregivers of people with dementia followed every six months for 5 years, caregiver depression was one of the most powerful predictors of the onset of new sleep impairment [274]. Some caregivers with depressive symptoms might wake up crying [237], and this can be associated with feelings of restless or non-restoring sleep the next morning. Moreover, depressive mood was associated with decreased total sleep time and sleep efficiency, and increased daytime dysfunction in cancer and non-cancer caregivers [27, 28, 232, 237, 265, 266, 274, 276, 285]. Depression may be a persistent risk factor for sleep disturbance even after adjusting for differences in caregiver coping strategies, type of personality [238], caregiver age, and number of sleep aids used

[264]. Nevertheless, additional confounding variables such as gender or patient disease status need to be taken into consideration [28, 237].

Coping strategies – The way caregivers cope with their indirect illness experience can influence the manifestation of feelings of anxiety and sadness that interfere with sleep. Those caregivers who avoid and/or deny their situation, or are passively resigned to that may be more distressed [286] and depressed [287], and therefore more prone to habitual sleep alterations. Perceived self-adequacy in the caregiving role was moderately associated with better sleep quality among 60 caregivers of persons with Alzheimer's disease, but the role of depression as a covariate in this relationship was not examined [266]. In only one study were the linkages between caregiver personality, coping and sleep problems explored [238]. Significant, yet moderate, positive associations between less functional coping and sleep problems, and between neuroticism and sleep problems among caregivers of patients with advanced cancer emerged. However, in further regression analyses depression was the only significant predictor of caregiver sleep problems. In this small sample of overly depressed individuals, the indirect effects of coping and personality on sleep were possibly overshadowed by the most prominent effects of depression.

Social support – Deficits in caregiver social support have been associated with ineffective ability to cope [288], and with greater depressive symptoms and negative affect [206, 289]. Hence, inadequate or unavailable social support can be claimed as indirectly related to perceptions of poor sleep quality among cancer caregivers [241, 277]. Chang et al. [30] reported that perceived absence of someone to share the responsibility of caregiving was associated with poorer subjective sleep quality in persons supporting women with early stage breast cancer during chemotherapy treatment; however, confounding factors of this relationship were not examined. Using structural equation modelling, Brummett et al. [271] demonstrated that dementia caregivers with inadequate social support might be more likely to develop sleep problems, an association that is possibly mediated by the effects of perceived poor social support on the development of high levels of negative affect.

3.6. Summary and Critique

Sleep research has only begun to increase our knowledge on an area of functioning that may be of paramount importance for individuals assuming caregiving roles in the context of cancer. Current evidence confirms the variability of sleep/wake problems experienced by in-

formal caregivers of people with cancer: at least four out of ten individuals may report at least one problem [182]. Diminished sleep duration, nocturnal awakenings, prolonged wakefulness after sleep onset, and daytime dysfunction seem to be the areas of greatest distress, irrespective of stage or type of disease; yet, circadian activity remains under-studied. In addition, despite a wide spectrum of potential triggers, no safe conclusions can be drawn upon that could direct clinicians' attention to factors that can be of definite significance in the onset and maintenance of sleep disturbances.

Current findings share a number of common drawbacks. First, the majority of data are skewed towards the more advanced stages of disease and more prolonged caring periods. Consequently, they mainly target persons profoundly affected by the patient's severity and chronicity of illness, and needs. Second, a predominant focus on female persons in caregiving roles is noted. Third, clarification of the effects of cancer type-specific experiences on caregivers' sleep/wake patterns is lacking. In other words, generalisability is limited only to populations with very specific demographic characteristics (Caucasian, older than 50 years of age, and spouses) or caregiving experiences (either very intense or rather minimal provision of actual care). Inclusion of diverse age, gender, racial and ethnic groups of informal family and non-family caregivers in future exploratory sleep studies is recommended.

An additional point for debate could well be whether prevalence of sleep/wake problems in caregivers of patients with cancer has been reliably measured thus far, and whether prevalence rates reflect clinical importance. For instance, Cho et al. [23] found that 80% of caregivers of outpatients with gastric cancer reported poor sleep quality with a mean total score of 5.81 (±2.20) on the PSQI, slightly over a cut-off score of 5. Very similar frequencies were reported by Carter et al. [27, 28, 237] in a series of studies conducted in the context of advanced cancer; however, in the latter studies, mean PSQI scores ranged between 8 and 11, thus indicating greatly disturbed sleep. It is possible that low specificity of the cut-off score selected in the study of Cho et al. [23] might have led to caregivers having been characterised as having poor sleep quality whereas actual perceptions might not have pointed to this conclusion. With respect to the use of the PSQI in populations of caregivers, insufficiently established self-report cut-off scores to characterise caregivers as being either those with or without sleep problems may propose that in some cases overall prevalence of caregiver sleep problems can well be virtual. Indeed, Dhruva et al. [243] reported that, within the same sample, 59% and 38.6% of caregivers were identified as poor sleepers based on cut-off scores of two different measures, thus confirming the need for more validation studies to take place in the future.

Several other points should be noted as well. Given the presence of only a limited number of longitudinal studies in caregivers of patients with cancer [28, 29, 244], trends of over time changes in caregiver sleep/wake patterns remain practically unexplained. The infrequent utilisation of objective sleep measures in the studies reviewed means that even fewer have gathered data on caregivers' sleep/wake patterns or have used combinations of self-report and objective sleep measures as per current recommendations [49]. One additional key finding is the systematic use of a rather secluded terminology to define caregivers, thus merely focusing on family caregivers. Even in the studies where a broader definition was adopted, sampling strategies failed to include adequate numbers of non-family caregivers [231, 232]. Therefore, between groups comparisons to identify differences in sleep patterns of family and non-family members in caregiving roles are inexistent. This is a clear indication for a more comprehensive sampling methodology to be pursued to augment inclusion of relatively equal numbers of recruited family and non-family caregivers. Finally, a considerable trend can be noted in terms of the studies' cultural derivation. Although the majority of studies have been conducted in the United States, the rest of available data derive from eastern cultures (Korea, Taiwan, Turkey) [23, 30, 241]. Strong sociocultural demands for more intensive and uninterrupted caregiving in some cultural/ethnic contexts can result in greater burden and disrupted or restricted sleep, which however might not be replicated in studies of caregivers of different ethnic/cultural backgrounds.

Clearly, more research is needed to elucidate the experience of sleep disturbances in this growing population. Adequately powered, longitudinal quantitative studies are needed to examine the onset of alterations in sleep/wake patterns, describe changes and establish associations with time and transition points. What is more, well-designed qualitative studies are also warranted to shed light on the true meaning of disturbed sleep in the lives of informal caregivers who go through the experience of cancer, explore practices/behaviours that predispose carers to sleep loss, and enhance our understanding of what caregivers would consider the most important sleep/wake deficits they would wish help for.

Whilst the contribution of an array of factors is recognisable, current evidence only partially supports their causal relationship to sleep problems. This lack is mainly due to the cross-sectional nature of the vast majority of studies conducted. Although links between several factors and disrupted sleep patterns have been reported, it is largely unknown whether this 'desirable' direction of relationship is actually true. Especially for caregivers of patients with cancer, the limited targeted sleep research surrounds evidence with even more uncertainty. In turn, this lack of information often leads researchers to complement cancer-specific data

by ‘borrowing’ evidence derived from other caregiving populations, which may be true for cancer caregivers as well, but to what extent? Similarly, current literature has focused more on some rather than other effects on caregivers’ sleep; therefore, relationships between sleep and possible explanatory factors are in part based on either weak correlations or findings from the general population. Consequently, unique cancer-specific data such as those relating to the nature, frequency, severity, or patterns of occurrence of factors affecting sleep regulation when caring for patients in different disease stages or disease types, might still remain hidden. For instance, the relative risk for caregiver sleep deprivation associated with the various demographic/clinical/lifestyle characteristics remains to be clarified in future comparative studies.

Despite the fact that advanced cancer has been linked to increased patient needs that may increase caregiver burden, sleep disruption/deprivation warrants exploration beyond this limited area. Are the current incongruous findings sufficient to establish a link between patient disease stage and caregiver sleep problems? Clearly, evidence is so limited in extent and so heterogeneous in terms of basic participant characteristics that drawing safe, general conclusions becomes impossible. Although there seems to be a trend towards greater sleep disruption/deprivation during caregiving for patients with advanced cancer, the nature and range of sleep problems experienced by caregivers may manifest themselves irrespective of patient disease severity, and fluctuate according to the overall caregiving situation. Several additional factors might contribute in complex ways to the occurrence and perception of sleep problems in cancer caregivers. Hence, perceptions of disturbed nocturnal sleep might be greatly associated with additional correlates such as caregiving or other responsibilities, duration of caregiving, or caregiver symptoms and concerns. Such important parameters have scarcely been taken into consideration in the relevant studies. In other cases, caregiver burden might be only temporal; closely related only to specific events rather than to the whole illness experience. This temporality might be related only to transient caregiver sleep disturbances as well; once the stressors cease, sleep patterns might return to habitual. In that sense, despite the temporary deficits in their sleep, caregivers in such situations might not perceive their sleep patterns as particularly affected. Such a hypothesis could represent an additional reason as to why thus far caregiver burden has not been consistently or highly associated to caregiver sleep problems.

As previously mentioned, current evidence derives from diverse samples of individual, cross-sectional studies only. Whether there is a true prospective impact on sleep/wake patterns, or evidence is only influenced by different characteristics of these diverse samples remains to be found. More longitudinal, mixed-methods and comparison studies will need to

explore the onset and maintenance of sleep/wake impairments based on the gravity of the caregiving situation in the context of diverse types of cancer and disease severity. Whether the relation between sleep hygiene practices and sleep can be extrapolated from other populations to caregivers of patients with cancer remains unknown. Even in the studies where multi-component sleep interventions were tested [29, 270], it is questionable whether their positive effects could also be attributed to their sleep hygiene component, or whether they could be attributed to sleep hygiene only. Positive sleep hygiene practices can be a powerful protective factor against sleep loss, and clarification of the extent to which disruptive habits are associated to poor sleep can be a useful adjunct to design more effective sleep interventions for caregivers.

Fatigue-related daytime dysfunction can be manifested as excessive sleepiness and prolonged napping that can adversely affect regulation of the sleep/wake cycle and lead to nocturnal arousal. Whether baseline and ongoing fatigue can be regarded as a predictor of over time daytime dysfunction in caregivers of patients with cancer also remains to be confirmed in future, adequately powered, prospective studies. Such research efforts will also be required to clarify the degree to which the relationship between fatigue and sleep is a matter of subjective perception, or perceived fatigue can be equally correlated to objective sleep measurements. The same is true for the sleep-impairing effects of psychological burden. A pilot study conducted over a relatively short follow-up period of ten weeks reported abrupt swings from week to week in both sleep and depressive symptom scores of advanced cancer caregivers [28]. Although overall fluctuations might have coincided in this very small sample size (n=10), a link between these two variables was not established. In such samples of overly burdened caregivers, both sleep disturbances and psychological distress could certainly coexist without, however, their onset necessarily originating from one another. Because of the lack of longitudinal comparisons and associations, the direction of this relationship in cancer caregivers has only in part been replicated, whereas its nature in caregivers of patients with early-stage cancers, or those who provide care during specific major event-related periods of time, remains unclear still. Lastly, longitudinal data could clarify whether positive coping styles and personality traits can be regarded as truly linked to caregiver sleep quality, through a protective mechanism that possibly leads to reduction of caregiver psychological distress. To this direction, application of a comprehensive theoretical framework or model could effectively guide nursing research to explore the effects of sleep-impairing factors in this population [61].

CHAPTER 4.

Patient-Caregiver Dyads and the Experience of Sleep/Wake Impairments

4.1. The Patient-Caregiver Dyad: Beyond Individualism

In the previous discussion, there has been a conscious effort to present disparate accounts of concept-related and sleep-related research data pertinent to women with breast cancer and their informal caregivers. However, this distinction was implemented for the purposes of data presentation and analysis only; in reality, changes in the lives of the person receiving cancer care and the person providing informal care take place in partnership, and illness is often experienced and managed in the context of a complex network of relationships [290]. In the majority of early studies however, patients' and caregivers' experiences have been regarded rather independently. Schumacher [203] argues that it was the perceived frailty of the care receiver and resulting dependency that instilled individualism in this relationship.

Nevertheless, research literature, now more than ever, supports the fundamental idea of dyadic interdependency: cancer is considered to be a shared experience that impacts upon individuals on a level that transcends mere individualistic limits and cannot be understood solely within person-centred models of care [290-292], but instead, through a whole-systems framework [290]. In that sense, interdependence between parties of close relationships may exist, which has been accounted as the defining feature of human relationships [293]. At the level of a dyad (that is to say, a pair of closely related persons), interdependence can influence the ways in which persons grow and thrive, as well as cope, in the wake of major events and challenges. Illingworth et al. [290] analysed patients' and caregivers' narratives within the first year of cancer diagnosis, confirming this shared nature of cancer experience: participants often experienced cancer at the dyadic level, where it was jointly and interactionally owned and processed. A dyadic focus seems to be a more appropriate approach for people affected by cancer, and active-phase treatment such as chemotherapy has been proposed as one – yet, not the only one – time point in a patient's cancer trajectory, where care is viewed as an area of endeavour in which both patient and caregiver actively participate [203].

4.2. The Added Value of a Concurrent Assessment of Health Outcomes in Patient-Caregiver Dyads

The notion that the patient-caregiver relationship is made of two people, both of whom influence and are influenced by the other, has been stressed as particularly relevant to health care in general [294, 295]. Several health- and quality of life-related variables have been frequently conceptualised in an individualistic way; however, social contextual models argue that health outcomes are likely to co-vary in close relationships, as in the patient-caregiver relationship. For instance, any change in the functioning of one individual can affect the functioning of their significant others, and vice-versa [296]. Similarly, although external factors such as disease severity and social support may affect patients' and caregiver's physical and psychosocial well-being directly and uni-directionally, patient and caregiver interdependence may contribute to a bidirectional situation, in which the well-being of each individual in the dyad also affects the well-being of the other [297].

By accepting the probability of complex interactions in their relationship, it is reasonable to argue that patients and their caregivers may react to cancer as a unit; as a result, they both have legitimate interrelated needs for help from health care professionals [298, 299]. There is general consensus among clinicians and researchers that when patients and caregivers are treated simultaneously, important synergies can be achieved contributing to the well-being of each person [217, 300]. In any case, when these interrelated and often concurrent needs are neglected, patient-caregiver dyads are denied the opportunity to obtain optimal care. Therefore, Northouse et al. [298] claim that in order to provide optimal comprehensive cancer care, the care plan must focus on these patient-caregiver units. To address and confirm dyadic reciprocity and establish the effects of such dyadic approach, a shift in health research is evident towards inclusion of patient-caregiver dyads rather than merely patients or caregivers alone. In turn, this novel approach promises to enhance care by revealing salient aspects lying within the mutuality of the patient-caregiver relationship.

A scoping review of the most recent literature was undertaken, which made apparent the importance attributed to concurrent evaluation of patient and caregiver health outcomes throughout major chronic illness/disorder experiences. A wide range of health care contexts was involved, including cancer [218, 224, 226, 301-309]; renal disease [295, 310] and haemodialysis [311]; psychiatric illness (bipolar disorder [312], schizophrenia [313]); mental illness (dementia [314-316], Alzheimer's disease [317, 318]); cardiovascular diseases (heart failures [319, 320], stroke [321, 322]); degenerative diseases (Parkinson's disease [323], multiple sclerosis [324]); as well as diabetes [325] and spinal cord injury [326]. By examin-

ing the content of this body of literature, two important and contrasting issues emerged: *diversity in the perspectives* employed to capture and demonstrate benefits associated with inclusion of patient-caregiver dyads in health care, as well as *wide variability in limitations* that urges for greater consistency in future research so that benefits can irrevocably be established.

These methodologically diverse studies implementing a dyadic approach were classified in three broad clusters of sources of evidence. In the first cluster, studies were included where exploratory methods were employed to describe the dyadic nature of key health outcomes and identify key predictors of reciprocal influences [295, 310, 312, 319-322, 325]. Departing from these simple exploratory models, the second cluster comprised studies evaluating the effects and benefits of caregiver-targeted interventions on both patient and caregiver health outcomes [313, 314, 317]. Studies of this type evaluate effectiveness of various interventions such as bio-behavioural [314] or psychoeducational/support programmes [313] on patient-caregiver dyads' functioning, well-being and quality of life, as well as caregiver social support, confidence, and patient dependence. These interventions have been accompanied by some significant reciprocal improvements in outcome variables, thus proposing that enhancement of the caregiving qualities can have a dual benefit for both caregivers and patients. Lastly, the third cluster included studies concurrently testing interventions for both patients and caregivers in order to demonstrate reciprocal effects on health outcomes, as well as achieve greater bidirectional benefits [311, 315, 326].

Existing evidence in the context of chronic illnesses other than cancer is indicative of greater overall distress and caregiver burden in patient-caregiver dyads where life satisfaction is discordantly low, and even greater in dyads reporting concordant dissatisfaction. Interestingly, even caregivers satisfied with life but whose care recipients are dissatisfied, might express caregiver burden [321]. Similarly, partners' abnormal personality traits might influence both patient and partner perceptions of the quality of their relationship, but this might be more evident in the context of a psychiatric disorder. Reversely, patients' psychiatric symptoms might be associated with poorer intimate relationship functioning in their partners [312]. Other dyadic models favour associations between support behaviours and relationship satisfaction: patients and partners who report both receiving protective buffering (i.e. hiding concerns or pretending) may also report relationship dissatisfaction; this might be especially true for those who at the same time report receiving low active engagement (i.e. refraining from openly discussing or asking how the other is feeling) [325]. In-home training programmes that value care partners as well as patients might be associated with dyads thriving in terms of well-being and relationship quality, as opposed to training that focus merely on

the patient at the expense of the partner [311]. Such an approach can be viewed as particularly useful in engaging patients and caregivers in open discussions that promote effective communication [315].

In the cancer care context, weak evidence ($r \leq .20$) indicates that patients' fear of disease recurrence might affect carers' own fear of recurrence and distress over time [327], but remains unclear whether this association extends beyond six months post-diagnosis, is influenced by dyadic adjustment to illness, or is true for dyads affected by cancers other than head and neck cancer. Along these lines, post-traumatic growth might present with greater differences between individuals in female patient-male partner pairs than in the reverse situation, possibly reflecting an effect of gender and role on dyads' interrelated experience of illness [309]. As discussed, examination of the intra- and inter-personal consequences of protective buffering among patients and their partners suggests that the more patients hide cancer-related thoughts and concerns from their partners, and the more they feel that their partner hides their own concerns, the lower their concurrent relationship satisfaction and the poorer their mental health might be [302]. As well, mutual avoidance and communication withdrawal can be responsible for poor perceived intimacy, ultimately leading to concurrent psychological distress in heterosexual couples in long-term relationships [303, 304]. Due to the absence of proven causality, however, the possibility that dissatisfied or distressed partners might exclude each other from their most intimate thoughts cannot be ruled out. Becoming increasingly dissatisfied and not feeling privileged in taking care of the sick spouse have been suggested as possible mediators of incongruence in patient and caregiver perceptions of quality of life [328]. Drawing on some of these findings, education interventions [329, 330] and stress-reduction programmes [331] have targeted the dyad for possible joint effects. In spite of some promising concurrent improvements in psychological distress [329, 331], mood [330, 331] and quality of life [330], there is still an outright need to establish superiority of dyadic interventions, not only over control groups, but also over groups where one member of the dyad receives the intervention (four-group designs); as inconclusive findings indicate [330], this can only happen where methodological rigour supersedes the above-mentioned limitations.

In its vast majority, evidence derives from studies conducted in the context of breast cancer [218, 224, 226, 305, 306, 308, 332-335]. For instance, the nature of the patient-partner dyad relationship might not be of particular significance for women's post-surgical adjustment, but intimate partners might be at greater risk for emotional and social adjustment issues compared to other family- or non-family members [306]. In any case, husband's and wife's difficulties with role adjustment one year after a diagnosis of breast disease might have a

direct, yet rather minimal, effect on the role adjustment of the other; very similar cross-partner effects regarding emotional distress have been also reported [224]. Concurrent linear drops in reports of marital satisfaction and family functioning might be evident over time, whereas elevated dyadic distress and role problems at diagnosis of breast cancer are likely to remain high at least one year later [336]. Complex interactions in mutual constructive communication between patients with breast cancer and their partners might also alleviate some of their concurrently experienced distress [226]. Correspondent trends and changes in women's and their partners' emotional well-being have been reported as well, possibly suggesting close covariance [305]. In the same sense, there is some evidence that a caregiver's impression rating of the patient's quality of life might act as a predictor of the patient's own quality of life [337], possibly due to negative attitudes of family members adversely affecting patients' clinical outcome [337]. In fact, males' relationship satisfaction has been suggested as a weak predictor of self-acceptance of body image in women with breast cancer [308]. Due to the absence of a long-term investigation, however, a causal relationship cannot be implied, nor can it be established whether this is a mere indirect association, possibly emanating from the effects of partners' views of the woman's body image on the woman's self-acceptance. Nevertheless, several couple-based intervention studies have been conducted, based on the grounds of this evidence. These have aimed at demonstrating concurrent improvements in couples' quality of life [335], psychosocial and physical adjustment [333, 334], relationship satisfaction [334] and functioning [332, 334], and psychological functioning [332]. Although the beneficial effects of a dyadic interventional approach have been praised, its superiority over interventions targeting only the one member of the dyad remains to be established. Additionally, long-term effects over periods where major events occur, such as diagnosis, pre- and/or post-surgery, subsequent or initial treatment, ongoing recovery, survivorship or palliative care, need to be explored. One issue to be taken into consideration is the suggestion that younger women in short-term relationships who receive chemotherapy treatment might benefit more from a dyadic approach to their illness [335], but this also should be evaluated in studies where the focus shifts from married couples/partners to a broader patient-caregiver relationship including additional significant others such as children or friends.

Despite the aforementioned efforts, several limitations still undermine reproducibility, generalisability or/and reliability of their findings. In fact, in some cases these limitations may well have been responsible for an inability to demonstrate significant effects of the dyadic approach on health outcomes [316, 318, 323], whereas in other cases directionality of significant associations may still remain unclear due to cross-sectional designs not permitting repeated examination and verification. In addressing duality of health outcomes, studies in-

volving patients and their caregivers need to rely on a robust methodology and adequate design, prerequisites which have not been fully met as yet. In a largely analogous fashion and despite the benefits reported, dyadic research in cancer care can also be seen as suffering from the same methodological issues as the ones previously mentioned. Interestingly, the majority of studies have focused only on bi-directional associations of psychological distress with the dyads' well-being, quality of life, or other external predictors, whereas potentially interrelated bio-behavioural symptoms such as sleep or fatigue have yet to be fully examined in patient-caregiver dyads. Closely related to this gap, the association between the dyad's long-term adjustment and interrelated health outcomes has not been widely explored. This could be facilitated by conducting longitudinal, repeated-measures studies over extended periods of time, even one or two years after major events or transitions have taken place. Nonetheless, only a limited number of studies have implemented a truly adequate prospective design to test direction of associations, but this strategy does not necessarily ensure that generalisability is feasible.

The sample of studies examined suggests that relevant evidence needs to be evaluated with caution. Careful examination makes additional methodological issues rather evident: (a) non-inclusion of sample size estimation analyses may be seen as responsible for sample sizes inadequate to support multiple statistical procedures: in fact, testing of predictors may be limited only to a few variables despite hypotheses of multifactorial relationships; (b) sampling under-representativeness at the level of patient (for example, with regard to age, sex, cancer type, severity of disease, functional status, cultural background), caregiver (e.g., focus on family members only) and patient-caregiver dyad (e.g., recruitment or self-selection biases regarding dyads in low quality relationships, exclusion of minorities) may render findings relevant only to some patient-caregiver groups but not to others, especially for mid-age, Caucasian, married couples where the woman has been diagnosed with breast cancer; (c) albeit highly recommended, adequate statistical analyses, such as multilevel modelling or structural equation modelling [293], that take into consideration the existing interdependency within the dyad have been scarcely implemented. As opposed to classic analyses assuming independence of observations, appropriate dyadic data statistics treat the dyad as the unit of analysis. Yet, relative unfamiliarity may lead to advanced statistics being seen as the last, and thus avoided, resort. Sadly, such practices can lead to mishandling of dyadic data that may hinder statistical comparisons. Furthermore, very commonly, exploration of dyadic changes of outcome variables has taken place over selected time points thereby unlinked to transition to the different phases of cancer experience, such as prospective re-assessments conducted following diagnosis (e.g., 6- or 12-month follow-ups) or during survivorship or remission. It is, however, interesting for interrelated outcomes to be examined at time points

where major events occur, such as post-diagnosis and before, during and after active treatment, during transition from one treatment modality to another, at relapse and related health care decisions, or before, during and after hospice or palliative care. Bearing in mind these important limitations, supporting findings need to be treated as only indicative, but certainly not definitive, of a complex interaction between patient- and caregiver-related outcomes in the context of cancer. Most importantly, the most needed longitudinal intervention studies that demonstrate the benefits of a dyadic approach over an individualistic one by comparing groups of dyads where intervention is applied to one or other member, both or none, and where participants are followed-up over time, have only recently begun to emerge.

4.3. A Dyadic Approach in Sleep Research: A Novel Concept

In Chapter 1, it was argued that onset and maintenance of sleep are dependent on the satisfaction of a series of physiological conditions [11]. Aside from that, sleep is considered to be a vulnerable state that, in part, occurs, or otherwise is optimised, when one feels a sense of physical and emotional safety and security to down-regulate vigilance and cease alertness [338, 339]. Across the lifespan, such feelings are largely derived from the social environment [340]. Thus, for humans, sleep has evolved beyond its biological nature to one that is embedded in a social context, a fundamental attachment behaviour that may be regulated within and affected by close human relationships [338, 341] such as the patient-caregiver relationship. In that sense, the fact that the science of sleep has tended to view sleep as an entirely individual phenomenon can be described as a rather confined approach, impeding assessment and management of sleep disorders that might manifest themselves especially during periods of adjustment to illness. As described earlier, interdependence is a defining feature of relationships and it might also be a defining feature for sleep as seen in the context of a close patient-caregiver relationship [342].

Attachment theory has been implemented to provide a perspective of the link between close relationships and sleep [338]. This theory posits that early interactions with caregivers lead to the development of expectations to the degree to which a caregiver will be responsive to one's needs [338, 343]. These key expectations are thought to mediate affect and arousal, particularly in times of real or perceived threat [340, 344]. This might suggest that the closer the relationship, the greater the odds of a good night's sleep, and vice versa. Despite recognition of the dyadic nature of sleep for most adults, there has been surprisingly little investi-

gation of human sleep patterns in a paired manner. Within the scope of a broader review of the literature (see below), a systematic search for publications addressing the issue of concurrent examination of sleep/wake patterns in adult couples was conducted. Seventeen original studies were retrieved, where research was focused on the nocturnal sleep patterns and daytime impairments of co-sleeping heterosexual couples either in the absence of a medical illness or in the presence of a primary sleep disorder such as obstructive sleep apnoea (OSA).

In the general population, Meadows et al. [342] reported that the variables showing the most significant couple interdependency in co-habiting heterosexual couples were actual bed time, sleep latency, light/dark movement ratio (i.e. the difference between amount of movement during daytime and night-time), and wake bouts (i.e. the number of nocturnal awakenings). In addition to this interesting, yet inconclusive, evidence suggesting a close interrelation in couples' sleep patterns, presence of a bed-partner has also been viewed as a potential source of sleep disturbance. The relevant research has demonstrated significantly lower levels of Stage 4 NREM sleep [345], a concomitant increase in REM sleep [345], and a greater number of movements during sleep [345, 346] on the nights when participants slept with their partners rather than when slept alone. In spite of this reciprocal impact on one another's sleep, participants have reported less satisfaction with their sleep when sleeping alone [345, 346]. In a sample of couples without sleep disorders, Pankhurst and Horne [346] observed more movements in men than in women, with women reporting that their sleep was affected by their partners' sleep more than did men. Men are also more often loud snorers [347], and the sound of snoring can be a major disturbing factor of the sleep of their bed-partner, who might report symptoms of insomnia, morning headache, daytime sleepiness and fatigue [348]. However, whether 'sleeping alone' improves substantially sleep in partners of snorers is shrouded in ambiguity [349] and might be related to the actual duration of the intervention. Similarly, several efforts have been made to identify a link between reported or observed sleep disturbances within the couple with relationship functioning or quality [350-352] and attachment behaviours [353-355]. Although a positive unidirectional association has been established, evidence is mainly based on either cross-sectional dyadic studies [352, 353] or single-arm studies [350, 351, 354, 355]. In a cross-sectional study among married couples, attachment anxiety predicted poor sleep quality, but no cross-partner effects were identified [353], possibly due to non-homogeneity of the study sample and use of self-report sleep measures which might have been biased by participants' levels of mood. Nonetheless, in a very recent longitudinal study of 29 young adult couples, Hasler and Troxel [356] showed the existence of some bidirectional associations between interpersonal interaction and sleep parameters, specifically sleep efficiency and sleep concordance (i.e. agrre-

ment/similarity in sleep timing and onset within the couples). Women who reported more positive daytime partner interaction were found with greater perceived sleep efficiency, and this was also true for their male partners [356]. These results imply existence of interdependence in night-time sleep and daytime relationships; however, aside from the small study sample and several inconsistencies in data derived from both objective and subjective sleep measures, findings also seem to be largely confined in the limited context of young, happy and childless couples with no concurrent illnesses, who are good sleepers.

On the other hand, OSA has been referred to as a "disease of listeners" [357]; aside from snoring, increased arousals often adversely affect both the bed-partner's and the individual's sleep [348, 358]. In particular, Beninati et al. [359] observed less consolidated sleep in partners of individuals with OSA, a feature which tended to correspond with the patient's disrupted sleep patterns. The effects of OSA-related features on the partner's sleep patterns can be difficult to subside: in an inadequately powered pseudo-experimental study studying the effect of continuous positive airway pressure (CPAP) treatment of individuals with sleep apnoea/hypopnoea syndrome – a subtype of OSA – on sleep quality, McArdle et al. [358] reported improvement in partners' subjective sleep quality after a one-month period, but no evidence of a benefit on objectively measured sleep quality was found. OSA has been associated with excessive daytime sleepiness, irritability, energy deficits, and depressive symptoms [360], all of which might be manifested in both the individual and their spouse; as yet, this remains a mere prediction or hypothesis as relevant literature has not systematically assessed such issues in a longitudinal, dyadic manner. Moreover, in the studies examining the role of CPAP in improving the sleep quality of co-sleeping couples [359, 361], no follow-up of home use or whether the couple continued to sleep together were reported, thus precluding knowledge on the long-term effects of the intervention.

Excerpts from Sections 4.1 through 4.3, as well as Section 4.4 that follows, have been published in a peer-reviewed journal and can be found in Kotronoulas et al. [209] (see Appendix 7).

4.4. Sleep/Wake Patterns of Patients and Informal Caregivers: A Matter of Dyads

To date, attachment theory has been used to guide research models in the relationship between couples' relationship functioning and sleep [338]. However, this theory could, to a

certain extent, justify the value of concurrent assessment of sleep/wake patterns of patients and their primary informal caregiver, either in a family [340] or a wider support context. Caregivers who, regardless of their actual caregiving tasks, value their role as important for them and for the patient they care for, might be more affectionate towards the patient; this in turn could lead to patients feeling more secure in their relationship and sleeping better.

Importantly, as patients and caregivers go through the experience of illness together, their emotional reactions and distress affect one another in a relatively proportionate manner, adding to one's own concerns and worries when they reach a peak, or relieving from additional distress when they simmer down, and possibly resulting in corresponding changes in sleep patterns. In a similar manner, effective or dysfunctional coping strategies of the dyad might co-affect their sleep through a psycho-behavioural mechanism. Moreover, it is more than obvious that patient symptom distress can lead to increased caregiving efforts. However, impaired caregiver sleep patterns, coupled with daytime sleepiness and increased fatigue can equally lead to poor caregiving performance, which might in turn inhibit the management of patient symptoms influencing sleep, or disordered sleep itself. What is more, although not all patients and caregivers share the same bed or the same room, co-sleeping or co-habiting dyads might be co-affected by poor sleep hygiene practices or by disrupted sleep patterns related to the illness experience. Such sleep-impairing factors might well interfere with the prerequisites necessary for a good night's sleep at a level that transcends the individual.

Crossley [362] suggests that in a situation involving the co-presence of persons, the parties to that situation need to secure cooperation from each other to achieve their sleep ritual, whether this involves the choice of common bed times and sleep conditions or different but complementary patterns, with each party respecting the needs of the other. In co-habiting or co-sleeping patients and caregivers, this 'cooperation' becomes blurred given that patient symptom experience, caregiver burden and associated frustration can alter sleep habits/rituals or restrict actual sleep of the dyad in a way that concordance might be no longer feasible.

Drawing on the above arguments, it is more than reasonable to assume that implementation of this dyadic approach would augment our understanding of co-occurrence of sleep problems in patient-caregiver dyads, trends of concurrent transformation of these sleep problems across time, and covariates/factors that appear to contribute to these patterns within the dyad and across time. Some argue that this is key to the development of truly effective treatment strategies [278, 338, 363].

A systematic search for published studies that utilised concurrent examination of sleep/wake patterns/impairments in patient-caregiver dyads was conducted. This systematic review aimed to answer two questions:

c. What do research findings report about concurrent sleep/wake patterns/changes/impairments in dyads of patients and informal caregivers irrespective of health care context?

d. What are the methodological and research gaps in this body of evidence?

The literature review aimed to identify original research studies where sleep/wake patterns were concurrently assessed in couples or patient-caregiver dyads, either in the absence of a disease or in the context of chronic illness. The review was conducted in a two-fold manner to address its two objectives. Initially, all relevant publications were retrieved irrespective of presence or type of illness, study design, or primary or secondary focus on sleep/wake patterns. These studies would form a large pool of evidence. From this pool of studies original papers were extracted that concurrently examined sleep/wake patterns of patients and informal caregivers in the context of chronic illness.

Studies were identified by systematically searching three research and evidence databases, namely Medline (1948-2011 May week 02), CINAHL (Beginning-2011), and EMBASE (1980-2011 Week 18). An initial search strategy was devised and subsequently revised through an iterative process (Appendix 6). Using a snowballing strategy, the reference lists of retrieved studies were also examined for any studies that may have been overlooked. The reference list of a key topical research review also was examined [338, 364]. Additional literature was sought through use of the search engine Google Scholar to locate relevant publications using the aforementioned key words.

Studies were eligible in the review if they were written in the English language; were conducted with adult (>18 years of age) individuals; examined sleep as a primary variable in a concurrent fashion in couples or dyads of individuals; and were published as original articles in peer-reviewed journals from January 1990 to July 2011 representing the period in which studies of sleep within different clinical populations emerged. Both quantitative and qualitative studies were included. In the second step, only studies concurrently assessing sleep/wake patterns in patient-caregiver dyads irrespective of the context of illness were regarded. Unpublished studies, dissertation studies, or conference presentations were not included in the present review.

A shortlist of papers was initially compiled, where titles and abstracts were screened to assess relevance to the review. Potentially eligible papers were retrieved in full and checked for adherence using the afore-mentioned inclusion and exclusion criteria, thus forming a pool of papers. Papers reporting on sleep/wake patterns of couples/dyads in the absence of a chronic illness were introduced in a narrative synthesis. In a second step, additional criteria were applied to identify studies examining sleep of patient-caregiver dyads irrespective of the context of illness. Study characteristics of these latter studies were extracted using a systematic scheme. Findings of the studies retrieved regarded in this step were critically analysed and categorised in major themes. However, due to heterogeneity of these studies, meta-analysis of findings was not feasible.

Studies reporting on patient-caregiver dyads' sleep/wake patterns were evaluated for methodological quality using a validated scoring system for the systematic appraisal of empirical studies with varied methodologies [365]. However, no studies were excluded on the grounds of quality, given the lack of agreement in the application and interpretation of quality criteria [118]. The evidence categories employed by the DOHNSF (2001) [116] were also used for levelling evidence, and aiding appraisal of quality of the papers reviewed. This framework was used because it has been piloted for use with both peer-reviewed and non-peer-reviewed research [117]. **Table 5-A2** outlines the levels of evidence as established using the DOHNSF validated grading hierarchy. No studies were excluded on the grounds of quality.

The selected studies were summarised, analysed and synthesised at a higher level. Irrespective of the illness context, evidence regarding bidirectional associations in the sleep of care recipient-caregiver dyads is still inconclusive and in some cases contrasting. Nevertheless, interesting and promising preliminary findings/associations were reported in the studies reviewed. These findings were organised into two broad thematic categories: sleep/wake patterns/problems, and sleep-impairing factors. **Table 4.1** summarises evidence according to the level of clarification established in the relevant literature. A brief description of the characteristics of the included studies can be found in Appendix 6. Findings presented below and in Appendix 6 were published in a peer-reviewed journal and can be found in Kotronoulas et al. [366] (see Appendix 7).

4.4.1. Sleep/Wake Patterns/Problems of Care Recipient-Caregiver Dyads

In agreement with the concept of care recipients and caregivers living in close relationships, similarities in nocturnal and daytime sleep behaviours within dyads were reported in three studies, where close synchronisation of bedtimes and wake times [242, 247, 278], daytime

naps [278], as well as sleep duration [247] was found. Caregivers had generally later bedtimes (ranging from 35-42 minutes on average) [247, 367] and earlier awakening times (ranging from 4-36 minutes on average) [242, 247, 367], thus demonstrating organisation of their sleep routines around the patient. What is more, the notion that a caregiver's sleep can be a function of the patient's sleep, and vice versa, was investigated and partly verified in the studies reviewed [242, 247, 278, 285, 367, 368]. Where positive significant correlations emerged, these were moderate to strong [242, 247, 367], derived from dyads sharing the same bed/room [242, 247, 367], and were pertinent to the objectively recorded nocturnal sleep parameters of sleep onset latency [242], wakefulness after sleep onset [242], nighttime activity [278, 368], number of nocturnal awakenings [242], sleep efficiency [242, 367], and total sleep time [242, 247, 367]. In a study that involved 7 days of actigraphic recordings, however, sleep variables that showed the greatest night-to-night stability and variability were different between patients with Alzheimer's disease and family caregivers, thus suggesting that sleep deficits within the dyad are not necessarily interrelated [363]. In addition, the frequency and magnitude of correlations between self-reported sleep data were far less in the studies [242, 285], mainly regarding perceived sleep quality [242, 285], sleep duration [242] and early awakenings [242]. Conversely, daytime behaviours between members of the dyads seemed to be uncoupled, given the consistent absence of significant correlations in their activity levels and total daytime sleep [242, 278, 285, 367, 368].

Where sleep/wake disturbances were investigated [233, 242, 244, 251, 285, 363, 367], patterns of frequency, concurrency, and, in some cases, comparability of nocturnal sleep problems, were described in the dyads. Similarities in the occurrence of poor sleep for care recipients and caregivers were reported in the majority of the studies [233, 242, 244, 251, 285, 367], with complaints of poor sleep accounting for approximately 30% to 50% in either group. Yet, two studies revealed that in only 20%-23% of the pairs both parties reported not sleeping well, while in 41%-45% only the patient or the caregiver reported not sleeping well [244, 363]. Irrespective of whether statistical significance was reached, trends of clinically greater sleep deficits in patients were apparent in all studies. Even though studies were split as some concluded with no statistical differences between patients' and caregivers' sleep deficits [242, 244, 367], whereas others reported greater sleep problems in care recipients than in caregivers [285, 363], nocturnal sleep problems in the caregivers were not unimportant and in some cases comparable to those manifested in care recipients. Conversely, despite the absence of perfect agreement [242], less daytime activity, increased time in immobility, greater daytime dysfunction and/or higher levels of daytime sleepiness were reported in care recipients than in caregivers in three studies [244, 278, 285], which might reflect the consequences of a restless night and/or a severe disease. Two studies revealed

dampened circadian rhythms (particularly, amplitude) which could explain patterns of excessive daytime inactivity in care recipients [278, 367]. Even so, caregiver reports of daytime sleepiness and dysfunction were far from insignificant. Lastly, the infrequent use of sleep medications in care recipients (22-23%), but especially in informal caregivers (10-20%), was highlighted in two studies [244, 363], with a further study confirming patients' greater need to medicate for poor sleep [242]. In any case, McCurry et al. [363] reported that dyads of concurrent poor sleepers were more likely to include a care recipient who was using sleep aids.

Table 4.1. Summary of Associations in Sleep/Wake Patterns of Care Recipient-Caregiver Dyads According to the Level of Clarification Established in the Literature [366]

Probable /Definite Associations	▪ Nocturnal interactions in co-residing dyads. ▪ Worse daytime activity levels/greater daytime sleepiness in care recipients versus caregivers. ▪ Clinically poorer nocturnal sleep in care recipients versus caregivers. ▪ Close synchronisation of bed-times/wake-times in the dyads. ▪ Absence of correlation between care recipient and caregiver daytime activity levels/behaviours. ▪ Infrequent use of sleep medications in the dyads, especially in caregivers.
Possible /Inconclusive Associations	▪ Effects of sharing a bed/room on the dyad's sleep. ▪ Organisation of a caregiver's sleep around the care recipient. ▪ Frequent/strong correlations between objective nocturnal sleep parameters in the dyads. ▪ Infrequent/weak correlations between subjective nocturnal sleep parameters in the dyads. ▪ Comparability in sleep fragmentation and night-time movement in the dyads. ▪ Synchronisation of the dyad's occurrence of daytime naps. ▪ Occurrence of concurrent sleep disturbances in the dyads. ▪ Dampened circadian rhythms in care recipients versus caregivers/infrequent, weak correlations in rhythm activity parameters. ▪ Frequency of use of sleep aids as a predictor of dyads in 'sleep distress'. ▪ Direction of disruptive nocturnal interactions: patients' sleep deficits affect caregivers' sleep. ▪ Psychological/physical distress, caregiver burden, coping strategies, disease severity/chronicity as predictors of poor sleep in the dyads.

4.4.2. Sleep-Impairing Factors in Care Recipient-Caregiver Dyads

With night-time interactions between care-recipients and informal caregivers being apparent [368], two studies suggested mutuality in the way poor sleep is experienced within these dyads [242, 247]. In that sense, each party could be rendered responsible for the other's sleep disturbance. However, this notion was only partially examined in the studies reviewed, half of which provided some inconclusive evidence suggesting interactions mainly initiated by the care recipients [233, 244, 285, 363, 368]. Indeed, while partner's sleep showed little ability to predict ratings of poor sleep in persons with Parkinson's disease, it was identified as a slight contributor of poor sleep in female caregivers, with a four-fold increase in the relative risk for poor sleep among caregivers whose care recipient also experienced problems with their sleep [233]. Several significant, moderate-to-high inter-correlations were also reported in a further study in the same population: greater patient sleep disturbance and diminished caregiver sleep duration, as well as poorer patient sleep and greater caregiver daytime dysfunction [285]. Yet, on spontaneous reports, only a small part of caregivers (just below 30%) claimed to have been disturbed by the patient [244].

Co-habitation and room-sharing were examined in four studies as potential mediators of sleep impairments [278, 363, 367, 368]. Findings among the studies were similarly discrepant. One study suggested that, especially in dyads who shared the same bed, and in co-habiting pairs, it was mainly the elders who initiated nocturnal interactions; yet, it remained unclear whether such interactions were also truly associated with sleep interruptions in the dyads [368]. In a concurrent study, no significant effects of co-habitation were found for both daytime and night-time activity, thus implying a dissociation between elder nocturnal activity and caregiver sleep disruption [278]. Possible explanations might be caregivers not sharing the same bedroom with the elders, and caregivers not spending much time with elders given that the majority of caregivers in this study were elders' adult children [278]. In the context of dementia, two studies also failed to show direct effects of room-sharing on the dyads' sleep [363, 367]. In the first study, sharing a room was not a significant predictor of dyads of concordant poor sleepers [363], whereas in the second study between-groups analyses yielded no differences in either self-report or objective baseline sleep measures between caregivers sharing and not sharing a bedroom [367].

In spite of the absence of findings based on prospective inter-correlations, four studies identified psychological distress in the form of mood disturbance and anxiety as a potential contributor to a dyad's sleep deficits [233, 244, 285, 363]. In three studies, poor sleep was consistently associated to one's own poor psychological well-being [233, 244, 285], whereas in dyads of persons with Alzheimer's disease and their family caregivers, patient psychological

co-morbidity and caregiver ineffective coping strategies were significant predictors of concurrently manifested poor sleep [363]. However, one study concluded with less nocturnal interactions in pairs whose elders reported high levels of depression [368]. One possible, yet unexplored, explanation might be that depressed elders disengaged themselves from their caregivers, which in turn might have led to caregivers experiencing less sleep disruption/deprivation over-night.

Disease severity and chronicity, heavily impacting on the patient's physical functioning and rendering the caregiving situation even more demanding, especially where the situation also involves physically affected caregivers, was highlighted – although not explicitly confirmed – as a potential sleep-impairing factor in some of the studies reviewed [233, 244, 251, 363]. One study revealed that approximately 45% of persons with Parkinson's disease and 30% of caregiving spouses claimed that their sleep had been at least moderately affected by the disease itself [251]. Among patients with advanced cancer and their family caregivers, patients' bodily pain and caregivers' global distress were associated with significant sleep deficits, even though potential interactions were not explored [244]. Similarly, McCurry et al. [363] reported that in dyads in which both the patient and the caregiver slept poorly, the overall caregiving situation was more difficult, co-affected by disease chronicity and patients' lower physical functioning. Surprisingly enough, however, caregiver health-related outcomes were not significant predictors of concordant poor sleep [363], but data on predictive variables were collected only at baseline, thus affecting emergence of associations and limiting reliability of the findings on possible changes across time.

4.5. Summary and Critique

Despite the dearth of studies in the field, promising findings have been yielded suggesting bi-directional associations in the sleep of care recipient-caregiver dyads. Concurrent and relatively comparable nocturnal sleep disruption/deprivation may be evident, where poor sleep quality, decreased sleep duration, and multiple awakenings may correlate with each other within the dyad. Alternatively, daytime activity levels may be uncoupled. In any event, care recipients' and caregivers' night and day rest patterns can be synchronised, particularly in co-residing dyads and/or in those in which caregivers organise their sleep around the patient. As a potential consequence, where the illness is more severe, and the overall situation is

more intense, distressful, and prolonged, patient-caregiver dyads may be at greater risk of concurrent sleep disturbances.

On closer look, however, evidence is largely compromised by several limitations, which undermine its generalisability and question its reproducibility. Firstly, the majority of studies relied on relatively small to moderate sample sizes (range 6 to 60 dyads) in the absence of a priori power estimation analyses, a fact that in itself poses a question as to whether larger sample sizes would allow for emergence of more [244, 247, 278, 367] or larger [285, 363, 368] associations between dyads' sleep variables [244, 247, 278, 363, 367, 368] and between sleep variables and impairing factors [278, 285, 363, 367, 368]. Multiple statistical comparisons in the presence of such small sample sizes might have increased the risk for Type I errors. Even studies with more than 100 dyads were cross-sectional in nature [233, 242, 251], thus precluding causal inferences.

Secondly, with the exception of one study where assessment spanned over a six-week period [367], prospective assessments took place over a limited period of three days [247], and one [244, 363] or approximately one (ranging from 6 to 9 days) [278, 368] week. While the exploratory nature of these studies as well as difficulties to obtain objective data on sleep for extensive periods of time are certainly acknowledged, this narrow time frame of observation may have been inadequate to allow for latent co-variances in the sleep of dyads to emerge. One such example is the inconsistent findings regarding the impact of sharing a bedroom on the dyads' sleep. Furthermore, in two studies, unavailability of data for all days of assessment was reported, which may have produced an even more confined true assessment period [247, 363]; similarly, Pollak et al. [368] reported variability in the assessment period ranging from 6 to 8 days. It is reasonable to assume that such inconsistencies might also have interfered with study findings.

Thirdly, all but one [367] study aimed to recruit partners or family members rather than using a broader definition of the caregiver; yet, even in the study of Lee et al. [367] the final sample exclusively consisted of family members, in their vast majority (~80%) patients' spouses. One reason for this might be the short sampling period unable to allow for inclusion of all possible categories of caregivers. Closely related to this trend, the majority (63%-100%) of caregivers were women over a mean age of 55. This fact may have influenced reports of incidence of sleep disturbance, as poor sleep might have been the result of associated menopausal symptoms, hyperarousability or past sleep problems, rather than just the caregiving experience itself or patients' sleep patterns. Perhaps, inclusion of predominantly or exclusively male caregivers could result in different associations.

Fourthly, only one study systematically explored triggers of concurrent sleep disturbances in the context of dementia [363], whereas three only explored the impact of sharing a bedroom [367, 368] or providing care for patients versus healthy elders [278]. Another study, while gathering some pertinent data, never went on to explore the possible associations between these triggers and dyadic sleep/wake patterns [244]. Especially with regard to the latter, evidence as to the nature of factors that co-affect sleep of patients with cancer and their caregivers still remains near to zero.

Fifthly, all studies were conducted in a phase of illness experience where no major events were taking place, such as diagnosis, active treatment, health-care transition, or relapse, while in at least two studies [242, 244], patients' functional status was good to very good in the majority of the sample. In addition, in at least four studies [233, 285, 363, 367], time since diagnosis exceeded an average of approximately four years. Seen together, these facts might have led to inclusion of dyads who, in the absence of major influential situations, might have found a balance in their sleeping arrangements so as to avoid the considerable effects of possible disordered sleep patterns and overall needs on one another. Consequently, a gap in the relevant research seems to exist.

Lastly, in the study of Gibbins et al. [244], inappropriate statistical methods may have obstructed associations from emerging, while inadequate association of the definition of daytime naps with individuals' inactivity may have led to overestimation of the actigraphic measurements. These serious limitations further limit relevant knowledge in the context of cancer care, but at the same time dictate the need for more systematic research.

PART II

CHAPTER 5.
Study Methodology

5.1. Introduction and Research Problem

Thus far, analysis of current research evidence has emphasised that altered sleep/wake patterns represent a highly disturbing symptom that can severely affect a person's life in multiple ways and, depending on its nature, potentially over extended periods of time (Chapter 1) [49]. Chapter 2 clearly demonstrated that women diagnosed with breast cancer constitute a patient population susceptible to sleep impairment, which can be considerably exacerbated throughout chemotherapy treatment. Of note, night-time restlessness and daytime sleepiness may be present before, maximised during, and persist even after treatment for reasons related to a host of individualistic triggers whose underlying link to sleep disruption/deprivation is yet to be understood. Furthermore, Chapter 3 confirmed that persons providing informal care to people with cancer may also suffer from sleep loss that is possibly, yet not exclusively, related to the experience of providing continuous care during the intense period of patient treatment. Drawing upon theoretical frameworks (attachment theory [338]; "sleep ritual" theory [369]) proposing a link between close relationships and sleep regulation, it was then argued (Chapter 4) that within such closely related pairs as a patient-caregiver dyad, poor sleep may be simultaneously experienced. In a similar fashion, because important aspects of the care recipient's and caregiver's well-being – sleep functioning included – are linked through an interactive and dynamic process known as interdependence [370], it was postulated that individualistic and dyadic triggers of sleep deprivation and/or disruption [62] may be concurrently present and exert important cross-partner effects on a dyad's sleep.

Women with early stage breast cancer and their caregivers should be able to continue their lives free of sleep problems and the associated discomfort. To this end, effective sleep assessment methods are required that go beyond the individual: data are simultaneously taken into account, synthesised, and contrasted to establish a dyad's levels of sleep quality and sleep disturbance [366]. Including the perspectives of both care recipient and caregiver can increase our understanding of dyadic processes that take place during the natural course of caregiving, facilitate the investigation of latent interactions, and highlight potential areas that may hinder or enhance implementation of interventions [371]. Moreover, if these dependen-

cies were examined over time, trajectories of change could be charted, and individual and/or dyad characteristics related to change could be determined [371]. In this sense, it is important to conduct studies that provide longitudinal and simultaneous data on sleep/wake patterns/problems for both populations, and identify key time points and impairing, protecting, and/or interacting factors to form a knowledge base for further intervention and guide development of effective treatments targeted to the specific needs of care dyads.

Despite its important implications, to date, dyadic sleep research in the context of cancer care is scarce and less than optimal [366]. Current knowledge is lacking in that (a) sleep/wake pattern trajectories of people with cancer and their informal caregivers have never been concurrently investigated at distinct time points during active-phase treatment; (b) sleep/wake patterns of people with cancer and their informal caregivers have never been prospectively assessed in true dyadic studies; (c) sleep quality and sleep disturbances of informal caregivers of people with cancer has never been prospectively assessed; (d) interacting sleep-impairing factors and their patterns of change over time have not yet been explored in women with breast cancer and their caregivers; (e) sleep history and sleep hygiene have never been explored as covariates of alterations in the sleep patterns of people with cancer and their informal caregivers; and (f) sophisticated statistical procedures to analyse dyadic sleep data have only scarcely been used in previous studies of care dyads, but never in the context of cancer care.

In light of the aforementioned limitations, this Chapter will discuss issues pertinent to the design of a dyadic sleep study and the analysis of dyadic data. Furthermore, rationale for the selection of variables and relevant measures used in the research project conducted also will be provided.

5.2. Deciding upon the Research Method and Design

Whilst the necessity for mixed-methods studies integrating quantitative and qualitative data to aid clarification of underlying mechanisms in the development of dyadic sleep disturbances has been previously acknowledged [366], unforeseen budget restrictions in the current study (see also Section 8.2) prevented inclusion of both quantitative and qualitative components as well as purchase of important measurement equipment (i.e. wrist actigraph devices) [49], and inevitably led to re-examination of all initial methodological and design plans. Therefore, it was decided that for this exploratory, observational study only quantitative

methods based on collection of self-reported sleep data would be used as a first step to investigate and compare trajectories of change in different sleep and wakefulness parameters, and explore relationships that could point to statistically and clinically significant predictors of sleep impairment in care dyads. In line with the study's aims and research questions, self-reported quantitative sleep data were regarded to be appropriate for testing inter-relationships among key variables within a certain time point, between the time points of observation, and between the two groups of participants. In any case, study limitations arising as a consequence of the afore-mentioned developments/decisions are explicitly acknowledged in the Chapter 8.

With the amount of dyadic sleep research being sparse, a descriptive, correlational research design was pursued, which allowed for factor-isolating ("what is this?") and factor-relating ("what is happening here?") questions to be asked as originally proposed in Dickoff and James' hierarchy of researchable questions [372]. Moreover, in line with current recommendations for sleep research [10, 43, 49], distinct assessment points over the course of chemotherapy were identified to allow for potential changes in the care dyads' sleep/wake patterns to be explored. This prospective, repeated-measures design was considered to be particularly useful in order to support inferences regarding the role of sleep correlates in the development of sleep deficits in the dyads, as well as to allow the directionality of the relationships to be tested. Four time points have been regarded as critical for the examination of a patient's sleep patterns throughout adjuvant chemotherapy for breast cancer [119]: the period close to treatment initiation; the week after the first CThC; the weeks after the third and/or fourth CThC; and the period following the end of treatment. These time points were considered for inclusion in the present study. Adopting time points similar to those reported in the literature was also viewed as a means to increase the study's external validity, including comparability with relevant research and generalizability [373].

Importantly, the present study was conceptualised as a true dyadic one [371], where both members of the care dyad would be invited to provide data, and dyads rather than individuals would be used as the unit of analysis (see Section 5.5) [293, 371]. Lyons and Sayer [371, 374] argue that methods that fail to address the hierarchical nature of the dyad also fail to demonstrate variation, both within and between dyad processes that are paramount to understand them [371, 374]. What is more, the *standard dyadic design* was adopted, in which each person is linked to one, and only one, other person; in other words, each person is member of one and only one dyad [293]. In the standard dyadic design, not only both persons are measured, but also, at least for some of the variables, both are measured on the same variables (i.e. reciprocal design) and with the same (or equivalent) measures [293]. Where feasi-

ble, measurement of a variable of common interest was conducted using versions of the same questionnaire for patients and caregivers. In addition, in longitudinal models points of assessment must be the same for both members of the dyad so that comparisons between patients' and caregivers' variables can be tested. Given the scarcity of longitudinal sleep research in caregivers of people with cancer [10], time points for the assessment of informal caregivers' sleep/wake patterns were selected to be the same as those for the patients.

5.3. Selecting Outcome and Predictor Variables

Outcome Variables: Sleep/Wake Parameters

Drawing upon current recommendations [43, 49], data on the dyad members' subjective sleep quality, subjective sleep efficiency, sleep latency, total sleep time, nocturnal awakenings, wakefulness after sleep onset, daytime sleepiness, and use of sleep aids were planned to be collected. As analysed in Paragraph 1.4, information on individuals' need for napping in the daytime, duration of daytime naps, leg restlessness, early morning awakenings, and feelings of restfulness upon wakening is considered equally important to adequately describe impaired sleep and wake patterns, therefore they were also included as outcome variables to be explored.

Predictor Variables and Covariates: Health Outcome Parameters

The following physical and psycho-behavioural parameters were considered for inclusion in the final set of predictors: sleep hygiene, nocturnal disturbance, physical symptom burden (patients), psychological burden, coping strategies, and caregiver burden (caregivers). All analyses were also adjusted for the effects of demographic/clinical covariates, for which a link to sleep/wake patterns has been proposed, such as past sleep history, performance status and physical activity. Predictor variables and covariates were selected based on findings of recent literature reviews [119, 182, 366], and according to the theoretical frameworks of sleep/wake impairment analysed in Chapter 1 in line with current guidelines [61]. First, according to Lee et al.'s Conceptual Model of Impaired Sleep [62], a number of triggers were considered that may lead to sleep deprivation (e.g. inadequate sleep hygiene, caregiving burden etc.) or disruption (e.g. psychological and physical burden, nocturnal disturbance), and

eventually result in sleep loss. Second, Spielman's Three-Factor Insomnia Model [64] guided the selection of predisposing (e.g. sleep hygiene), precipitating (e.g. psychological and physical burden, nocturnal disturbance, caregiver burden), and perpetuating (e.g. sleep hygiene, psychological burden, coping styles) predictors of sleep loss. The same model was used to form the set of covariates (confounding variables): predisposing (e.g. age, past sleep history), precipitating (e.g. treatment-related stressors), and perpetuating (e.g. reduced physical activity) were considered. Third, in line with the dyadic paradigm [293, 294, 366, 374], not only individualistic but also dyadic covariates were considered (e.g. sharing the same house/bedroom, type and duration of relationship). Importantly, the ever-changing and possibly non-linear nature of sleep-impairing factors was acknowledged [61], which informed the inclusion of both time-invariant (measured once) and time-varying (measured repeatedly) predictors [375, 376].

5.4. Screening for Adequate Measures

Whilst it was anticipated that demographic and clinical information would be provided by the participants themselves, or extracted from patient case notes, completion of a set of validated questionnaires was planned to form the basis of data collection activities. Two parameters have been identified as being particularly important in this context [377]. First, psychometric efficiency (i.e. validity, reliability, responsiveness to change) of the selected questionnaires is required to ensure that internal validity of a study is preserved. Second, proved acceptability and feasibility (i.e. readability, length) are paramount to prevent data collection from creating unwanted burden to participants. Therefore, a systematic search for available measures according to variable category was performed. The questionnaires identified were contrasted and compared taking into consideration the afore-mentioned criteria, which ultimately led to the selection of the most appropriate measure per variable category. Of note, given the multi-factorial nature of the study which posed the requirement for use of a number of different questionnaires, it was decided that, where possible, brief rather than lengthy psychometrically fit questionnaires would be preferably selected.

Performance Status

In oncology, the two most commonly used scales to assess performance status (PS) are the Karnofsky Performance Status scale (KPS) [378] and the Eastern Cooperative Oncology

Group Performance Status scale (ECOG PS) [379]. Compared to the KPS which is a 10-item measure, ECOG PS is simpler (5 items) and can be more easily used by patients and caregivers [380]. Although the scale is generally completed by health professionals [380-382], research has shown that patients can make reliable self-assessments of their PS, thus further enhancing assessment precision [381]. Therefore, in line with current recommendations, self-assessments of PS were planned to be performed in this study via use of the ECOG PS scale.

Physical Activity

Methods to measure physical activity are classified as direct or concurrent (e.g. measurement of bodily movements or energy expenditure) and indirect or surrogate [383]. Indirect or surrogate methods include physiologic measures (e.g. cardiorespiratory fitness, percentage of body fat) and self-report measures such as surveys, multi- or single-item questionnaires, activity diaries, and recall interviews [383]. In this context, questionnaires are inexpensive, do not have a large participant burden, and can provide prevalence estimates of intensity, frequency and duration of physical activity that can be used to categorise respondents into activity categories [383]. Admittedly, these questionnaires share the weaknesses of introducing recall bias and of being unable to account for all types of activity performed [383, 384]. However, well-established and validated questionnaires can be usefully introduced in observational studies. Over fifteen physical activity scales exist [384-389], the majority are lengthy ones and are used infrequently with patients with cancer or informal caregivers. As previously mentioned, to prevent participant burden, focus was directed on the shorter scales, preferably those comprised of one item. Nine studies were identified in the relevant literature where single items were used to rate frequency and intensity of moderate and/or vigorous physical activity [240, 390-397]. However, a series of limitations, including lack of proper validation [240, 390-396], unclear definition of ‘inactive versus active’ [240, 390], and exclusive focus on either moderate [391] or vigorous [394, 395] physical activity, led to the retention of a psychometrically fit (validity, test-retest reliability) [398], single-item scale (Appendix 10) previously used in a study of survivors of Hodgkin’s lymphoma [397]. Although this scale has not been used previously with patients with breast cancer or informal carers, it is not disease- or context-specific and therefore it was deemed appropriate in this context.

Sleep/Wake Parameters

Although sleep/wake patterns can be assessed objectively by a number of different modalities, including polysomnography, sleep latency testing, and actigraphy, self-reported sleep measures serve as a non-invasive substitute that have been validated and verified to be useful instruments for research purposes [43, 49]. To ensure that all available options in the collection of subjective sleep data had been examined, the use of daily sleep diaries or sleep questionnaires, or a combination of the two, was taken into consideration. Daily recorded sleep diaries/logs can be usefully implemented to monitor sleep/wake patterns over a week's period; yet, they are not always standardised as research tools and also can be much harder to keep for prolonged periods than standardised questionnaires [182]. This burden is of importance to studies implementing a longitudinal design, and seeking to recruit people otherwise occupied during an active treatment period. Therefore, to prevent participant burden and avoid high rates of missing data, the option of using validated sleep questionnaires seemed more feasible, practical and reasonable. As previously mentioned, self-report research questionnaires are easy to obtain, administer and complete [4]. They also measure perceptions; hence, they can provide data on the more qualitative features of sleep such as sleep quality, feelings upon arising, or daytime sleepiness and dysfunction [49]. Certainly, several limitations in their use exist (e.g. potential for recall bias; lack of flexibility due to time frames for recall; unclear psychometric properties), which are acknowledged and explicitly discussed in Chapter 8. However, as subjective sleep data may correlate more strongly with self-reports of health-related outcomes, data deriving from sleep questionnaires can allow for intra- and inter-personal relationships to be more thoroughly examined. Therefore, in the context of this exploratory study, their inclusion has been instrumental in the explicit investigation of (inter-) relationships within and between the dyads.

Numerous sleep questionnaires have been identified in the relevant literature [13, 43, 49, 251, 399-403], which can be generally classified into two broad categories: generic measures of sleep/wake parameters and measures of daytime sleepiness (such as the Epworth Sleepiness Scale [404], the Functional Outcomes of Sleep Questionnaire [405], and the Stanford Sleepiness Scale [406]). Given that the present study aimed to explore a wide range of sleep/wake patterns rather than merely focusing on daytime sleepiness/dysfunction, only generic sleep measures were taken into consideration. Of these, ten questionnaires had been used in previous studies with patients with cancer, and were further examined (**Table 16-A2**). Comparisons revealed that the Pittsburgh Sleep Quality Index (PSQI) [407], the Medical Outcomes Study-Sleep Scale (MOS-SS) [408] and the Insomnia Severity Index (ISI) [409] had undergone the most extensive psychometric evaluation. These instruments

have been used in diverse clinical populations and are similar in length and ease of use. Originally, the PSQI and the MOS-SS assess sleep over the past 28 to 30 days, whereas the ISI has a shorter recall time frame (past 14 days). However, the ISI does not elicit information on the person's bed/wake-times, sleep efficiency, sleep latency, and sleep duration as the PSQI and partly the MOS-SS do. Therefore, it was excluded from further consideration. Conversely, the PSQI was found to have a stronger established validity, reliability, responsiveness and interpretability, whereas the MOS-SS has minimal data on responsiveness and no available data on interpretability. In addition, the PSQI is the most widely used self-report questionnaire among patients with breast cancer [119] and caregivers of adults with cancer [182]. Given that psychometric soundness for a self-report sleep measure is of utmost importance, and that comparability of similar studies in this context is highly desirable, the PSQI was considered to be the most appropriate instrument for this study.

Bearing in mind that no perfect self-report sleep measure exists, a number of questions were also considered to assess additional essential sleep parameters reported in the literature [119], but not covered or not thoroughly addressed in the PSQI. In brief, these questions addressed the following sleep parameters: (a) need for daytime napping and average duration of naps per day; (b) feelings of restfulness upon arising in the morning regarding the extent of restfulness; (c) occurrence and frequency of leg restlessness; (d) early, unplanned awakenings in the morning; (e) extent of daytime sleepiness; and (f) average number of nocturnal awakenings per night. These parameters were combined to formulate a separate form that was administered to participants alongside the PSQI.

Sleep History

Sleep history questionnaires are commonly used in clinical practice to elicit information regarding an individual's past and current sleep habits, and can be a useful adjunct in identifying persons at risk for disordered sleep [410]. Numerous, and in most cases considerably extensive, sleep history questionnaires are available online, with their content reflecting the needs of different professionals caring for clinically different individuals in different sleep clinics. This abundance suggests that development of these questionnaires to date has been largely arbitrary; hence, no questionnaires with definitely established properties exist. For the purposes of the present study, six questions were extracted from a standardised sleep history used in a previous study of people with advanced cancer and their informal caregivers [244]. Questions referred to past sleep history, sleep problems due to cancer diagnosis, nico-

tine/alcohol consumption, and sleeping arrangements. Although validity remains questionable, it was nevertheless believed that comparability between the studies could be promoted.

Sleep Hygiene

Sleep hygiene questionnaires are useful diagnostic tools for patients and their partners [411]; yet, no studies have tested the use of such instruments with people with cancer and their informal caregivers [182]. Upon systematically searching for reliable and valid tools, four instruments addressing sleep hygiene practices were identified that have been used with healthy individuals, insomniacs, or people with post-traumatic stress disorder [412-415]. These tools were compared regarding their brevity, suitability, and psychometric properties (**Table 17–A2**). Admittedly, each of these measures has problematic features, and questionable reliability and validity. Nonetheless, the Sleep Hygiene Index (SHI) was deemed the most appropriate questionnaire for the purposes of this study for its brevity, ease of use, and acceptable psychometric properties. What is more, the SHI yields a global score that can be usefully implemented in statistical analyses.

Physical and Psychological Burden

Current guidelines suggest that symptom assessment instruments should be comprehensive capturing symptom prevalence, severity and distress, easy to understand and complete, accurate, reliable, repeatable, and sufficient for decision-making [416]. Yet, no questionnaire exists that meets all criteria for an ideal instrument, hence the final choice very much depends on the purpose of each individual study [416]. In a recent systematic review of cancer symptom assessment instruments, Kirkova et al. [416] identified twenty-one tools appropriate for use in cancer care practice. Selection of the most appropriate tool for the present study was informed by the results of this review. Seven instruments were symptom-targeted and/or included less than five items, thus they were not taken into further consideration. Moreover, since this study aimed at collecting data based on patient and caregiver self-reports, two instruments (Reduced Expanded Support Team Assessment Schedule [417], and Pain and Symptom Assessment Record [418]) were excluded as they are observer-rated. One tool (A Computerized Symptom Assessment Instrument [15]) was excluded as completion is computer-assisted rather than paper-and-pencil, and is recommended for use in the radiotherapy setting. Two more instruments (Cambridge Palliative Assessment Schedule [419],

and The Symptom Monitor [420]) were excluded as they had been developed for use in the palliative care setting only. Therefore, nine instruments (Symptom Distress Scale [421], Rotterdam Symptom Checklist [RSCL] [422], Edmonton Symptom Assessment Scale [423], Memorial Symptom Assessment Scale [MSAS] [424], Oncology Treatment Toxicity Assessment Tool [425], Worthing Chemotherapy Questionnaire [426], M. D. Anderson Symptom Inventory [MDASI] [427], The Symptom Experience Scale [428], and the Canberra Symptom Score Card [429]) were deemed appropriate for the purposes of this study and their properties were fully examined. Of these, it was determined that the RSCL, the MSAS, and the MDASI had undergone the most extensive psychometric validation and were comprehensive, yet not too long to cause participant burden. However, the MSAS had a stronger established validity, reliability, responsiveness and interpretability than the RSCL, and it covered more areas of symptom burden and was easier to understand than the MDASI. In addition, the MSAS addressed all three important symptom parameters (i.e. duration, severity and distress) compared to only one (distress) addressed by the RSCL and two (frequency, severity) addressed by the MDASI. For these reasons the MSAS was considered to be most appropriate for this study.

It should be stated here that a separate systematic search was initially conducted for validated measures of psychological burden, namely measures of anxiety and depression. The State-Trait Anxiety Inventory (STAI) [430], the Center for Epidemiologic Studies-Depression (CES-D) [431], the Beck Anxiety Inventory [432], the Beck Depression Inventory [433], and the Hospital Anxiety and Depression Scale (HADS) [434] emerged as the most frequently used measurement tools in studies with people affected by cancer [435]. Whereas the psychometric properties of the STAI and the CES-D have been extensively tested in this population [435, 436], the scales are lengthy (measuring 40 and 20 items, respectively) and may prove burdensome. Therefore, the need for a more brief measure led to the retention of the HADS, which has acceptable validity and reliability [435, 437], and also benefits from a concurrent assessment of individuals' levels of anxiety and depression. Nevertheless, during ethical approval review of the current study, the Research Ethics Committee (REC) raised concerns to the use of a measure of emotional distress in the specific context on the grounds of emotionally evocative questions possibly increasing the levels of distress of vulnerable patients and carers at a sensitive point after cancer diagnosis. To avoid unwanted participant distress and to meet the REC's requirements, it was decided that the HADS be removed from the study's instrumentation set. Psychological burden was measured through the MSAS psychological subscale instead.

Coping Strategies

Livneh and Martz [438] point out that despite the gradual improvement of conceptual, structural and psychometric aspects of the available coping scales, many inadequacies still remain. Lack of conceptual clarity, questionable factor structure, and inappropriate reliability estimates are only a few of the aspects criticised in the literature [439], which may in part stem from inconsistencies inherent in the definition and conceptualisation of coping itself [438, 440]. For instance, dispositional (or trait-like) and situational (process or state-like) views of coping can result in two types of assessment tools [438]. As previously stated, selection of the coping scale to be used in this study was based on a measure's brevity, comprehensiveness, and psychometric soundness [440]. A situation-oriented instrument was regarded to be most suitable for the prospective nature of the study. In addition, and in agreement with previous research, the selection process favoured instruments which can provide measures of approach or engagement coping, and avoidance or disengagement coping that have been associated with salutary and poor psychosocial outcomes, respectively. Seventeen instruments were identified as being commonly used to assess individual coping styles. Three of them had been originally developed to evaluate responses or adjustment to cancer (Mental Adjustment to Cancer [441], Mini-Mental Adjustment to Cancer [442]) and mastery skills (Mastery Scale [443]) rather than coping, whereas the Coping Strategies Questionnaire [444] assesses coping strategies exclusively related to pain. Hence, these measures were not taken into further consideration. Thirteen measures underwent full examination of their properties (**Table 18-A2**). In order to avoid increasing participant burden, six instruments (Ways of Coping Checklist [445], Ways of Coping Questionnaire [446], Coping Strategies Inventory [447], Measure of Daily Coping [448], COPE Inventory [449], Jalowiec Coping Scale [450]) were excluded as they were deemed too long (ranging from 55 to 72 items). Moreover, due to their dispositional orientation, three instruments (Brief Approach/Avoidance Coping Questionnaire [451], Coping Strategy Indicator [452], Coping Inventory for Stressful Situations [453]) were not deemed suitable for this study. Similarly, the Life Situations Inventory [454] was disregarded because it only addressed a hypothetical situation and had no established psychometric data in populations of people affected by cancer. Because of the lack of validation data in cancer populations and of an ambiguous scoring system, the Coping Responses Indices scale [455] was also excluded. Of the two remaining instruments, the Cancer Coping Questionnaire [456] uses a patient-oriented format rather than a neutral one, thus rendering administration to informal caregivers difficult without prior vast adaptation, which might influence criterion validity. Therefore, the Brief COPE scale [457] was considered to be the most appropriate for use in the present study.

Caregiving Burden

Over the last three decades, caregiver burden has evolved as one of the most rigorously researched areas in the caregiving experience [458]. Closely related to this trend, development of burden assessment instruments has grown in terms of theoretical soundness, complexity and rigour of psychometric testing [458]. Two systematic reviews of the relevant literature identified seventeen burden instruments for use with informal caregivers of chronically ill people, developed between 1980 and 2002 [216, 458]. Considerable variation, strengths and limitations of these instruments were reported, which informed selection of the most appropriate measure for this study. A measure assessing both objective and subjective aspects of burden was regarded most desirable. However, none of these few instruments (Caregiver Subjective and Objective Burden Scale [459], Burden Assessment Scale [460]) had undergone rigorous testing, and selection of a generally poor measure of burden was definitely unwanted. Therefore, all available measures were examined irrespective of their specific focus. Upon initial inspection, eight instruments were deemed to be the least psychometrically sufficient and/or feasible to be taken into further consideration. Yet, of the remaining nine measures, seven instruments were also excluded for various additional reasons including the following:

- Absence of data on the instrument's factor structure (Zarit Burden Interview [461], Caregiver Appraisal Scale [462], Burden Assessment Scale [460], Caregiver Burden Scale [463])
- Uni-dimensionality in the assessment of subjective burden (Zarit Burden Interview [461])
- Dichotomous response format that limited sensitivity of the instrument (Caregiver Strain Index [464], Caregiver Perceived Burden Scale [465])
- Questionable content validity (Caregiver Perceived Burden Scale [465], Burden Assessment Scale [460])
- Instrument length exceeding 50 items, possibly increasing participant burden (Caregiver Experience Assessment [466])
- Questionable scoring system (Caregiver Experience Assessment [466]).

After the Caregiver Reaction Assessment Scale (CRAS) [467] and the revised Bakas' Caregiving Outcomes Scale (BCOS) [468] having been thoroughly examined, it was

determined that only minimal data on the BCOS's psychometric properties in caregivers of patients with cancer were available. Therefore, the CRAS was retained for use in the present study.

In sum, the final instrumentation set for the current study comprised the following measures: the ECOG performance status scale; a single-item physical activity scale; the PSQI; a study-specific form addressing additional sleep/wake parameters; a sleep history inventory; the SHI; the MSAS; the Brief COPE; and the CRAS.

5.5. Analysing Data from Dyadic Studies

There are a number of challenges to consider when analysing data deriving from dyads. First, observations from individuals within the same dyad are most likely non-independent [371]. This is because members of the care dyad are likely influenced by similar contextual factors, or influence one another directly [293, 371, 469]. Kenny et al. [293] defined dyadic non-independence as follows: if two scores from the two members of the dyad are compared and found to be non-independent, then those scores are likely to be more similar to (or different from) one another than are two scores from two people who do not belong to the same dyad. In this case, there is less unique information than the total sample size would suggest [371]. Ignoring the nested structure of this type of data leads to bias in the estimates of the error variance, which in turn distorts the estimates of standard errors, *p*-values, confidence intervals and effect sizes [293, 371, 469].

Second, ordinary least squares (OLS) procedures used to measure dyads such as bivariate correlations, intraclass correlations, paired samples *t*-tests, analysis of variance (ANOVA) and repeated measures ANOVA have limitations in processing dyadic data, basically because they create measures of dyadic properties from individual level data [370, 374]. What is more, standard errors can be underestimated in these procedures, especially as variance within dyads increases, thus leading to biased estimates of coefficients and a greater risk of Type I errors. Therefore, the use of analytic methods that take into consideration (and control) for the shared variance within the dyad has been emphasised as being critical [293, 374].

Multilevel modelling (MLM) (that is to say, hierarchical linear modelling) provides a powerful and flexible framework for analysing dyadic data [293, 374]. As the name suggests, in a

multilevel data structure, there are multiple levels within the data; in other words, there is a hierarchy of units, with one set of units nested within another [293]. In MLM for dyads the responses of the members of the dyad are conceived as Level 1 units nested within the Level 2 unit, the dyad [371, 374]. In over-time data from dyads, there is one additional factor: time. However, the two-level structure of the data is retained, given that time and person are usually crossed, not nested [293]. This means that, for a given dyad, the level of time is the same for the two persons at each time point [293] (see **Figure 5-1**).

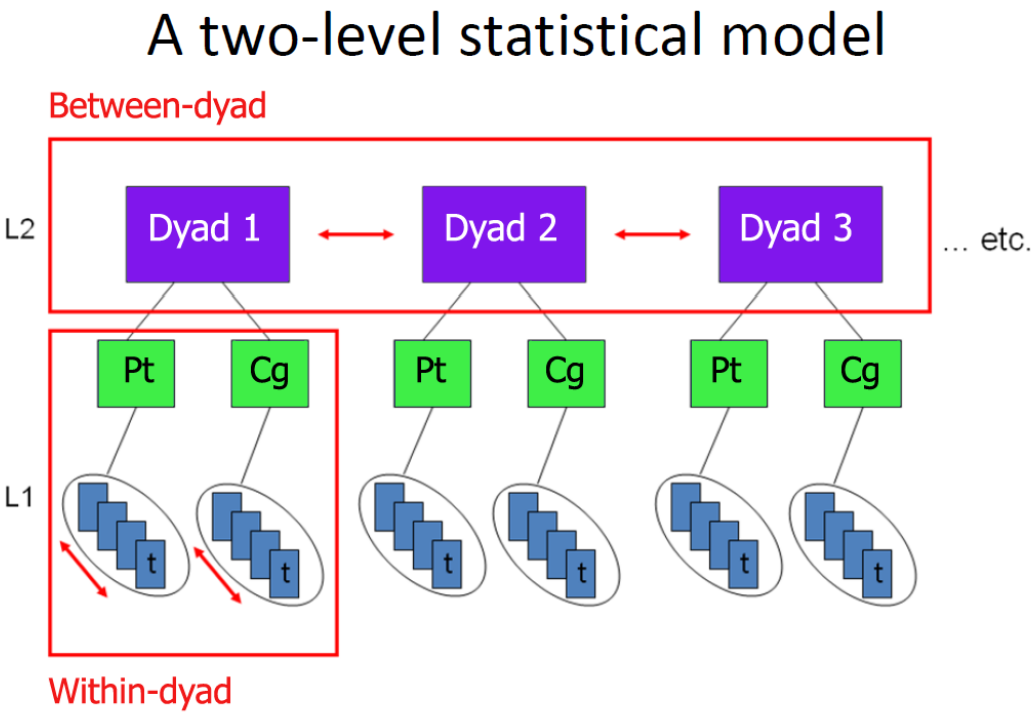

Figure 5-1. A two-level statistical model for patient-caregiver dyads (*Note:* Pt – patient; Cg – caregiver; L1 – level 1; L2 – level 2; t – assessment point). *Adapted from:* HLMs for dyadic data: Multivariate Outcomes Approach. School of Psychology; UMass Amherst. http://www.psych.umass.edu/uploads/people/79/Dyads_with_Multivariate_Outcomes.pdf

The multivariate hierarchical linear model (MHLM) proposed by Raudenbush et al. [376] is a combination of the cross-sectional model for matched pairs and the longitudinal model for individual change. This longitudinal matched-pairs model is fit to the repeated assessments of the outcome variables for both members of the dyad, and compares patterns of change in

trajectories for both of them [374]. This approach uses indicator variables to identify patient and caregiver variables within one model so that it can demonstrate how dyad members may change differently over time while controlling for the non-independence of scores among the dyad members [371].

There are compelling advantages in the use of MLM when estimating longitudinal trajectory models for dyads over the more traditional OLS procedures [370, 374]. First, each member of the dyad can have a unique trajectory, specified to differ in pattern (e.g., change can be linear for patients and nonlinear for caregivers) and magnitude (e.g., the rate of change can be steeply negative for patients and flat for caregivers) [374]. MLM allows the incongruence of the average trajectories for each member of the dyad to be directly tested for significant differences at the intercept (the predicted score at a specific occasion of measurement), the slope (rate of change), or both, using a generalised multivariate hypothesis test [370, 374]. Second, MLM takes into consideration non-independence within dyads, controls for the autocorrelation among the repeated measures, and adjusts the error variance for the interdependence of member outcomes within the same dyad. This adjustment results in more accurate standard errors and their associated hypothesis tests [370, 374]. Third, the model allows for unbalanced study designs in models for dyadic data and permits inclusion of data from a dyad even when one partner is missing data points under missing at-random assumptions [371, 376]. Conversely, repeated measures ANOVA requires a full dataset with no missing values, whereby any data missing lead to the automatic listwise deletion of cases. With MLM it is possible for only one member of the dyad to contribute data or for the pattern of missing responses to be different for each partner; however, no cases are excluded due to incomplete data. Fourth, MLM allows for uneven spacing between assessment points and variation in the number of assessments completed by participants [470]. Last but not least, MLM allows for variables that might affect dyads' trajectories to be investigated. Given the importance of longitudinal MLM in the estimation of dyadic models over time [293], this statistical method was chosen to facilitate interpretation of changes in the sleep patterns of dyads in the present study.

5.6. Summary

A number of instrumental methodological issues were taken into consideration that shaped overall design procedures for this study. Identification of gaps in the current relevant re-

search was a crucial first step. Findings deriving from comprehensive literature reviews (rigorously analysed in the previous chapters and recapitulated here) constituted the basis upon which theories were applied and hypotheses were generated. The correlational nature of these hypotheses, the dyadic nature of the relationships to be investigated and the requirement for robust procedures to measure change over time and grasp relationship direction subsequently informed decisions about the appropriateness of the research design to be employed. Identification of the outcome (dependent) and predictor (independent) variables was the next important step. This was followed by careful consideration of measurement issues (e.g. current recommendations, feasibility, acceptability, reliability, validity, comprehensiveness) that guided the screening process for the selection of adequate available measures. Inextricably linked to all afore-mentioned issues, a data analytic strategy was devised that took into consideration advantages and disadvantages of different analytic approaches in answering the questions posed in the current study.

CHAPTER 6.

Study Aims and Methods

Reporting of this study was conducted in accordance to guidelines contained within the STROBE Statement [141, 142]. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations were developed to improve the quality of reporting of observational studies, to enable strengths and weaknesses of a study to be revealed, as well as sound interpretation and application of study results to be facilitated [141]. **Table 7-A2** provides a checklist of the twenty-two items required to be addressed in reports of observational studies as included into the STROBE Statement.

6.1. Aims & Research Questions

The primary aim of this PhD study was to longitudinally explore sleep/wake patterns of dyads of women with early stage breast cancer and their informal caregivers throughout adjuvant chemotherapy treatment, thus identifying interrelations in their sleep/wake parameters. Related hypotheses included the following:

Hypothesis 1: In patient-caregiver dyads living in a close caring relationship, similarities in the shape of their trajectories of sleep/wake parameters exist as dyads go through the different stages of adjuvant chemotherapy for breast cancer.

Hypothesis 2: In patient-caregiver dyads living in a close caring relationship, sleep/wake parameters and/or changes in sleep/wake parameters are moderately correlated as dyads go through the different stages of adjuvant chemotherapy for breast cancer.

Hypothesis 3: In patient-caregiver dyads living in a close caring relationship, sleep/wake impairments of caregivers are comparable (in terms of frequency/severity) to that of patients going through the different stages of adjuvant chemotherapy for breast cancer.

Based on existing literature, a secondary aim was to examine how different sleep-impairing factors may affect patients' and caregivers' sleep/wake patterns over time, also taking into consideration the complexity of mechanisms interfering with a dyad's sleep quality, where a woman's sleep may not only be influenced by her own distress but also by her carer's, and vice versa. Relevant hypotheses included the following:

Hypothesis 4: Increases in own physical and psychological burden, disruptive sleep hygiene behaviours, nocturnal sleep disturbance, and maladaptive coping strategies, controlled for significant demographic/clinical covariates, are independently predictive of poor sleep/wake outcomes in women receiving adjuvant chemotherapy for breast cancer.

Hypothesis 5: Increases in own psychological burden, caregiving burden, disruptive sleep hygiene behaviours, nocturnal sleep disturbance, and maladaptive coping strategies, controlled for significant demographic/clinical covariates, are independently predictive of poor sleep/wake outcomes in informal caregivers of women receiving adjuvant chemotherapy for breast cancer.

Hypothesis 6: Cross-partner effects of the afore-mentioned sleep-impairing factors exist, where dyad members' sleep/wake patterns not only are influenced by own distress but also by their care partners'.

Thus, the research questions for this study were:

1. What are the trajectories of change of patients' and caregivers' sleep/wake parameters throughout the period of adjuvant chemotherapy for breast cancer?
    - How similar or dissimilar are patients' and caregivers' trajectories of change of their sleep/wake patterns?
    - Which sleep/wake parameters show the greatest interdependence across the dyads?
2. How are changes in triggers of sleep deprivation associated with changes in the patient's and caregiver's sleep quality adjusted for own demographic/clinical covariates emerging at both the individual and dyadic level?
    a. Are changes in women's physical burden, caregiver's health burden, and dyads' sleep hygiene practices and psychological burden associated with changes in their own sleep/wake parameters?

b. Are there cross-care-partner effects of the aforementioned triggers on the dyad members' sleep/wake parameters?

6.2. Study Design

This was a descriptive, observational, repeated-measures dyadic study, conducted to explore sleep/wake patterns and sleep-impairing factors in patients with early stage breast cancer and their informal caregivers throughout adjuvant chemotherapy treatment.

6.3. Setting

Women diagnosed with early stage breast cancer and scheduled to receive adjuvant chemotherapy on an outpatient basis at four ambulatory oncology NHS clinics in Scotland were screened for eligibility and invited to take part in the present study along with their primary informal caregiver.

6.4. Population and Sample

A convenience sample of all newly diagnosed women with early stage breast cancer and their primary informal caregiver – as nominated by the patient – upon their consultation appointment for chemotherapy planning were considered as possible candidates, based on prespecified eligibility criteria (see below).

In order to promote sample homogeneity, only those women scheduled to receive adjuvant chemotherapy were considered for inclusion in this study; women scheduled to receive neoadjuvant treatment were excluded. Specifically, it was postulated that differences in the degree of distress (mainly due to women with adjuvant chemotherapy having also undergone surgery, and women receiving neo-adjuvant treatment being closer to diagnosis) would render these groups not exactly comparable in terms of sleep problems.

For the purposes of the study, the term 'informal caregiver' was also chosen to encourage patient self-identification of an individual, who had an important role in providing support post-diagnosis and during chemotherapy experience. This term acknowledges the variety of individuals that may have a primary caregiving role and may include family members, friends or neighbours [229].

6.4.1. Patient Eligibility Criteria

Patients eligible to this study were adult (>18 years of age) women recently diagnosed with clinical stage I-IIIA (TNM-UICC) [71] breast cancer, at least 2 weeks post-initial breast surgery, with no previous cancer diagnosis or previous administration of chemotherapy, and scheduled to receive ≥6 cycles of adjuvant chemotherapy. Changes in chemotherapy doses or regimens were allowed in this study. Women were also required to have adequate knowledge of English and a satisfactory level of communication and to be able to provide written informed consent. Patients with inflammatory locally advanced or metastatic disease, with a diagnosed or clinically suspected primary sleep disorder (such us primary insomnia, narcolepsy, or sleep apnoea), and/or cognitive or mental impairment, were excluded from this study.

6.4.2. Informal Caregiver Eligibility criteria

Primary informal caregivers eligible to this study were nominated by patients as the person who the woman felt closest to, and who provided most physical and emotional care and support to her during that period of time. In this sense, participating caregivers could be a woman's husband/partner, parent/child, other family member, friend, or neighbour. Caregivers were required to be adults (>18 years of age), have adequate knowledge of English and a satisfactory level of communication, and to be able to provide written informed consent. Similarly to patients, individuals with a diagnosed or clinically suspected primary sleep disorder (such us primary insomnia, narcolepsy, or sleep apnoea), and/or cognitive or mental impairment were excluded from this study.

6.5. Data Collection Scheme

Repeated assessments of each woman and her caregiver took place starting prior to initial chemotherapy (T0; baseline), during active-phase treatment (T1-T2), and at the end of treatment (T3), three weeks post-completion of the last chemotherapy cycle. Detailed information about each time point and its purpose is given below. A data collection schedule including the four time points of assessment is outlined in **Figure 6-1**.

- **Time point T0**: Baseline assessment prior to Treatment 1 (CThC1). Data collection was conducted the week before a woman's first appointment for chemotherapy, where participants were asked to reflect on the study variables for the past 15 days. Baseline data served as a starting point, to which subsequent changes in the dyads' sleep/wake patterns during and after chemotherapy were compared.

- **Time point T1**: Post-administration of Treatment 1 (CThC1). Data collection was conducted two weeks after administration of CThC1, where participants were asked to reflect on the study variables for the past 15 days. Data collected at this time point allowed for the initial impact of chemotherapy administration on patients' sleep/wake patterns, as well as that of caring for patients who had experienced chemotherapy for the first time, on caregivers' sleep/wake parameters to be examined.

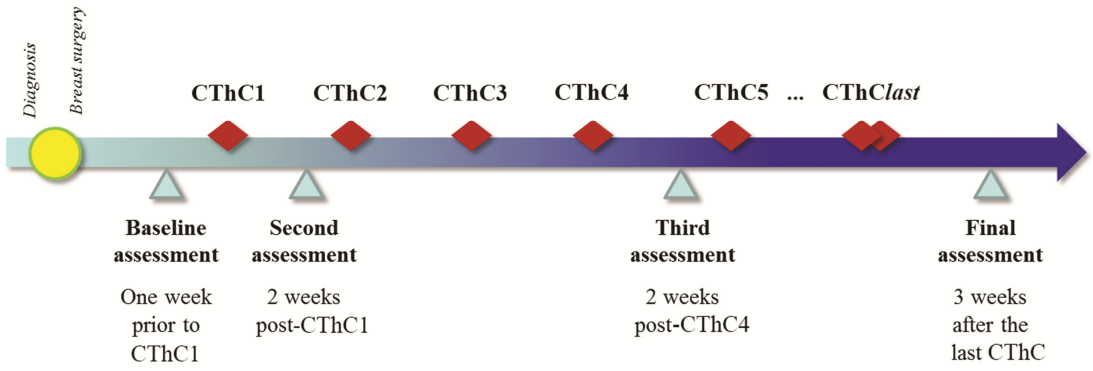

Figure 6-1. Schematic of data collection points (*Note:* CThC – Chemotherapy cycle).

- **Time point T2**: Post-administration of Treatment 4 (CThC4). Data collection was conducted two weeks after administration of CThC4, where participants were asked to reflect on the study variables for the past 15 days. Data collected at this time point al-

lowed for assessing patients' and caregivers' sleep/wake impairment during chemotherapy continuation, at a period where cumulative distress reaches a peak after successive cycles of chemotherapy [119, 128].

- **Time point T3**: Three weeks post-administration of the last cycle of chemotherapy (≥CThC6). Participants were asked to reflect on the study variables for the past 15 days. T3 was selected at 3 weeks after the end of treatment to avoid possible confounding variables (e.g. anticipatory anxiety) from interfering with sleep assessment by including patients (and their caregivers) scheduled to initiate radiation therapy 3 or more weeks after chemotherapy was complete. Data collected at this time point allowed for assessing patients' and caregivers' sleep/wake patterns at the end of chemotherapy and before patients go ahead with additional adjuvant treatment modalities [119].

6.6. Research Ethics

The study protocol was granted approval by the Tayside Committee on Medical Research Ethics A (10/S1401/41) (see Appendix 8), and the study was undertaken in accordance with the guidelines of the Declaration of Helsinki and its current revision [471].

6.7. Recruitment and Participation Procedures

Based on the fundamental principles of research ethics of beneficence, non-malfeasance, respect for individuals' autonomy, and justice [472], recruitment and consent procedures aimed to protect eligible individuals by ensuring that:

1. Information and consent documents were readily understandable by all individuals.
2. Each individual understood the nature and purpose of the study, and consented voluntarily.
3. Each individual had the opportunity to ask questions.

4. Individuals were free to take part, if they so wished, but they were equally free to decline, and subsequently withdraw, if they changed their minds, without this affecting in any way the quality of care they received.

5. The researcher was aware of verbal and nonverbal cues of the patient/caregiver implying that they felt uncomfortable during the initial approach, and was flexible during this assessment to each individual's needs.

6. The individual wished to continue in the study prior to follow-up assessments.

A local collaborator was identified at all recruitment NHS sites involved in the present study. Clinical collaborators were also the researcher's clinical supervisors at the specific site, allowing for the researcher to establish a relationship with each site and be able to access clinical areas and patient case notes. Local collaborators were responsible for identifying newly diagnosed patients with early stage breast cancer, for whom a plan to commence adjuvant chemotherapy had been settled.

Upon their appointment for consultation and chemotherapy treatment planning, the local collaborator checked patient eligibility and was the first to approach the patient and invite her to participate in the study through the use of a one-page invitation flyer (Appendix 9). No formal training of the local collaborators was required as they only handed flyers out to patients; however, they all were aware of the procedures of recruitment to be followed.

Patients interested in the study were given a Participant Information Sheet – Patient (PIS-P) (Appendix 9) to read at home and consider their willingness to take part in the study. In addition, patients were asked to nominate their primary informal caregiver. If the caregiver was present, they were also given a caregiver information sheet (PIS-C) to read (Appendix 9); if not, patients were asked to give a PIS-C to their caregiver. In three study sites, clinical collaborators handed patients and caregivers the respective PIS. In the fourth site, the researcher met in person with the potential candidate and handed the PIS, under the clinical collaborator's supervision.

Patients were informed that the researcher was intending to contact them after no less than 24 hours to confirm their consent to participate, therefore they were asked for their permission for this to be done. The researcher contacted patients and briefly explained the purpose of the call, ensuring that they understood the purpose of the study, the voluntary nature of their participation, and their liberty to withdraw at any time, as well as re-enforcing the is-

sues of confidentiality and anonymity with them. He then answered possible queries and confirmed whether patients agreed to take part in the study or not. If they wished to take part in the study, they were informed that a questionnaire pack would be mailed to them within the following two days. Patients were also asked to provide the contact details of their caregiver. Similarly, the researcher contacted nominated caregivers after no less than 24 hours after they were invited to the study so as to confirm eligibility, answer all possible queries, and find out whether they wished to participate in the study or not.

It was anticipated that not all eligible individuals would agree to take part in this study. Consequently, four different situations would occur:

1. Both agreed to participate;
2. Both refused to participate;
3. Patient agreed, whereas caregiver refused;
4. Patient refused, whereas caregiver agreed.

In situations 1, 3 and 4, all individuals who agreed to participate were sent an informed consent form to sign (two copies) (Appendix 9). All patients were also asked to provide consent for their General Practitioner (GP) to be notified about their participation in the study. Those patients who returned a signed copy were considered to be participants in the study thereafter. Although the study aimed to recruit dyads of patients and their caregivers, there was no specific reason as to why to exclude individuals who still wished to take part in the study, even if their caregiver refused participation or no caregiver was identified, and vice versa. Data derived from these individuals were planned to be used as supplemental material in secondary within-group analyses and presented as part of future publications. In situation 2 (as well as in situations 3 and 4, where refusal occurred), patients and/or caregivers were thanked for their time and again reassured that their decision would in no way compromise their rights and standard of care they received.

Furthermore, it was recognised that some participants would drop out during this study. In the case that a patient or a caregiver did drop out of the study, their relevant data for time points already completed were still included in the analysis. If a patient withdrew from the study at any point, their carer was still considered to be participant in the study, and vice versa. To effectively deal with a large number of withdrawals undermining the study's statistical power, a plan for recruitment of additional patient-caregiver dyads was put in place, taking into consideration the associated timelines.

Table 6.1 provides a summary of measurement procedures at each time point and for both groups of participants. At each assessment point, patient and caregiver case report forms (CRF) were mailed to participants at their home address. Patients and caregivers were given adequate time to complete the questionnaires, but were asked to refrain from sharing their responses with each other. They were then asked to return the CRFs via mail to the researcher himself at a time most convenient to them. If queries were posed by the participants during baseline completion of the questionnaires, they were invited to contact the researcher, who then provided explanations in such a manner that prevented both manipulation of responses and occurrence of missing data due to participants skipping questions because of becoming perplexed.

Table 6.1. Data Collection Timetable

	Time-points			
	T0	**T1**	**T2**	**T3**
Participant Group & Measure	**Pre-treatment**	**Two weeks post CThC1**	**Two weeks post CThC4**	**End-treatment**
Patients				
DCF-PT	×			
CCF-PT	×	×	×	×
Brief Sleep History-PT	×			
SHI	×	×	×	×
PSQI	×	×	×	×
Additional Sleep/Wake parameters Form	×	×	×	×
MSAS-PHYS and PSYCH	×	×	×	×
Brief COPE scale-PT	×	×	×	×
Caregivers				
DCF-CG	×			
CCF-CG	×	×	×	×
Brief Sleep History-CG	×			
SHI	×	×	×	×
PSQI	×	×	×	×
Additional Sleep/Wake parameters Form	×	×	×	×
MSAS-PSYCH	×	×	×	×
Brief COPE scale-CG	×	×	×	×
CRAS	×	×	×	×

Abbreviations: PT – Patient; CG – Caregiver; CThC – Chemotherapy cycle; DCF – Demographic Characteristics Form; CCF – Clinical Characteristics Form; SHI – Sleep Hygiene Index; PSQI – Pittsburgh Sleep Quality Index; MSAS-PHYS – Memorial Symptom Assessment Scale-Physical symptoms subscale; MSAS-PSYCH – Memorial Symptom Assessment Scale-Psychological symptoms subscale; CRAS – Caregiver Reaction Assessment Scale.

The researcher maintained regular contact with patients and caregivers during the study by sending short updates of the project and brief informal reminders throughout their involvement to prevent missing data due to non-response. In addition, in those cases where not all questionnaires had been returned two months after a dyad's anticipated final assessment, a letter was sent to participants as a final reminder regarding the study. Whilst all reminders posed a request to participants to complete and return questionnaires, or return any completed questionnaires (final letter), they explicitly acknowledged the voluntary nature of participation in this study and participants' right to withdraw at any time.

6.7.1. Risks, Burdens and Benefits

Patients affected by cancer and their caregivers constitute potentially vulnerable populations; hence, considerable care was taken to avoid causing any distress to them during the study. However, it was recognised that completion of questionnaires could encourage patients and/or carers to focus more on their experiences than if they had not been asked to complete them, as well as lead to discussions about illness, treatment and associated experiences which some participants could find distressing. At each assessment point, a Macmillan Cancer Relief support flyer with contact information was sent to all participants along with study questionnaires should anyone have felt the need to receive consultation. Should they desired additional support, patients were also reminded to report to their GP, who was previously formally informed of the patient's participation in the study (Letter to GP; Appendix 9). Moreover, at each assessment point, the researcher reinforced with participants that should they desire to withdraw from the study, they were absolutely free to do so without being required to give a reason about this decision. Similarly, it was recognised that the prospective nature of the study involving repeated measures of health outcomes could become tiresome for some participants. Given that participation was voluntary, willingness to continue in the study was reconfirmed at each contact point throughout the study.

Although they may have not directly benefited from taking part in this study, participants may have found their participation beneficial in an indirect manner. Through completing the questionnaires, participants had the opportunity to reflect on their experience, which might have urged them to discuss their feelings with members of the health care team, and thus seek and receive more help. In addition, the goal of this study was to inform and educate health care professionals involved in patients' and their caregivers' care regarding the experience of sleep problems during chemotherapy in order for them to provide increasingly bet-

ter care. Given the study's goal to inform new strategies for the improvement of sleep in patients with cancer and their caregivers, participants could benefit from these in the future.

6.7.2. Issues of Confidentiality and Data Handling

All research data recorded throughout this study were regarded as confidential. Contact details provided were only used by the researcher to contact participants so as to invite them in the study, to reconfirm participation during the study and to send short update reports on the progress of the project. These contact details were stored separately and securely in a locked cabinet and they will be destroyed following 6 to 12 months after the last assessment contact, according to University of Dundee policy. Participants were reassured that their details would be kept confidential at all times.

All research data collected were stored securely in a separate locked cabinet in the School of Nursing and Midwifery at the University of Dundee, and were only available to members of the research team (i.e. the PhD student and his supervisors), who needed access for data analysis purposes. These data were transferred to an electronic password-protected database, which again was accessed by the research team for data collection and analysis purposes. Following the completion of data collection, all demographic and clinical data and completed questionnaires were archived, and will be stored securely for 5 years, according to University of Dundee policy.

No identifiable information was associated to any of the data generated from the study. Neither patients nor caregivers were asked to fill out their name in any questionnaire. A participant-specific code number was matched to respondents' actual name and this was used throughout their participation in the study. These code numbers had already been applied to the questionnaires given to the participants at each time point, along with a plain envelope. Patients and carers were returning their completed questionnaires in the sealed envelope to the researcher himself. Participants had been informed at the start of the first assessment of this intention, but it was stressed that this code number would in no way be associated to their own name and would be used only when referring to their experience within the context of the project.

If queries were posed by the participants during completion of the questionnaires, the researcher provided explanations in such a manner that prevented manipulation of their responses. Finally, participants were assured that any conversations they possibly had with the researcher would remain confidential between the participant and the researcher – for exam-

ple, if a patient was involved, they were assured that details of the conversations would not be revealed to their carer, and vice versa.

6.8. Study Variables

Outcome variables

A number of sleep parameters were used as outcome variables in all analyses in order to explore within-groups longitudinal changes, examine between-groups interrelations, and identify predictors of poor sleep in both the women and their caregivers. Outcome variables included the following 8 sleep parameters: perceived sleep quality (PSQf); daily disturbance (DDISTf), habitual sleep efficiency (HSE); sleep latency (SL); total sleep time (TST); wakefulness after sleep onset (WASO); daytime napping duration (NAPTIME); and overall sleep/wake impairment (GSQI; based on global PSQI scores).

Two sleep parameters, bedtime and wake time, were only descriptively explored given limitations in the multilevel modelling software package functionality to manage time/date variables. Additional sleep parameters, including need for daytime napping, nocturnal awakenings, early morning awakenings, daytime sleepiness, restless legs, feelings of restfulness upon arising in the morning, and sleep aid use were also descriptively explored but they were not entered into multivariate models with the aim of limiting the number of statistical analyses.

Predictor variables

To address the study's secondary aim, a number of physical and psycho-behavioural parameters were used as independent variables based on results from recent literature reviews [182, 366]. Potential predictors of poor sleep in the women and their caregivers included the behavioural variables of sleep hygiene (SHPT/CG; frequency of sleep disruptive practices/behaviours), patient physical burden (PHYSPT; aggregated frequency, severity and distress levels), caregiving burden focussing on impact on health and disruption in schedule (CRACBCG), psychological burden (PSYCHPT/CG; aggregated frequency, severity and distress levels), negative/maladaptive coping strategies (COPNEGPT/CG; frequency of use), and nocturnal sleep disturbance (SDSTRBPT/CG; frequency of occurrence).

Covariates (confounding variables)

Predictive models were adjusted for the effects of important socio-demographic and medical covariates of sleep/wake impairment based on results from a preliminary correlational analysis. Covariates included (a) person variables: age (AGEPT/CG); caregiver gender (SEXCG); employment status (EMPLOYPT/CG); educational background (EDUCPT/CG); patient body mass index (BMIPT); time since patient diagnosis/surgery (DIAGNTM; SURGTM); disease stage (BCSTAGE); type of surgery (SURGTYP); chemotherapy protocol (REGIMTYP); patient menopausal status (MENOPPT); presence of comorbid illnesses (CMRBDTPT/CG); past history of sleep problems (SLPAST); sleep affected by cancer diagnosis (SLCA); performance status (PSPT/CG); physical activity (PAPT/CG); smoking (SMKNGPT/CG); and alcohol consumption (ALCHLPT/CG); and (b) dyadic variables, including type of relationship (RELTYPE); duration of relationship (RELDUR); and sharing of the same house/room (SLSROOM; SLSHOUS).

6.9. Instrumentation

Data pertinent to the outcome and predictor variables were collected through the use of a set of well-established and valid questionnaires as part of the study CRFs. These questionnaires were selected from a pool of available measures after a comprehensive review of the relevant literature was performed (see Chapter 5). Measures regarded for inclusion were those which were relatively brief in order to prevent participant burden, were psychometrically sound, and had been previously tested in studies with people with (breast) cancer and informal caregivers.

All questionnaires asked or were set to ask participants to reflect on the past 2 weeks at all time-points. This is a critical time period for the assessment of sleep: it is neither too narrow (e.g. past week) to neglect features of sleep/wake patterns that manifest themselves earlier than one week before assessment, nor too wide (e.g. past month) making it difficult for the participants to reflect on their sleep/wake patterns thus providing inaccurate or inadequate information.

6.9.1. Demographic and Clinical data

A patient demographic characteristics form (DCF-P) was used to collect information on age (years), educational background (high school versus college/university), marital status, and household yearly income (£) (Appendix 10). A similar caregiver DCF-C was used to collect information on age (years), gender, educational background (high school versus college/university), marital status, household yearly income (£), relation to patient, and duration of relationship (months; except for a parent-to-child relationship) (Appendix 10).

A patient clinical characteristics form (CCF-P) was used to collect information on menopausal status (pre-; peri-; or post-menopausal), comorbid diseases (yes/no), use of dexamethasone (yes/no), and use of alternative/complementary therapies (yes/no) (Appendix 10). Additional disease- and treatment-related clinical data– body mass index (kg/m^2); time since diagnosis/surgery (days); disease stage (I, IIA/B, IIIA according to TNM-UICC [71]); type of surgery (mastectomy v. lumpectomy); chemotherapy protocol – were file sourced through use of patient case notes. A caregiver CCF-C was used to collect information on concurrent diseases (yes/no) and use of prescribed and over-the-counter medications (yes/no) (Appendix 10).

6.9.2. ECOG Performance Status

At all time-points, patients and caregivers were asked to indicate their level of functional capacity on the Eastern Cooperative Oncology Group Performance Status scale (ECOG PS) (Appendix 10) [379]. The scale allows assessment of the individual's actual level of function and ability of self-care, ranging from 0 (fully active) to 4 (completely incapable and dependent on others) [379]. The scale's clinimetric properties have been widely established [382, 473].

6.9.3. Level of Physical Activity Scale

Levels of physical activity were evaluated through use of a single-item scale (Appendix 10) previously used in survivors of Hodgkin's lymphoma [397], which addressed two levels of activity. The first described duration of activities at a low level, such as walking; the other described duration of activities at a high level that leads to sweating and breathlessness. According to their combined levels of physical activity, participants were divided into two groups, namely those minimally active (i.e. independent of the duration of low-level activity,

no high level activity or < 1 hour per week) and those highly active (i.e. independent of the duration of low-level activity, high level activity ≥ 1 hour per week) [397]. Validity and repeatability of the scale have been established through comparisons with direct measures of physical activity [398].

6.9.4. Pittsburgh Sleep Quality Index (PSQI)

The PSQI consists of four open-ended questions regarding sleep timing and multiple-choice questions regarding sleep quality, and takes approximately 10 minutes to complete. Although the scale assesses quality of sleep patterns over the *past month*, in order to measure with greater precision the sleep quality of participants during this study, the scale was modified to measure changes from the *past 2 weeks*. A similar approach has been successfully followed in previous studies [21, 474-476].

Nineteen multiple-choice and free-text questions are used to elicit information pertinent to sleep/wake parameters (Appendix 10). These questions can be used to generate the following seven component scores: sleep quality (C1), sleep latency (C2), sleep duration (C3), habitual sleep efficiency (C4), sleep disturbances (C5), use of sleep medications (C6), and daytime dysfunction (C7). The seven components can be added together to give a global score (GSQI) ranging from zero to 21 [407]. Higher scores signify greater overall sleep/wake impairment. A GSQI score > 5 indicates possible sleep pathology. This score has yielded a diagnostic sensitivity of 89.6% and specificity of 86.5% in distinguishing good and poor sleepers. However, in patients with breast cancer a cut-off score of 8 has been suggested as a more valid criterion for identifying bad sleepers [477]. Overall, good measures of internal homogeneity, consistency (test-retest reliability), and validity have been obtained on the questionnaire's wide psychometric testing [478]. In women with breast cancer, Cronbach's alpha for the GSQI was .80 [33]. In the present study, internal consistency was α=.78, .79, .76, and .69 for the patient group, and α=.75, .60, .73, and .73 for the caregiver group. Nevertheless, recent reports argue on the instrument's multidimensional scoring system compared to the traditional one-factor structure [479-483]. Confirmatory factor analysis has supported a three-factor model with Perceived Sleep Quality (PSQf; C1, 2, 6), Sleep Efficiency (SEf; C3, 4), and Daily Disturbances (DDISTf; C5, 7) as separate indices of sleep quality in an attempt to improve the questionnaire's sensitivity [480].

For the purposes of the current study, ten outcome variables and one predictor variable were created that derived from free-text questions and aggregation of components of the PSQI.

Table 6.2 provides an overview of the variables created based on the PSQI, and how these were derived.

Table 6.2. Sleep/wake variables created based on PSQI data

Variable	PSQI source	Metric
Outcome		
HSE	Calculated as the ratio of TST divided by the total time spent in bed (x100); Free-text items 1, 3, 4	Per cent (%)
SL	Free-text item 2	Minutes
TST	Free-text item 4	Minutes
WASO	Calculated by subtracting TST and SL from the total time spent in bed (free-text items 1, 3)	Minutes
PSQf	Components 1, 2, 6	Numerical scale 0-9
DDISTf	Components 5, 7	Numerical scale 0-9
GSQI	Sum of Components 1-7	Numerical scale 0-21
BEDTM	Free-text item 1	24-hour time
WAKETM	Free-text item 3	24-hour time
SAU	Item 6	Numerical scale 0-3 (converted to binary variable: yes/no)
Predictor		
SDSTRB	Items 5b-5j	Numerical scale 0-27

Abbreviations: HSE – Habitual sleep efficiency; SL – Sleep latency; TST – Total sleep time; WASO – Wakefulness after sleep onset; PSQf – PSQI Factor 1 indicating Perceived Sleep Quality; DDISTf – PSQI Factor 3 indicating Daily Disturbances; GSQI – Global Sleep Quality Index (indicating sleep/wake impairment); SDSTRB – Nocturnal sleep disturbances; BEDTM – Bedtime; WAKETM – Wake time; SAU – Sleep aid use; PSQI – Pittsburgh Sleep Quality Index

Notes: With the the exception of HSE, TST, BEDTM and WAKETM, higher values are indicative of poorer sleep/wake outcomes.

A number of questions were also used to assess additional essential sleep/wake parameters reported in the literature [119], but not addressed in the PSQI. These included need for daytime napping (NAPNEED) and average duration of naps per day (NAPTIME; minutes); feelings upon arising in the morning regarding the extent of restfulness (MORNFEEL); occurrence and frequency of leg restlessness (RSTLSSLG); early, unplanned awakenings in the morning (EARLAW); extent of daytime sleepiness (SLPNSS); and average number of nocturnal awakenings per night (NOCAW). These questions and their response format are presented in Appendix 10. Questions were adapted from existing sleep questionnaires (**Table 16-A2**). Where appropriate, their original response format was retained the same; in all

other cases, the multiple-choice response format of the PSQI was implemented to enhance consistency.

6.9.5. Sleep History

For the purposes of the present study, six relevant questions were extracted from a standardised sleep history used in a previous study of people with advanced cancer and their informal caregivers [244]. In that way, comparability between the studies could be promoted. Questions included asked participants to give information on the following (Appendix 10): (a) past history of sleep problems (yes/no); (b) sleep problems as a result of the diagnosis of cancer (yes/no); lifestyle habits, i.e. (c) smoking (yes/no) and (d) alcohol consumption (never/only occasionally/every day); and sleeping arrangements, i.e. patient/caregiver sharing (e) the same bedroom (yes/no) and/or (f) house (yes/no).

6.9.6. Sleep Hygiene Index (SHI)

The SHI is a brief (13-item) self-report scale designed to assess the presence of behaviours that comprise sleep hygiene (Appendix 10) [415]. Individuals are asked to indicate how frequently they engage in specific sleep behaviours. Each item is rated on a 5-point scale. Item scores are summed to provide a global assessment of sleep hygiene, and higher scores are indicative of more maladaptive sleep hygiene status, with total scores ranging from 0 to 52. The scale has moderate internal consistency (Cronbach's $\alpha = .66$), but test-retest reliability over a 5 week interval is good [415]. In addition, it has acceptable content validity, while construct validity has been established through its positive correlation with all of the associated features of inadequate sleep hygiene as determined by the American Sleep Disorders Association [484], as well as with self-report measures of sleep quality and daytime sleepiness [415]. In the present study, internal consistency was $\alpha = .63$, .61, .59, and .60 for the patient group, and $\alpha = .61$, .57, .58, and .63 for the caregiver group.

6.9.7. Memorial Symptom Assessment Scale (MSAS)

The MSAS is a self-report questionnaire designed to measure the multidimensional experience of symptoms (Appendix 10). It has been widely used in the context of cancer care [244, 485, 486]. The original version of MSAS evaluates 32 physical and psychological symptoms, according to their frequency, severity and distress/bother to the person. Respondents

are asked to indicate whether or not they have experienced each symptom (in the past 2 weeks). If they have, they are asked to rate its severity, frequency of occurrence, and distress. Symptom severity is measured using a five-point Likert scale (i.e., 0 = not at all, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe) [424]. This measure has shown high correlation with quality of life and clinical status. Internal consistency of the scale is high with Cronbach's alphas ranging from .83 to .88. The MSAS questionnaire takes approximately 20 minutes to complete [424].

For the purposes of the present study, 14 physical symptoms with direct effect on sleep (PHYS) and 4 psychological symptoms (PSYCH) were selected from the MSAS. A similar approach has been successfully followed in previous studies as well [485, 487]. The physical symptoms assessed included pain, lack of energy, cough, dry mouth, nausea, numbness/tingling in hands/feet, feeling bloated, problems with urination, vomiting, shortness of breath, diarrhoea, sweats, itching, and dizziness. Psychological symptoms included worrying, feeling nervous, feeling sad, and feeling irritable. The PSYCH subscale was also given to caregivers to assess impact of psychological symptoms on their sleep. Total scores produced from these subscales were used as predictors of the patient's sleep. In the present study, internal consistency was α = .79, .83, .85, and .85 for the PHYS subscale. For the PSYCH subscale, alphas were .66, .71, .72, and .70 for the patient group, and .73, .77, .76, and .69 for the caregiver group.

6.9.8. Brief COPE scale

The Brief COPE scale is a self-report measure proposed to assess a broad scope of coping behaviour among adults for all conditions, illnesses or non-illnesses [457]. It is an abbreviated version of the COPE Inventory [449]. Although the Brief COPE scale is conceived as a dispositional measure, it is flexible and a situational version of it can be used after rephrasing items to denote a real-life experience and asking individuals to recall a specific time period [449]. A situational format was used in this study (Appendix 10). The instrument comprises 28 items rated on a 4-point Likert scale, ranging from "I haven't been doing this at all" (1) to "I have been doing this a lot" (4). A higher score represents greater coping strategies used by the respondents [449, 457]. In total, 14 dimensions (two items for every dimension) are put forward by this scale, assessing 14 conceptually different ways people respond to stress. They are self-distraction, active coping, denial, substance use, use of emotional support, use of instrumental support, behavioural disengagement, venting, positive reframing, planning, humour, acceptance, religion and self-blame.

A rigid factor structure of the coping strategies assessed by the Brief COPE does not exist [440], therefore researchers are invited to choose to flexibly and creatively use all or a subset of the dimensions according to the purposes of their research [457]. The Brief COPE scale does not produce an overall score. However, it has been recommended that researchers create second-order factors from among the items or dimensions based on own data, and use the extracted factors as predictors [449]. However, previous research using factor analysis favours a two-factor structure format of adaptive/engagement and maladaptive/disengagement coping strategies [488-490]. This factor structure was used in the present study, where two separate scores were calculated by aggregating scores of adaptive (COPPOS) and maladaptive coping styles (COPNEG); however, only maladaptive coping strategies were considered as a potential predictor of sleep alterations in further analyses given that past research has failed to conclude with significant association between adaptive coping and sleep [110]. Brief COPE has been successfully used in previous breast cancer-related [488-494] and caregiver [495] research, where good reliability (internal consistency and stability) has been shown. In the original report the Brief COPE Scale exhibited acceptable internal consistencies across its dimensions with six dimensions exceeding .70, five dimensions exceeding .60, and three dimensions exceeding .50 [457]. In the present study, acceptable alphas were found for COPNEG in the patient (.66, .69, .66, .61) and caregiver groups (.62, .60, .67, .65).

6.9.9. Caregiver Reaction Assessment Scale (CRAS)

The CRAS is a self-rating scale assessing informal caregivers' reactions regarding providing care to a family member with a chronic physical and/or mental impairment (Appendix 10) [467]. There are 24 items with 5-point Likert-type response alternatives in the original version. It consists of five subscales that quantify negative as well as positive experience of caregivers when providing care. The subscale 'Disruption of Schedule' (CRADoS) quantifies to what extent caregiving interrupts the caregiver's activities (5 items). 'Impact on Finances' assesses the impact of caregiving upon the caregiver's financial situation and to what extent caregiving puts a strain on the financial situation in the family (3 items). 'Lack of Family Support' quantifies to what extent the caregiver receives help with caregiving and the caregiver's experience of being abandoned (5 items). The subscale 'Impact on Health' (CRAIoH) consists of items concerning the caregiver's health and experience of vigour in relation to caregiving (4 items). Finally, the subscale 'Caregiver Esteem' quantifies to what extent the caregiver experiences feelings of enjoyment and reward, or whether the situation arouses feelings of resentment (7 items) [467]. Of note, no total summary score is to be cal-

culated; instead, reporting of subscale total scores should be reported. For the purposes of this study, CRADoS and CRAIoH subscale scores were aggregated to yield an overall caregiving burden score (CRACB) that was considered to be a potential trigger of sleep disturbances. The CRAS has been used in research to assess experiences of caregivers to individuals with different types of cancer [200, 216, 496-498]. Satisfactory construct and convergent validity, internal consistency (subscale Cronbach's α = .82, .90, .85, .80, .81, respectively) and test-retest reliability, and sensitivity to change have been reported [499, 500]. In the present study, internal consistency of CRACB was good (α = .78, .77, .79, .76).

6.10. Potential Sources of Bias

The likelihood of research biases interfering with the present study was acknowledged early when the project was planned. Bias is a systematic deviation from the truth; it is typically introduced during the design or implementation of a study and it can threaten its internal and external validity [141]. Of the different sources of bias, three types – inclusion bias, response bias and attrition bias – were specifically assessed for this study with regard to their magnitude and direction.

Whilst every attempt was made for all eligible patients to be invited to take part in the study, the researcher and his collaborators were free to evaluate whether a patient was not psychologically fit to take part in a research study and choose not to introduce the study to them. Although this practice was introduced in only a few cases, it might have favoured patients with less psychological distress, more effective coping strategies, and therefore less likely sleep disturbances. Yet, the associated 'inclusion bias' was rather small.

Furthermore, in view of the moderate rates of patients who refused to participate in the study, the possibility of 'response bias' was examined by testing for differences in demographic and/or clinical characteristics between those who agreed and those who declined participation in the study.

As this was a prospective study involving the collection of data at several time points, a test for 'attrition bias' – that is, the non-random loss of participants from the study over time [501] – was performed. More specifically, the demographic characteristics of participants who remained in the study were compared with those of participants who withdrew (see Chapter 7).

A final potential source of bias could be patients and carers colluding over completion of the sleep and health outcome measures. Although participants were reminded at every time point to complete questionnaires independently from one another, it is possible that some of them did not fully comply. However, it is believed that the associated bias has been kept to a minimum.

6.11. Sample Size Estimation

Sample size for this study was estimated via a sample size analysis using the G*power general power analysis programme [502]. During the early design stages of this study, an initial analysis plan was devised that anticipated use of a Repeated Measures Analysis of Variance (RM-ANOVA) to answer the primary research question (i.e., over-time similarities/differences in sleep/wake patterns within each group) with GSQI scores selected as the main outcome variable. However, the data analytic strategy was revised during the study when more appropriate/flexible data analytic techniques came to the researcher's knowledge (see below); therefore, power estimation for this study was reconfirmed.

Initial sample size calculations were conducted to meet the requirement for a RM-ANOVA with time points as the within-subjects factor (time effect); based on means of global PSQI scores (i.e. measure of SQ in the study) of 6.03-8.29 with SD=2.31-3.62 from previous studies in patients with breast cancer [7, 122, 123, 125, 130] and for the anticipated time points, effect size to be tested was estimated as f^2=.02 (within-group ratio of effect variance to error variance) [503]. Cohen's guidelines [504] for univariate repeated measures analyses define effect sizes (f^2) as .01=small, .0625=medium, and .16=large, indicating that a relatively small effect size would be detected for the present study. Furthermore, magnitude of correlation among repeated measurements has been found to be .82 based on previous test-retest reliability analysis in patients with cancer for a 14-21 days interval [482]. Assuming that correlations between adjacent pairs are greater than correlations between more distant pairs [Autoregressive of order 1, AR(1)] [505], correlations between T1 and T2 were estimated to be 5% lower than .82, and between T2 and T3 10% lower than .82, thus giving an overall mean correlation of ρ=.80. Given that correlations are expected to differ between time points, the sphericity (ε) assumption is violated. To correct this, an adjustment to the degrees of freedom of the numerator (m-1) and the denominator [*N**(m-1)] was used (Greenhouse-Geisser epsilon, <ε>), where m=4 (number of levels of repeated factor, i.e. time points).

Choosing the worst case scenario, epsilon was considered as conservatively low as $<\varepsilon>=\varepsilon/(m-1)$, where $\varepsilon=1$ (i.e. sphericity assumed), i.e. $<\varepsilon>=0.33$. The non-centrality parameter was $\lambda=N*m*f^2/(1-\rho)$, where N is the size of the sample for the study. The technical point to be aware of is that G*power computes lambda as $\lambda=N*\boldsymbol{f^2}$, where $\boldsymbol{f^2}$ is the label of the effect size slot in the programme. Therefore, an estimated corrected effect size was calculated as $<\varepsilon>*m*f^2/(1-\rho)=.133$. Again, in factorial designs, Cohen [506, 507] defines $\boldsymbol{f^2}$ of .10, .25, and .40 as small, medium, and large effects, respectively. Based on the aforementioned data, sample size estimation indicated that n=61 consecutive patients would need to be recruited in order to achieve a power (1–β) of 80% (actual power achieved: 80.05%) for the study with a level of significance of .05. Since sleep/wake patterns in patients and caregivers were to be explored in a paired fashion, n=61 caregivers would also need to be recruited. Since this was a prospective study, issues of attrition needed to be co-estimated. With an anticipated overall 10% of attrition for the study (approximately 3% for each time point T1, T2, T3), the final total sample size for each group rose to 68 participants to preserve power of the study to the predetermined level even in the case of possible withdrawals.

As mentioned above, with inclusion of multilevel modelling as the main data analytic strategy, power calculations were re-run to ensure that a sample of 68 dyads would be adequate enough to permit the emergence of statistical associations. Previous dyadic sleep research has concluded with an aggregated moderate correlation (r=.30) between patient and caregiver GSQI scores [242, 285] (the aggregated Pearson's correlation coefficient was produced by converting individual r's to Z scores, calculating mean score, and reverting the aggregated Z score back to r). According to sampling tables presented in Kenny et al. [293], a sample of 90 dyads (adjusted for 10% attrition rate) would be required to detect this medium effect size of non-independence. Nevertheless, a sample size of 68 dyads would provide acceptable power to the study (70%) to detect a medium effect size of non-independence, but sufficient power (>80%) to detect a statistical difference between patients' and caregivers' GSQI scores [293] (adjusted effect size Cohen's d=.75 [285]). In light of these favourable results, and also taking into consideration budget constraints as well as challenging recruitment issues during the study's feasibility phase (see Paragraph 6.13) but mainly beyond that, no major amendment to this study was sought.

6.12. Data Analysis

The data analytic strategy for this study involved a combination of preliminary ordinary least squares (OLS) analyses and multilevel modelling (hierarchical linear modelling) techniques

to examine longitudinal change in the sleep patterns of patients and caregivers, as well as explore the effects of individual and dyadic correlates on the dyads' quality of sleep.

6.12.1. Data quality

Patient and caregiver raw data were first entered into Microsoft Excel® spreadsheets and coded into 'item-score' variables, thus creating an electronic database which was next transferred into IBM SPSS 17 (SPSS Inc.: An IBM Company; Chicago, IL) for a preliminary inspection. In this stage, data were first scanned for incomplete responses in the questionnaires returned, as well as for inaccurate responses possibly reflecting errors in data entry that required correction. To determine the extent of missing values in the questionnaires returned, frequency distributions were examined on a variable-by-variable basis [501]. Overall, information on almost all variables was found to be missing sporadically, accounting for less than 2% of the total amount of data. Missing values were treated with mean substitution by replacing a missing value with the mean of a given variable, calculated from all participants with non-missing data. Although mean substitution may lead to underestimation of variance, it can be used as an effective means to manage missing values when the percentage of missing values is very small [501]. Subscale and total scores were calculated and 'subscale-score' and 'total scale-score' variables were subsequently created. Next, data were re-examined for the presence of outliers through use of numerical summaries and graphs such as boxplots to identify whether they were legitimate values. An outlier was defined as *mild* if its data value laid between 1.5 and 3.0 times the variable's interquartile range (IQR) below quartile 1 (Q1) or above quartile 3 (Q3), and as *extreme* if its data value was more than 3.0 times the IQR below Q1 or above Q3 [501]. Only mild outliers were identified for certain variables; however, as they were legitimate values, they were not removed from further analyses.

In longitudinal research, data values can also be missing due to non-response (i.e. no questionnaires received). This often creates unbalanced datasets that may further complicate already complex analyses [376]. As this was a prospective study involving repeated measures, the extent of missing responses at each time point was specifically examined through use of the Missing Values Analysis (MVA) module within SPSS. One definite advantage of the analytic strategy employed in the main analyses part is that it produces efficient or unbiased estimates of all parameters under the assumption that data are missing at random (MAR). This assumption implies that missing data are 'conditionally random' [508], given that their status as missing is dependent on observed variables included in the

analysis [508, 509]. In other words, "the missing data for a variable are MAR if the likelihood of missing data on the variable is not related to the participant's score on the variable, *after controlling for other variables in the study*" (p. 1014) [508]. These other variables are considered to provide the *mechanism* for explaining the pattern of missingness and so can be used to impute the missing data. Among common mechanisms education, age, gender, or psychological well-being are those more often cited [508]. In longitudinal analyses, preceding values of the outcome also can predict missing data [509]. Within this context, MAR renders missingness as ignorable because of controlling for all earlier measures related to a participant's missing data. The crucial distinction is that predictors of missing data are observed and included in the analysis [509], and in most large exploratory studies several of these predictor variables are included [508]. Of note, these variables may or may not be part of the theoretical model employed in the study to explain the outcome variable [508]. Previsouly, it has been shown that in many realistic cases even an erroneous assumption of MAR may often have only a minor impact on model estimates [510]. Yet, Raudenbush et al. [376] suggest that in longitudinal research the relationship between a measured covariate and the probability of a missing value is nevertheless examined to confirm randomness of missing data. To examine whether attrition introduced systematic bias in this study, unpaired *t*-tests (or Mann-Whitney U tests; non-parametric data) were performed (see Paragraph 6.10). Specifically, respondents and non-respondents at each follow-up time point were compared in terms of their demographic characteristics and their baseline and T1 scores on outcome (perceived sleep quality; overall sleep/wake impairment) and predictor variables for significant differences. A dummy-coded missingness variable (coded 0 for observed and 1 for missing) was created to examine patterns of missingness throughout the study.

6.12.2. Descriptive analysis

In the second stage, descriptive statistics were computed to summarise patient and caregiver socio-demographic and clinical data, and to explore sleep patterns and covariates at each time point, using mean and standard deviations for parametric data, and median and range for non-parametric data. Distribution of continuous or interval-scale variables was confirmed through examination of histograms and a series of Shapiro-Wilk tests (especially recommended for datasets with < 50 cases) [511]. Where data were plausibly normal, parametric methods were chosen during preliminary analyses to test relationships; in cases of deviations from normality or examination of ordinal/categorical variables, non-parametric methods were used instead. Relative to outcome variables, only very modest deviations from normali-

ty (skewness index twice the value of its standard error [501]) were observed for some variables, but these were deemed plausibly normal through histogram examination. Yet, moderate deviations were found for SL (negatively skewed) and NAPTIME (positively skewed). In order to increase normality of these variables, square root and reversed square root transformations were used, respectively. Variable transformation is often recommended in the context of multilevel modelling when normality assumptions fail in the case of a continuous dependent variable [512]. However, due possibly to the small study sample, transformation did not considerably improve distribution, and in other cases even reversed the direction of skewness. In addition, Tabachnick and Fidell [513] argue that MLM results based on transformed and untransformed versions of a variable do not differ substantively. Therefore, in the interest of interpretability all variables were used untransformed in further analyses.

A series of bivariate tests was pursued to facilitate preliminary analyses. First, to compare sociodemographic and clinical data, and explore over-time similarities and/or differences in outcome and predictor variables between patients and caregivers, a series of ordinary least squares (OLS) statistical procedures such as paired *t*-tests (or Wilcoxon Signed Ranks tests), chi-square tests, Friedman tests, and Cochran's Q tests were used. With respect to Friedman and Cochran's Q tests, 'last observation carried forward' was used as an effective, yet somewhat conservative, method to impute missing values [501]. Second, inter-dyad correlations between sleep variables were tested to examine for the presence of non-independence [293], which would further support the use of dyadic data analytic techniques. Third, correlation coefficients were used to assess stability over time of each construct for each dyad member. Fourth, both within-patient and within-caregiver correlations between outcome and predictor variables (aggregated over 4 assessment points) were also investigated to establish whether they could be considered as distinct constructs, thus further supporting the use of separate growth curve models for further analyses. A similar correlational analysis was conducted between outcome variables (aggregated over 4 assessment points) and demographic/clinical variables to select important covariates for which final multivariate models would be controlled. Finally, within-person correlations between predictor variables and demographic/clinical covariates (repeatedly measured variables aggregated over 4 assessment points) were used to assess the presence of collinearity (see below).

A series of graphs and scatter plots were constructed within SPSS to complement multilevel modelling results, and illustrate and compare patterns of change in sleep variables across time and between members of the dyads.

6.12.3. Multilevel modelling

In the main analysis stage, multilevel modelling techniques were employed to investigate change over time (growth trajectories) in the sleep patterns of the dyads and examine the effects of covariates [512]. Analyses were conducted using the HLM 7 computer software (Scientific Software International, Inc.; Skokie, IL) [514] and employed the dyadic data analytic approaches described by Kenny et al. [293] and Lyons et al. [371]. The analytic strategy employed maximises data from all participants who have provided at least one wave of data, thus allowing interpretation of results as if no missing data were present [375, 512]. HLM 7 uses Maximum Likelihood to estimate parameter values based on all existing data across assessment points and data available at Level 2. Maximum Likelihood uses all available information in the data to obtain unbiased parameter estimates of change for each participant that have been adjusted for missingness. Importantly, the amount of data available for each participant only affects the reliability of the prediction, not the ability to estimate the trajectory. HLM 7 weights each estimated coefficient by this reliability so that those participants with less data have estimates closer to the mean. Through this process, HLM 7 not only effectively manages missing values in longitudinal data, but also eliminates the need for implementation of a missing values replacement technique and the associated risks of incorrect estimation of standard errors in analyses that may increase the chance of unwanted statistical errors [375].

Specifically, the multivariate two-level model for longitudinal dyadic data (multivariate hierarchical linear model [MHLM]) described by Raudenbush et al. [371, 376] was employed to enable simultaneous estimation of the average sleep pattern trajectories of the dyad members, as well as own and cross-partner predictor effects, while controlling for interdependencies in the data (see Paragraph 5.5). All dyads participating in at least one wave of assessment were included in the analysis. The MHLM involves two separate levels of analysis, a within-dyad model at Level 1 and a between-dyad model at Level 2. **Figure 5-A1** illustrates the organisation of data for analysis at Level 1. Two basic MHLMs were tested for each outcome variable: a Baseline/Unconditional MHLM, where trajectories of change in sleep parameters were examined; and an Explanatory MHLM, where the relation of these trajectories with time-varying and time-invariant covariates/predictors was explored. These were compared with each other and with a means-only model, namely a model containing only intercepts but no main predictor variables, to identify the most appropriate one for modelling the effects of time.

Baseline/Unconditional MHLM

Level 1 model: The Level 1 model represents change over time for both patients and caregivers described by dyad member-specific growth parameters (i.e. intercepts and slopes) that are allowed to vary across dyads, plus a residual term, *e*, that captures measurement error which is considered to be constant both within and across dyads. Separate Level 1 models were created for PSQf, DDISTf, HSE, SL, TST, WASO, SDSTRB and NAPTIME. As an example, a model where PSQf is considered to change in a linear fashion over time was specified as follows:

$$PSQf_{tp} = (\text{patient})[\beta_{1p} + \beta_{2p}(\text{timelin}_{tp})] + (\text{caregiver})[\beta_{3p} + \beta_{4p}(\text{timelin}_{tp})] + e_{tp}, \quad (1)$$

where $PSQf_{tp}$ represents perceived sleep quality (t=1, …K responses per dyad and point of assessment) for dyad p; β_{1p} and β_{3p} represent the intercepts for patient and caregiver (initial levels of sleep quality); and β_{2p} and β_{4p} represent the time effect (linear) for the patient and caregiver of perceived sleep quality, respectively. The indicator variable (patient) takes on a value of "1" if the response is obtained from the patient and "0" if it is obtained from the caregiver. The opposite is true for the (caregiver) indicator variable. The first set of brackets contains the latent growth parameters (coefficients) β_{1p} and β_{2p} characterising the trajectory for the patient; the second set contains the latent growth parameters (coefficients) β_{3p} and β_{4p} that characterise the trajectory for the caregiver. Seen together, each dyad has four coefficients that represent the true growth parameters for the dyad. The e_{tp} are the within-dyad residuals, which are assumed to be normally distributed, with a mean of 0 and variance σ^2. Within the statistical package HLM 7, the general intercept was removed and replaced with the dummy coded variables 'patient' and 'caregiver' [293, 515].

Definition of 'time zero' has been described as being of utmost importance in growth curve analyses [293, 371]. The intercept represents the predicted value of the outcome for time zero, that is to say, when time equals 0 or the origin [293, 371]. Often, time zero is set at the time of the first measurement; however, considerable flexibility exists so that alternatives in determining time zero can and should be considered depending on the nature of the research [293]. Because time zero affects the average intercept, the variance in the intercepts and the covariance of the slope and intercept [293], it can profoundly affect interpretation of the

growth curve trajectory parameters, and therefore should be weighed carefully [371]. Typically, the original recorded value of time is rescaled. In the present study, 1 was subtracted from each time point (i.e. 1, 2, 3 and 4) so that the intercept (time 0) was at the initial or baseline assessment (i.e. prior to chemotherapy initiation). The value 1 indicated the next assessment point, which took place two weeks post-CThC1, and the value 2 indicated the third point of assessment, which occurred two weeks after administration of CThC4. Finally, the value 3 indicated the final assessment point. Thus, a one-unit change in time represents the interval between one assessment point and the following one.

Previous research in women with breast cancer has shown that sleep disturbances gradually increase in prevalence and severity after initial administration and during continuation of adjuvant chemotherapy, with a tendency for slight improvement towards and/or close after the end of treatment [119]. A curvilinear pattern of change is therefore possible. What is more, the lack of longitudinal research in caregivers of women with breast cancer precludes any conclusions to be drawn with regard to the trajectories of their own sleep patterns [182], and warrants detailed examination. Therefore, alternative quadratic models were also estimated to identify the best fit to the data. MHLM for longitudinal data typically requires 4 or more waves of data to estimate quadratic effects so that the within-dyad measurement error variance can be estimated [376]. An example model where PSQf was considered to change in a curvilinear (i.e. quadratic) fashion over time was the following:

$$\begin{aligned} PSQf_{tp} = {} & (\text{patient})[\beta_{1p} + \beta_{2p}(\text{timelin}_{tp}) + \beta_{3p}(\text{timequad}_{tp})] \\ & + (\text{caregiver})[\beta_{4p} + \beta_{5p}(\text{timelin}_{tp}) + \beta_{6p}(\text{timequad}_{tp})] \\ & + e_{tp}, \end{aligned} \qquad (2)$$

where the β_{3p} and β_{6p} coefficients represent the time effect (quadratic) for the patient and caregiver of perceived sleep quality, respectively. In a quadratic model, the linear component is usually interpreted as the average velocity, whereas the quadratic component explains the curvature of growth [470, 512]. For instance, a negative linear term followed by a positive quadratic term may indicate the presence of a decline in a sleep parameter that levels off as time elapses. Conversely, a positive linear term and a negative quadratic term may indicate that there was an increase in a sleep parameter, which again decelerates over time.

Univariate hypothesis testing (*t* ratio) was performed to indicate whether, on average, patient and caregiver intercepts and slopes differed significantly from zero on the basis of values of

unstandardised coefficients calculated via the HLM 7 programme. To facilitate interpretation of these coefficients, effect sizes r_{ES} were calculated based on the formula $r_{ES}=\sqrt{[t^2/(t^2+df)]}$, where t refers to the value of the t-test and df are the degrees of freedom associated with the particular test. Small, medium and large effects were designated by r_{ES} of .10, .30, and .50, respectively [507]. In addition, since separate scores for each dyad member were obtained in the same model, multivariate hypothesis testing was conducted within the HLM 7 software to examine significant differences between average patient and caregiver trajectories, i.e. baseline status and rates of change over time [371, 376].

Level 2 model: The Level 2 model (between-dyad model) aggregates the person-level estimates thus providing estimates for the entire sample of patients and caregivers, respectively. At Level 2, growth parameters from Level 1 are modelled as outcomes to be explained by characteristics of the dyad. They are permitted to vary across all Level 2 units (i.e. dyads) and can take on different values for each dyad. In this stage, the first step is to fit an unconditional Level 2 model (i.e. a model with no predictor variables at Level 2), which for a quadratic change is specified as follows:

$$\beta_{1p} = \gamma_{10} + u_{1p} \quad (3)$$

$$\beta_{2p} = \gamma_{20} + u_{2p} \quad (4)$$

$$\beta_{3p} = \gamma_{30} + u_{3p} \quad (5)$$

$$\beta_{4p} = \gamma_{40} + u_{4p} \quad (6)$$

$$\beta_{5p} = \gamma_{50} + u_{5p} \quad (7)$$

$$\beta_{6p} = \gamma_{60} + u_{6p} \quad (8)$$

This unconditional model provided estimates of the population averages (known as the fixed effects of the model) for each growth parameter for the patient (γ_{10}, γ_{20}, and γ_{30}) and for the caregiver (γ_{40}, γ_{50}, and γ_{60}) across dyads. The Level 2 random effects u_{1p}, u_{2p}, u_{3p}, u_{4p}, u_{5p}, and u_{6p} represent the deviation of each dyad from the respective population average growth parameter. The variances of these random effects (τ_{00}, τ_{11}, τ_{22}, τ_{44}, τ_{55}, τ_{66}) represent the heterogeneity across dyads, and were estimated to test whether they were significantly different from zero in the population. Any significant results are indicative of significant variability across dyads, hence time-invariant predictors (variables that do not change or were measured only once) can be introduced to explain this variability in a conditional MHLM model [371,

376]. In addition, relationships among these Level-2 variance components were examined in an attempt to identify notable correlations representing the extent of shared variance in each outcome variable for the members of a care dyad. Tau-correlation coefficients and 95% confidence intervals were produced for this purpose. Not only can tau-correlations reveal the relationship in trajectories of the dyad members, but also provide support for one's decision to use multilevel modelling in the first place [374, 376].

Explanatory MHLM

In longitudinal dyad models, not only time-invariant predictors (variables that are enduring), but also time-varying covariates/predictors (variables change over time) may be incorporated to control for the effects of a predictor that is measured over time, and examine more complex associations with the outcome. In the present study, changes in sleep parameters and psychosocial variables were measured ('sleep' and 'behavioural' predictors), whose association with the outcome variables was decomposed into two parts. As an example, this decomposition allowed the effects of sleep hygiene (SH) on perceived sleep quality (PSQf) to be separated into (a) the relationship between changes in SH and changes in PSQf (time-varying), and (b) the relationship between mean SH and mean PSQf scores for both members of the dyad (time-invariant).

Level 1: The Level 1 model includes the time-varying component of specific time-varying predictor. In the quadratic Level 1 model for PSQf (2), the time-varying component of SH is specified as follows:

$$\begin{aligned} PSQf_{tp} = {} & (\text{patient})[\beta_{1p} + \beta_{2p}(\text{timelin}_{tp}) + \beta_{3p}(\text{timequad}_{tp}) + \beta_{4p}(\text{SHPT}_{tp} - \overline{\text{SHPT}}_{.p})] \\ & + (\text{caregiver})[\beta_{5p} + \beta_{6p}(\text{timelin}_{tp}) + \beta_{7p}(\text{timequad}) + \beta_{8p}(\text{SHCG}_{tp} - \overline{\text{SHCG}}_{.p})] \\ & + e_{tp}, \end{aligned} \tag{9}$$

In model (9), $PSQf_{tp}$ represents perceived sleep quality (t=1, …K responses per dyad and point of assessment) for dyad p; β_{1p} and β_{3p} represent the intercepts for patients and caregivers; β_{2p} and β_{6p} represent the linear slopes for patients and caregivers; and β_{3p} and β_{7p} represent the quadratic slopes for patients and caregivers, respectively. The values for sleep hygiene (SH) at each time are deviations from the individual's mean on that variable, which capture the fluctuations in SH over the study period. Therefore, β_{4p} and β_{8p} represent the

time-varying effect of the patient's SH (SHPT) and the caregiver's SH (SHCG) on their respective PSQf score over time. Within-person centring – deviations at each time point of each individual's SH score from own mean SH score (averaged over four assessment points) – is used to create the time-varying component. This procedure was followed in the present study for each repeatedly measured predictor.

Level 2: The aforementioned model has eight coefficients (β_{1p} … β_{8p}), which can take on different magnitudes within and across dyads, and become outcome variables at Level 2. In this stage, the time-invariant component of the example predictor (SH) is included, which represents the degree to which mean SH scores averaged over time (four assessment points) relate to mean PSQf scores. The time-invariant component is modelled at Level 2 grand mean centred. Hence, the following initial explanatory Level 2 model is specified:

$$\beta_{1p} = \gamma_{10} + \gamma_{11}(\text{MEAN SHPT}) + u_{1p} \quad (10)$$

$$\beta_{2p} = \gamma_{20} + u_{2p} \quad (11)$$

$$\beta_{3p} = \gamma_{30} + u_{3p} \quad (12)$$

$$\beta_{4p} = \gamma_{40} \quad (13)$$

$$\beta_{5p} = \gamma_{50} + \gamma_{51}(\text{MEAN SHCG}) + u_{5p} \quad (14)$$

$$\beta_{6p} = \gamma_{60} + u_{6p} \quad (15)$$

$$\beta_{7p} = \gamma_{70} + u_{7p} \quad (16)$$

$$\beta_{8p} = \gamma_{80} \quad (17)$$

The between-dyad model provides estimates of the population averages for the intercept (γ_{10}), linear (γ_{20}) and quadratic change (γ_{30}) in PSQf scores for the patient, and for the intercept (γ_{50}), linear (γ_{60}) and quadratic change (γ_{70}) in PSQf scores for the caregiver. Mean SH (MEAN SHPT/CG) is included here with γ_{11} and γ_{51} representing the effect of each individual's mean SH score on own level of mean PSQf score. Coefficients γ_{40} and γ_{80} capture the average time-varying effect of SH across dyads. The random effects (u_{1p}, u_{2p}, u_{3p}, u_{5p}, u_{6p}, u_{7p}) represent the deviation of each individual from the average intercept, linear and quadratic effect for patients and caregivers, respectively. Again, significant variability in these parameters allows for the introduction of additional predictors in an effort to explain this variability. Random effects for the time-varying covariates were not included (γ_{40} and γ_{80} are

specified as fixed) because the six βs already in the Level 1 model completely saturate the temporal component of variation [376].

After testing models including the effect of an individual's own predictor scores on their own outcome variables, cross-care-partner effects were tested. Each of these models included two additional time-varying covariates for each predictor (Level 1) representing (a) the effect of patient predictor changes on caregiver outcome variables and (b) the effect of caregiver predictor changes on patient outcome variables, as well as two time-invariant effects (Level 2) representing (c) the effect of mean patient predictor scores on mean caregiver outcome variables and (d) the effect of mean caregiver predictor scores on mean patient outcome variables. For the example model of the effects of SH on PSQf, the Level 1 model is specified as:

$$
\begin{aligned}
PSQf_{tp} = {} & (\text{patient})[\beta_{1p} + \beta_{2p}(\text{timelin}_{tp}) + \beta_{3p}(\text{timequad}_{tp}) \\
& + \beta_{4p}(\text{SHPT}_{tp} - \overline{\text{SHPT}}_{.p}) + \beta_{5p}(\text{SHCG}_{tp} - \overline{\text{SHCG}}_{.p})] \\
& + (\text{caregiver})[\beta_{6p} + \beta_{7p}(\text{timelin}_{tp}) + \beta_{8p}(\text{timequad}) \\
& + \beta_{9p}(\text{SHCG}_{tp} - \overline{\text{SHCG}}_{.p}) + \beta_{10p}(\text{SHPT}_{tp} - \overline{\text{SHPT}}_{.p})] \\
& + e_{tp}, \qquad (18)
\end{aligned}
$$

Whereas the Level 2 model is specified as:

$$\beta_{1p} = \gamma_{10} + \gamma_{11}(\text{MEAN SHPT}) + \gamma_{12}(\text{MEAN SHCG}) + u_{1p} \qquad (19)$$

$$\beta_{2p} = \gamma_{20} + u_{2p} \qquad (20)$$

$$\beta_{3p} = \gamma_{30} + u_{3p} \qquad (21)$$

$$\beta_{4p} = \gamma_{40} \qquad (22)$$

$$\beta_{5p} = \gamma_{50} \qquad (23)$$

$$\beta_{6p} = \gamma_{60} + \gamma_{61}(\text{MEAN SHCG}) + \gamma_{62}(\text{MEAN SHPT}) + u_{6p} \qquad (24)$$

$$\beta_{7p} = \gamma_{70} + u_{7p} \qquad (25)$$

$$\beta_{8p} = \gamma_{80} + u_{8p} \qquad (26)$$

$$\beta_{9p} = \gamma_{90} \quad (27)$$

$$\beta_{10p} = \gamma_{100} \quad (28)$$

All explanatory models were adjusted for the effects of significant demographic/clinical covariates of sleep/wake impairment based on the results of preliminary correlational analyses. As previously stated, before they were entered at Level 2, all predictors and covariates were examined for multicollinearity. In cases where inter-correlations between predictors/mediators were particularly high (r>.85) [501], only selected covariates were entered into the Level 2 model based on examination of the magnitude of within-patient and within-caregiver correlations between the outcome and predictor variables. Interval-scale predictor variables/covariates were centred around the sample grand mean before entered into the model [293]; ordinal-scale variables were dummy-coded (0-1) before entered in the model (e.g. PS); and nominal-scale variables were entered in the models with no further recoding. All predictors/covariates were entered into the Level 2 models simultaneously to examine their association with variation in the patient's and caregiver's trajectories of sleep patterns. Multivariate hypothesis testing was conducted within the HLM 7 software to examine differences in the strength of the relationship between patient and caregiver predictors and outcome variables. As previously, unadjusted effect sizes r_{ES} were calculated for predictors and covariates based on the formula $r_{ES}=\sqrt{[t^2/(t^2+df)]}$, where t refers to the value of the t-test and df are the degrees of freedom associated with the particular test. Small, medium and large effects were designated by r_{ES} of .10, .30, and .50, respectively [507]. From the above-mentioned formula it can be inferred that r_{ES} is always positive in sign; however, by convention, r_{ES} was positively or negatively signed in this study to match the corresponding t ratio. All tests were conducted with a two-tailed level of significance of .05. However, due to the exploratory nature of the study, trends towards significance (.10>p≥.05) were also showed.

Model fit

For each individual outcome variable, the linear model's (1) fit to the data was first compared to the means-only model. The means-only model outputs the deviance statistic (–2 log likelihood or –2LL) as a baseline that can be used for comparisons with later, more complex models [516]. In addition, it provides information for the calculation of the intraclass correlation coefficient (ICC), which is the usual test of whether multilevel modelling is needed [516]. ICC ranges from +1.0 (i.e. group means differ but there is no within-group variation)

to –1/(*N*–1) (i.e. no between-group variation but very large within-group variation). When ICC approaches 0 or is negative, multilevel modelling is not appropriate [516]. In this study, the magnitude of ICC was calculated as the intercept variance component in the null model divided by the total of variance components (intercept plus residual).

Model (1) and Model (2) fit to the data was also compared through their deviance statistics. The change in the deviance statistic is distributed as χ^2 and can be tested relative to the change in the degrees of freedom. The model with the best fit to the data was considered as the Baseline MHLM for a specific outcome variable. When predictor (own and cross-care-partner) and covariate effects were tested, a similar procedure was followed but with comparisons between the deviance statistic of Explanatory MHLMs (9) and (18). These adjusted models were compared not only with each other but also with the aforementioned unadjusted/baseline ones to identify their fit to the data. Analyses were performed with full maximum likelihood estimation (FML) using all available data from all patients and caregivers. The FML method provides deviance statistics that, as stated, are useful in describing the fit of the entire model (fixed and random effects) [470]. However, FML may produce biased estimates of variances with small, unbalanced datasets [293]; therefore, all models were also estimated with restricted maximum likelihood estimation (REML). The effects estimated with FML and REML were very similar, thus only results produced with FML are presented here.

6.13. Study Feasibility Phase

In order to ensure that any inconsistencies in the research design were effectively managed and problems in the implementation of the research plan were timely tackled, a study feasibility phase was planned to precede the actual study phase [517]. Feasibility studies are pieces of research done before a main study to estimate important parameters that are needed to design or verify the design of the main study. Yet, they are different from pilot studies, which are regarded as miniatures of large studies to be conducted. With feasibility studies, researchers are able to evaluate several key parameters: standard deviation of the outcome measure, which is needed in some cases to estimate sample size; number of eligible patients; appropriateness of eligibility criteria; willingness of participants to participate; willingness of clinicians to recruit participants; characteristics of the proposed outcome; appropriateness of the data collection plan; response rates to questionnaires and adherence/compliance rates;

or adequacy of financial resources [517]. Feasibility of the plan for this study was verified drawing on data derived from the first four dyads recruited. The feasibility phase spanned over three months from 1st November 2010 to 31st January 2011, after the study was granted R&D Management Approval to proceed at the first participating NHS site (Appendix 8). A number of methodology-, design-, and procedure-related parameters were evaluated for effectiveness. **Table 6.3** outlines all relevant parameters reviewed and evaluated for their effectiveness.

Table 6.3. Summary of key parameters evaluated during the project's feasibility phase

Parameter	**Evaluation***
Identification of patients easy?	⦿⦿⦿
Eligibility criteria realistic?	⦿⦿⦿
Availability of individuals?	⦿⦿○
Study design feasible?	⦿⦿⦿
Missing data rates satisfactorily low?	⦿⦿⦿
Data collection plan effective?	⦿⦿⦿
Time-points realistic?	⦿⦿⦿
Time-points acceptable to patients?	⦿⦿⦿
Time-points acceptable to health professionals?	⦿⦿○
Recruitment rates satisfactory?	⦿○○
Questionnaire mailing system effective?	⦿⦿○
Collaboration with the clinical team effective?	⦿⦿○
Recruitment strategy effective?	⦿⦿⦿
Patients willing to take part in the study?	⦿⦿⦿
Caregivers willing to take part in the study?	⦿⦿⦿
Rates of withdrawals low?	⦿⦿⦿
Financial resources adequate?	⦿⦿○

Note: ⦿⦿⦿ Yes; ⦿⦿○ Unclear; ⦿○○ No

In all, eligibility criteria proved realistic, also facilitating the identification of potential patients during the clinics. Similarly, the patient and caregiver recruitment strategy was regarded as effective, leading to four participating dyads out of a total of five approached. Not only were patients and caregivers willing to take part in the study, but they also freely expressed their eagerness to provide as much relevant information as possible throughout the study. In that sense, rates of withdrawals for the first four dyads were zero, while missing data rates were more than satisfactorily low as < 0.5% of variables were missing. Moreover, the study design was feasible and the data collection plan was effective, with time-points regarded as being both realistic and acceptable by both patients and clinicians. In spite of

some minor delays over the Christmas period (December 2010), the questionnaire mailing system was more than effective, with participants receiving questionnaires in a timely manner, and no questionnaires going missing.

The afore-mentioned positive outcomes signalled that the study could proceed to its actual phase. Yet, the availability of patients with early-stage breast cancer scheduled to receive adjuvant chemotherapy seemed to be unclear. Given the increased number of clinical trials concurrently taking place as the present study, only a small proportion of the total of diagnosed women eventually entered this study. As well, collaboration with the clinical team proved to be more than challenging because tight time schedules and increased overload prevented clinicians from giving the study the attention required; in conjunction with clinicians' unwillingness to overload patients with information on several different clinical trials, recruitment rates dropped considerably by the end of the third month of recruitment, leading to only three additional dyads entering the study out of five approached. In light of these developments, a decision was made to bring more recruitment sites on board to meet the study's timelines and deadlines. Therefore, contact was made with clinicians from February to June 2011 at three additional NHS sites, and R&D approval was granted for the study to take place at each site.

CHAPTER 7.
Results

7.1. Accrual Rates

From November 2010 to April 2012, 97 newly diagnosed women with early stage breast cancer were approached at the participating sites after eligibility to the study had been confirmed by local collaborators. All women received information on the study's purposes and goals and were subsequently invited to consider participation. Twenty women refused participation due to a variety of reasons, as outlined in **Figure 7-1**. For 7 more women no contact was made, either because they could not be reached over the phone (5 individuals) or because of a delay in the researcher's notification of a new eligible patient that eventually resulted in insufficient recruitment time before chemotherapy treatment initiation. Preliminary analyses indicated no statistical differences between women who refused (n=20) and those who gave verbal consent to the study (n=70) with regard to demographic (i.e. age) and clinical characteristics (i.e. breast cancer stage, type of surgery) (all p>.05).

Seventy women were contacted by the researcher, were fully informed on the study's procedures, were invited to identify their primary informal caregiver, and provided initial verbal consent; yet, two women called back before any data had been provided and requested to withdraw their consent. Consent forms were sent to the remaining 68 individuals. However, 7 women never returned written consent forms nor provided data to the study, and were consequently eliminated from the study. The remaining 61 women (62.9% of the eligible individuals) provided written informed consent, but only 52 were also able to identify a caregiver for the purposes of the study. Reasons for not being able to identify a carer are outlined in **Figure 7-1**. Preliminary analyses indicated no statistical differences between women who identified a carer (n=52) and those who did not (n=9) with regard to demographic and clinical characteristics (all p>.05), except for a statistical difference according to marital status: married women were more likely to identify a carer compared to those single, widowed or divorced/separated (89% v. 60%; $\chi^2(3)=9.276$; p=.026).

Informal caregivers were approached either at the clinic during the patient's appointment or contacted at a later point over the phone. All 52 carers provided initial verbal consent; how-

ever, 3 individuals failed to return a written consent form as well as data to the study. In addition, one patient also failed to provide data at any assessment point. Hence, in total, 60 patients and 49 caregivers participated in at least one wave of assessment. As the study focused on care dyads, women with breast cancer and their respective family caregivers were excluded from further analyses if no caregiver had been identified, or if the patient or the carer did not complete at least one wave of data collection. Therefore, the final sample consisted of 48 care dyads, who participated in at least one wave of assessment.

7.2. Attrition Rates and Patterns of Missingness

Information about the number of patients, caregivers and dyads who completed study questionnaires at each time of assessment is presented in **Figure 7-2**. Although 48 dyads participated in baseline assessments, data from only 42 patients, 37 caregivers and 36 dyads were received at the end of the study. These results are translated as an attrition rate of 12.5%, 22.9% and 25% for patients, caregivers and dyads, respectively. Across all assessment points, reasons for loss to follow-up included busy patient and caregiver schedules, family member's illness, preliminary termination of chemotherapy due to toxicity, caregiver working abroad, and caregiver death. Attrition in this repeated measures study created an unbalanced dataset, with unequal numbers and timing of assessments from individual to individual and from dyad to dyad. The structure of missingness is displayed in **Figure 7-3**, where a variety of missing data patterns is shown; in all, 34 dyads (70.8% of total) had complete data (four assessments for the patient and four for the caregiver).

In light of the aforementioned small to moderate attrition rates, separate analyses were pursued to examine the possibility of attrition bias interfering with the data. Firstly, participants who completed all four assessments (n=40 patients; n=34 caregivers) were contrasted with those who did not (n=8 patients; n=14 caregivers) in terms of baseline demographic and clinical characteristics. The only significant associations were found with regard to duration (t_{45}=3.14; p=.003) and type of relationship (p=.040; Fisher's exact test) for patients, and duration (t_{45}=2.36; p = .023) and type of relationship ($\chi^2(1)$=9.71; p=.002) for caregivers. In other words, patients and caregivers completing all four assessments were more likely to be in a long-standing relationship and be married/partnered.

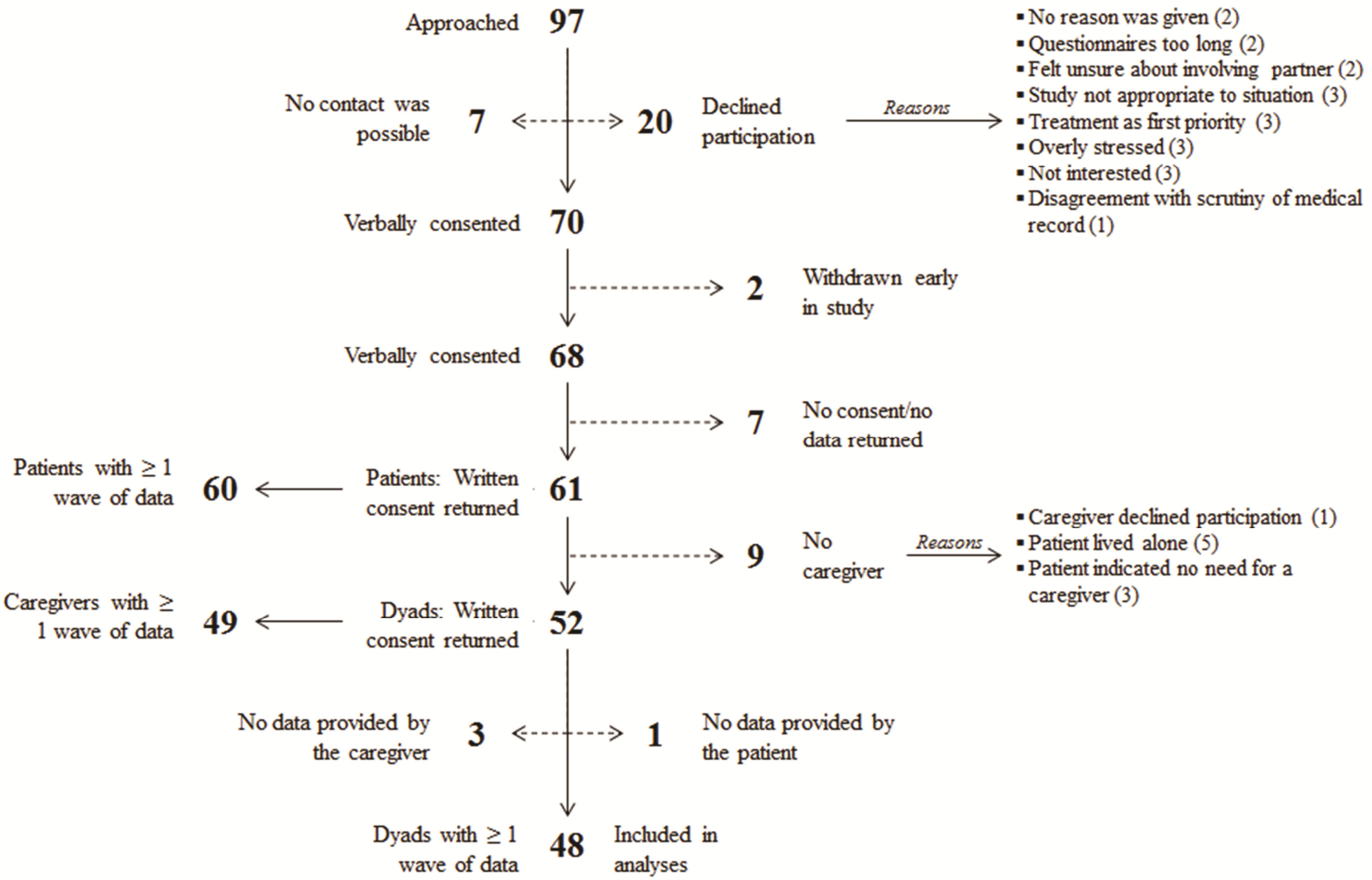

Figure 7-1. Summary of accrual rates.

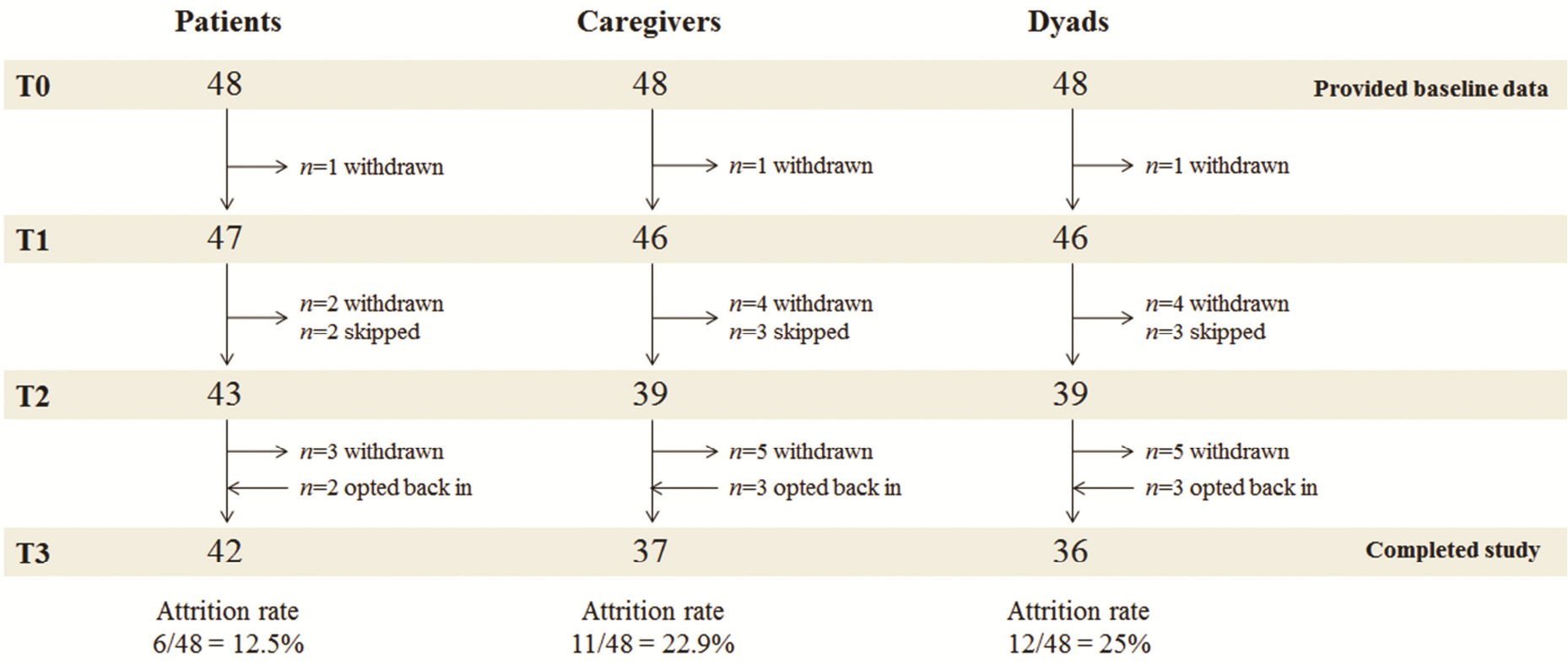

Figure 7-2. Summaries of patient, caregiver and dyad participation and attrition rates throughout the study.

Secondly, participants who completed the study irrespective of number of completed assessments (n=42 patients; n=37 caregivers) were similarly contrasted with those who did not (n=6 patients; n=11 caregivers). No statistical differences emerged (all p>.05). On the other hand, dyads who completed all four assessments (n=34) and those who did not (n=14) were contrasted. Significant differences were found with regard to patient employment status ($\chi^2(1)=4.55$; p=.033), duration of relationship ($t_{45}=2.36$; p=.023), type of relationship (p=.003; Fisher's exact test), and patient sleep affected by diagnosis ($\chi^2(1)=4.55$; p=.033). Dyads completing all four assessments were more likely to include retired or unemployed patients, individuals in long-standing relationships, spouses or partners, and patients whose sleep had not been affected by the diagnosis of breast cancer.

	Patients				
Caregivers	**1 Assessment**	**2 Assessments**	**3 Assessments**	**4 Assessments**	**Totals**
1 Assessment	–	–	–	1	1
2 Assessments	–	3	1	2	6
3 Assessments	–	1	3	3	7
4 Assessments	–	–	–	34	34
Totals	–	4	4	40	48

Figure 7-3. Patterns of missingness in the current study (*Note:* Each lightly-coloured cell indicates the number of assessments that members of a dyad completed in the study; numbers in these cells indicate the total number of dyads for a specific pattern of missingness).

Finally, when dyads who completed the study (irrespective of number of completed assessments) (n=36) and those who did not (n=12) were contrasted, the only significant difference that was found related to type of relationship (p=.036; Fisher's exact test); hence, dyads completing the final assessment were more likely to be those in a long-standing relationship. Overall, these non-significant findings provided good support to the assumption that data were not affected by attrition.

When baseline and T1 scores on PSQf, GSQI and predictor variables were similarly compared between completers and non-completers, no significant differences were found (all

p>.05). In conjunction with covariates for which significant differences emerged being accounted for in later analysis stages, the above analyses supported the assumption of missing-at-random data and, therefore, justified the use of multilevel modelling in the main analyses section.

7.3. Sample Characteristics

Demographic characteristics of the 48 care dyads are outlined in **Table 7.1**. The typical patient was 55 years old, had received high school education, was married and employed, with average to high yearly income. The typical caregiver was male, 54 years old, had received high school education, was married and employed, with average to high yearly income, and was the patient's spouse or heterosexual partner. The sample mainly consisted of wife-husband dyads (n=30; 62.5%), although heterosexual partners (n=10; 20.8%), mother-child dyads (n=7; 14.6%), and one dyad of friends were also present. Care dyads, on average, had well-established relationships, the mean length of which was 356.1 months (SD=161.3; range=18-624), or approximately 30 years. Analysis of variance indicated that mean length of relationship was greater in the spouse or mother-child dyads compared to the partner dyads ($F_{3,\ 43}$=22.15; p<.001). No differences were found between the patient and caregiver groups in terms of their demographic features, except for a significant difference in marital status: the patient group comprised of more divorced/separated or widowed women compared to the caregiver group in which individuals were more likely to be single ($\chi^2(3)$= 9.01; p=.029).

Table 7.2 summarises the clinical characteristics of the participating dyads. On average, women had been diagnosed 75 days and underwent breast surgery 41 days prior to chemotherapy initiation. In their majority, women were diagnosed with stage II breast cancer (62.5%) and underwent breast conserving surgery (58.3%) with axillary node clearance. Sixty-five per cent of the women received 21-day cycles of FEC (Fluorouracil, Epirubicin 75 or 80 mg/m^2, Cyclophosphamide). For 9 additional women, FEC was complemented by additional cycles of Paclitaxel or Docetaxel. Other chemotherapy regimens included AC (Adriamycin, Cyclophosphamide), CAF (Cyclophosphamide, Adriamycin, and Fluorouracil) or TC (Paclitaxel, Cyclophosphamide) of diverse length. In line with administration guidelines for highly emetogenic chemotherapy regimens, prior to each cycle women received intravascular pre-medication consisted of a combination of

corticosteroid (e.g. dexamethasone 8 mg) and anti-emetic (e.g. granisetron 8 mg, ondansetron 8 mg) and/or anti-histaminic agents (e.g. ranitidine); they were also prescribed dexamethasone to be taken orally for the first 3-4 days after chemotherapy administration. Three women were excluded from this medication scheme as they had also been diagnosed with Type II diabetes. Whereas the majority of patients completed treatment without breaches in the chemotherapy protocol, three women experienced haematological toxicity that caused one week's delay in treatment continuation, whereas one additional woman experienced severe cardiotoxicity which required her treatment to change to another regimen.

Table 7.1. Participant demographic characteristics (*n*=48 dyads).

Variable/Category	Patients	Caregivers	Test statistic (*df*)
	***M* (SD); Range**	***M* (SD); Range**	
Age (years)	55.44 (8.89); 38-74	53.81 (14.51); 18-89	1.05 (47)[ns,a]
	***n* (%)**	***n* (%)**	
Gender			
Male		43 (89.6)	NA
Female	48 (100.0)	5 (10.4)	
Marital status			
Married/partnered	39 (81.3)	40 (83.3)	9.01 (3)*[,b]
Single	0 (0.0)	5 (10.4)	
Divorced/separated	6 (12.5)	3 (6.3)	
Widowed	3 (6.3)	0 (0.0)	
Educational background			
High school	32 (66.7)	33* (70.2)	.14 (1)[ns,b]
College/university	16 (33.3)	14 (29.8)	
Employment status			
Employed (FTM/PTM)	30 (62.5)	33 (68.8)	.42 (1)[ns,b]
Unemployed/retired	18 (37.5)	15 (31.3)	
Yearly household income			
≤ £10,000	6* (13.0)	6* (12.8)	.12 (3)[ns,b]
£10,001-20,000	8 (17.4)	9 (19.1)	
£20,001-50,000	22 (47.8)	21 (44.7)	
> £50,000	10 (21.8)	11 (23.4)	
Relation to patient			
Husband/partner		40 (83.3)	NA
Child		7 (14.6)	
Friend		1 (2.1)	

Abbreviations: FTM – full-time; PTM – part-time; NA – not applicable; *df* – degrees of freedom; SD – Standard Deviation.
[a] Paired samples *t*-test.; [b] Chi-square test.
*Valid percentages accounted for missing values

Table 7.2. Participant baseline clinical characteristics (*n*=48 dyads).

Variable	Patients	Caregivers	Test statistic (*df*)
	***M* (SD); Range**		
Time since diagnosis (days)	74.7 (26.7); 21-155		NA
Time since surgery (days)	41.0 (14.7); 13-87		NA
BMI (kg/m^2)‡	29.2 (7.6); 18.6-49.2		NA
	***n* (%)**	***n* (%)**	
Breast cancer stage			
I	6 (12.5)		NA
II	30 (62.5)		
IIIA	12 (25.0)		
Type of surgery			
Mastectomy	20 (41.7)		NA
Wide local excision	28 (58.3)		
Chemotherapy regimen			
FEC	31 (64.6)		NA
FEC + Taxanes	9 (18.8)		
Other	8 (16.6)		
Menopausal status			
Pre-menopausal	15 (31.3)		NA
Peri-menopausal	8 (16.6)		
Post-menopausal	25 (52.1)		
Number of comorbidities			
0	17 (35.4)	22 (45.8)	–2.22[ns,a]
1-2	23 (48.0)	22 (45.8)	
≥ 3	8 (16.6)	4 (8.4)	
ECOG Performance status			
0	21 (43.7)	39 (81.3)	–2.80**[,a]
1	26 (54.2)	6 (12.4)	
2	1 (2.1)	3 (6.3)	
Physical activity			
Minimally active	23 (47.9)	23 (47.9)	.00 (1)[ns,b]
Highly active	25 (52.1)	25 (52.1)	
Smoking status (Yes)	5 (10.4)	17 (35.4)	8.49 (1)**[,b]
Alcohol consumption			
Never	5 (10.4)	5 (10.4)	.39 (2)[ns,b]
Only occasionally	38 (79.2)	36 (75.0)	
Daily	5 (10.4)	7 (14.6)	
Pain medications use (Yes)	15 (31.3)		NA
Alternative therapies use (Yes)	4 (8.3)		NA
Prescribed medications use (Yes)		24 (51.1)*	NA
OTC medications use (Yes)		6 (12.5)	NA

Abbreviations: NA – not applicable; *df* – degrees of freedom; FEC – Fluorouracil, Epirubicin, Cyclophosphamide; BMI – Body mass index; ECOG – Eastern Cooperative Oncology Group; OTC – Over-the-counter; SD – Standard deviation.

[a] Wilcoxon signed ranks test.; [b] Chi-square test.; ‡ *n*=45

*Valid percentages accounted for missing values

The majority of women in this sample were either overweight (24.4%; BMI=25.0-29.9 kg/m^2) or obese (44.5%; BMI≥30 kg/m^2). At baseline, 52.1% of women self-reported as being in menopause, whereas the remaining described themselves as either pre- (31.3%) or peri-menopausal (16.6%). At the end of the study (T3), only six women self-reported as being pre-menopausal, whereas 24.4% and 62.2% of the sample were either peri- or post-menopausal, respectively. This was a statistically significant change with more women moving into or close to menopause as a result of chemotherapy compared to pre-treatment (McNemar (2)=9.00; *p*=.011). In addition, 31.3% of women reported the use of pain medications at baseline. **Figure 7-4** illustrates changes in the frequency of pain medication use. Cochran's Q test revealed a statistically significant difference (Q_3=9.17; *p*=.027) with prevalence of pain medication use steadily increasing from T0 through T2 and then decreasing at T3. Examples of agents with analgesic properties throughout the study included paracetamol, ibuprofen, diclofenac, codeine and tramadol. What is more, **Figure 7-4** presents changes in the patient frequency of complementary/alternative (CAM) therapies use, which for this study was particularly low (8.3%-16.3%) at every time-point. Although frequency of CAM use showed a slight increase at T1 and T2, this was not statistically significant (Q_3=5.40; *p*=.145). Examples of CAM therapies used included reflexology, self-hypnosis, aromatherapy, Reiki, and acupuncture. Approximately half of the caregivers (51.1%) indicated the use of prescribed medications at baseline. Yet, over-the-counter medication use was particularly low (12.5%) at this time-point.

As a group, the majority of women (64.6%) were experiencing at least one concurrent chronic health condition to breast cancer. These ranged from hypothyroidism, hypertension, and hypercholesterolaemia to arthritis, asthma, diabetes, diverticular disease, fibromyalgia, and systemic lupus erythematosus. Similarly, 54.2% of informal caregivers were experiencing at least one chronic health condition, including hypertension, hypercholesterolaemia, angina, arthritis, chronic obstructive pulmonary disease, diabetes, benign prostatic hyperplasia, and HIV infection. Paired groups analyses indicated that statistically significantly women suffered from more chronic health conditions compared to their caregivers (Z=–2.22; *p*=.026).

In spite of these chronic conditions, the majority of both patients and caregivers maintained high levels of leisure time physical activity at baseline (**Table 7.2**), with at least 3 hours of mild activity and at least 1 hour of moderate to strenuous activity per week. This seemed to be analogous to the infrequent smoking and the occasional consumption of alcohol per week in both groups. No significant fluctuation in patients' (Q_3=.94; *p*=.816) and caregivers' (Q_3=4.86; *p*=.183) activity levels was found throughout the study. Moreover, no significant

between-group differences were found at any of the four assessment points (all $p>.05$; chi-square analyses not shown), thus suggesting that patients and caregivers maintained similar levels of leisure time physical activity throughout the patient's treatment.

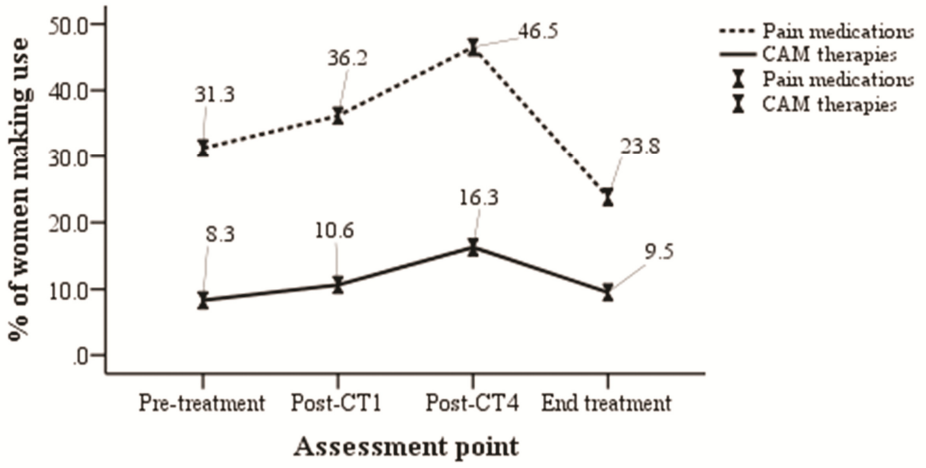

Figure 7-4. Over-time fluctuations in pain medication and CAM therapies use in the patient group over the chemotherapy treatment period (n=40-48 individuals).

In terms of overall physical functioning, women reported good (54.2%) to excellent (43.7%) performance status at baseline; conversely, in their vast majority (81.3%) caregivers indicated excellent performance status at the same time-point. At baseline, caregivers had statistically significantly better performance status than the women they were caring for ($Z=–2.80$; $p=.005$). Although a decline in performance status was apparent for both groups (especially for patients) from T0 to T1 and from T1 to T2, this was statistically significant only for patients (Friedman test; $\chi^2(3)=24.30$; $p<.001$) but not for caregivers (Friedman test; $\chi^2(3)=4.15$; $p<.246$) (**Figure 7-5**). However, throughout the study performance status of caregivers was consistently better than that of women they were caring for (all $p<.001$; Wilcoxon Signed Rank test analyses not shown).

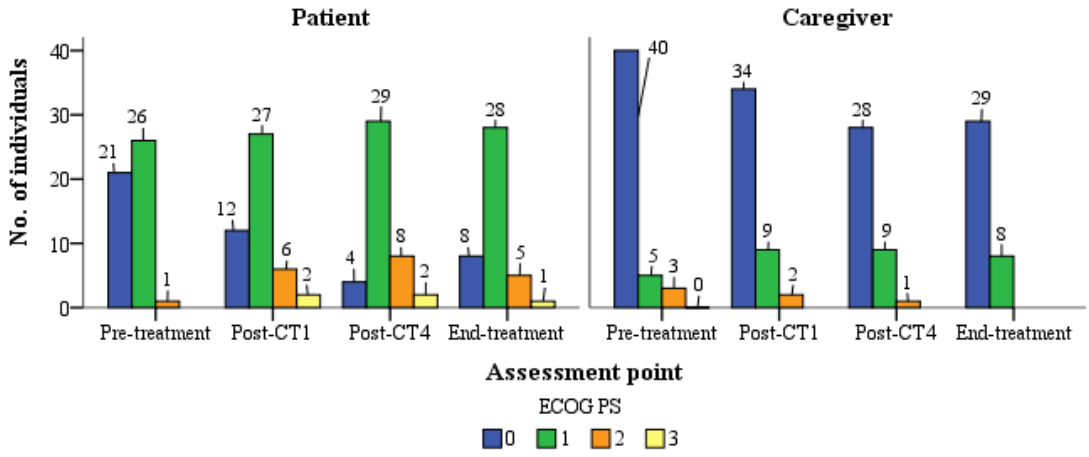

Figure 7-5. Graphical representation of fluctuations in patient and caregiver performance status throughout the study (*Note:* Higher scores indicate poorer performance status).

7.4. Descriptive Analysis of Dyadic Sleep and Predictor Variables

Tables 7.3 and **7.4** provide an overview of means, standard deviations and ranges for all patient and caregiver sleep and predictor variables as these were measured throughout the study. At all time-points, mean GSQI scores for both patients and caregivers exceeded an established cut-off score of 5 for clinically significant sleep/wake impairment. Based on this cut-off point, 52.1-76.7% of patients and 35.1-48.7% of caregivers could be identified as experiencing impaired sleep/wake patterns throughout the study (**Figure 7-6**). At T1 and T2, mean patient GSQI scores also exceeded a cancer-specific threshold of 8. Based on this threshold, 33.3-44.7% of the women were classified as having clinically significant sleep disturbance throughout the study. **Figure 7-7** presents results similar to the afore-mentioned findings seen from a dyadic standpoint. It is apparent that, at baseline, 65% of the dyads consisted of one or two poor sleepers. However, over treatment continuation, dyads with one poor sleeper exceeded 45%, whereas for an additional 35%, both the patient and the caregiver experienced poor sleep.

Table 7.3. Descriptive data of patient and caregiver outcome variables throughout the study.

	Patients				Caregivers			
	T0 (*n*=48)	**T1 (*n*=47)**	**T2 (*n*=43)**	**T3 (*n*=42)**	**T0 (*n*=48)**	**T1 (*n*=46)**	**T2 (*n*=39)**	**T3 (*n*=37)**
Bedtime (24h time)								
M (SD)	22:47 (0:45)^{ns}	22:36 (0:56)^{ns}	22:27 (0:55)*	22:34 (0:57)*	22:51 (0:59)	22:49 (0:58)	22:45 (0:55)	22:45 (0:50)
Range	21:30-01:00	19:45-01:00	20:30-01:00	20:00-01:00	21:00-01:00	21:00-02:00	21:00-01:00	21:00-00:00
Wake time (24h time)								
M (SD)	07:49 (1:00)***	07:54 (1:02)**	07:51 (1:00)*	07:53 (0:55)***	07:00 (1:15)	07:12 (1:34)	07:12 (1:25)	07:03 (1:12)
Range	06:00-11:00	05:00-10:00	05:00-10:00	06:00-10:00	04:00-10:00	04:00-12:00	03:30-11:00	04:30-09:00
GSQI (0-21)								
M (SD)	6.58 (4.25)^{ns}	8.19 (4.03)***	8.47 (4.18)**	7.29 (3.34)*	5.54 (3.48)	5.50 (3.26)	5.82 (3.77)	5.19 (3.41)
Range	0-18	1-17	2-17	1-13	1-15	1-15	0-14	1-14
PSQf (0-9)								
M (SD)	2.73 (2.20)†	3.32 (2.16)**	3.26 (2.40)*	2.60 (1.52)*	2.08 (1.61)	1.91 (1.56)	2.28 (1.70)	1.81 (1.53)
Range	0-9	0-8	0-9	0-6	0-6	0-6	0-6	0-6
DDISTf (0-6)								
M (SD)	1.90 (.97)^{ns}	2.23 (.91)^{ns}	2.63 (1.00)***	2.57 (1.17)**	1.96 (1.05)	2.02 (1.15)	1.85 (.96)	1.95 (1.10)
Range	0-4	1-5	1-5	1-5	0-4	0-5	0-4	0-5
HSE (%)								
M (SD)	75.95 (13.54)*	71.15 (16.43)***	72.09 (12.41)**	75.33 (12.11)*	81.88 (12.77)	82.52 (11.69)	80.03 (11.99)	81.82 (10.32)
Range	41.38-96.77	33.33-94.73	45.00-95.65	48.00-100.00	37.04-100.00	50.00-100.00	50.00-100.00	56.25-94.73
SL (minutes)								
M (SD)	26.06 (17.76)*	32.00 (29.27)**	30.74 (20.33)^{ns}	24.74 (18.07)^{ns}	20.54 (13.02)	18.70 (15.61)	29.03 (35.43)	20.59 (12.63)
Range	2-90	1-150	2-90	5-90	2-60	5-90	5-185	5-60
TST (minutes)								
M (SD)	408.75 (70.79)^{ns}	396.51 (97.75)^{ns}	407.09 (96.25)^{ns}	417.86 (76.81)^{ns}	404.67 (85.50)	420.00 (98.74)	405.00 (88.88)	407.84 (73.98)
Range	180-480	150-570	150-660	300-600	90-600	90-720	120-600	180-540
WASO (minutes)								
M (SD)	105.08 (73.10)**	130.74	125.65 (67.39)**	112.95 (66.09)**	68.60 (50.95)	67.50 (54.57)	73.54 (57.54)	70.49 (50.37)

	Patients				Caregivers			
	T0 (*n*=48)	**T1 (*n*=47)**	**T2 (*n*=43)**	**T3 (*n*=42)**	**T0 (*n*=48)**	**T1 (*n*=46)**	**T2 (*n*=39)**	**T3 (*n*=37)**
		(93.37)***						
Range	0-320	10-375	20-315	0-352	0-195	0-210	0-220	10-195
NAPTIME (minutes)								
M (SD)	22.00 (29.25)†	35.34 (44.29)*	45.19 (51.77)*	33.64 (36.78)**	11.88 (19.64)	16.91 (32.09)	20.69 (35.88)	15.78 (19.42)
Range	0-120	0-240	0-300	0-120	0-75	0-180	0-180	0-60
NOCAW (0-3)								
M (SD)	1.42 (.85)^{ns}	1.68 (.76)*	1.58 (.70)†	1.60 (.73)^{ns}	1.46 (.90)	1.33 (.94)	1.31 (.77)	1.41 (.80)
Range	0-3	1-3	1-3	0-3	0-3	0-3	0-3	0-3
EARLAW (0-3)								
M (SD)	1.38 (1.10)^{ns}	1.36 (1.13)†	1.58 (1.12)^{ns}	1.48 (1.02)^{ns}	1.21 (1.25)	0.91 (1.09)	1.33 (1.33)	1.11 (1.17)
Range	0-3	0-3	0-3	0-3	0-3	0-3	0-3	0-3
SLPNSS (0-3)								
M (SD)	.83 (.59)^{ns}	1.06 (.60)†	1.33 (.61)**	1.19 (0.59)**	.79 (.74)	.85 (.56)	.85 (.67)	.76 (.60)
Range	0-2	0-2	0-3	0-3	0-3	0-2	0-2	0-2
RSTLSSLG (0-3)								
M (SD)	.50 (1.01)^{ns}	.40 (.88)^{ns}	.58 (.96)^{ns}	.52 (.99)^{ns}	.56 (1.01)	.41 (.83)	.38 (.82)	.54 (1.02)
Range	0-3	0-3	0-3	0-3	0-3	0-3	0-3	0-3
MORNFEEL (0-3)								
M (SD)	1.23 (.83)^{ns}	1.26 (.82)^{ns}	1.44 (.88)^{ns}	1.64 (.69)*	1.40 (.96)	1.33 (.92)	1.23 (.93)	1.22 (.89)
Range	0-3	0-3	0-3	0-3	0-3	0-3	0-3	0-3
NAPNEED Yes %	50.0^{ns}	74.5**	76.7†	66.7^{ns}	41.7	47.8	56.4	56.8
SAU Yes %	18.8†	19.1^{ns}	23.3^{ns}	7.1^{ns}	6.3	10.9	10.3	5.4

Abbreviations: GSQI – Global Pittsburgh Sleep Quality Index score; PSQf – Perceived Sleep Quality factor; SEf – Sleep Efficiency factor; DDISTf – Daily Disturbances factor; HSE – Habitual Sleep Efficiency; SL – Sleep Latency; TST – Total Sleep Time; WASO – Wakefulness after Sleep Onset; TIMENAP – Duration of Daytime Napping; NOCAW – Nocturnal Awakenings score; EARLAW – Early Awakenings score; SLPNSS – Daytime Sleepiness score; RSTLSSLG – Restless Legs score; MORNFEEL – Feelings Upon Morning Awakening score; NAPNEED – Need for Daytime Napping; SAU – Sleep Aid Use.

Note: Whilst sample size varies for each assessment time-point, sample sizes are the same for all sleep variables because missing values were treated with mean substitution given the very low extent of missing data due to non-response. Paired samples t-tests and Wilcoxon Signed Ranks tests were used to compare patients and caregivers on different sleep variables at each time point, except for NAPNEED and SAU where χ^2 tests were used instead: $^{ns}p>10$; $^{\dagger}p<.10$; $^{*}p<.05$; $^{**}p<.01$; $^{***}p<.001$.

Table 7.4. Descriptive data of patient and caregiver 'behavioural' predictor variables throughout the study.

	Patients				Caregivers			
	T0 (*n*=48)	**T1 (*n*=47)**	**T2 (*n*=43)**	**T3 (*n*=42)**	**T0 (*n*=48)**	**T1 (*n*=46)**	**T2 (*n*=39)**	**T3 (*n*=37)**
SH (0-52)								
M (SD)	10.60 (4.73)^{ns}	8.47 (4.92)^{ns}	8.60 (5.44)^{ns}	8.74 (5.16)^{ns}	10.33 (6.78)	10.52 (8.30)	9.92 (6.75)	8.30 (6.75)
Range	0-23	0-22	0-22	0-19	1-29	0-42	0-26	0-24
PHYSPT (0-4)								
M (SD)	.382 (.284)	.663 (.385)	.856 (.495)	.746 (.478)	–	–	–	–
Range	.000-1.119	.110-1.786	.109-2.309	.000-2.352				
PSYCH (0-4)								
M (SD)	1.20 (.83)^{ns}	.72 (.79)**	.81 (.79)^{ns}	.93 (.85)^{ns}	1.43 (.79)	1.12 (.81)	.97 (.89)	.92 (.92)
Range	.00-2.87	.00-3.17	.00-2.85	.00-3.13	.00-3.00	.00-2.99	.00-2.83	.00-2.77
COPNEG (12-48)								
M (SD)	18.73 (4.29)**	17.09 (3.36)^{ns}	16.51 (3.47)^{ns}	15.93 (2.99)^{ns}	15.73 (3.97)	16.09 (4.49)	15.87 (5.49)	15.84 (5.46)
Range	12-37	12-23	12-23	12-24	12-30	12-32	12-37	12-38
CRACB (9-45)								
M (SD)	–	–	–	–	18.65 (6.02)	19.35 (6.15)	19.13 (5.82)	18.41 (5.80)
Range					9-33	9-31	9-30	9-31
SDSTRB (0-27)								
M (SD)	8.02 (4.58)^{ns}	8.79 (4.30)*	9.51 (5.13)**	9.52 (4.75)**	7.79 (4.61)	7.07 (4.33)	6.41 (4.13)	6.38 (4.40)
Range	0-19	1-19	1-24	2-20	0-20	0-21	0-15	0-19

Abbreviations: SH – Sleep Hygiene Index total score; PHYSPT – Patient Physical Distress score from MSAS; PSYCH – Psychological Distress score from MSAS; COPNEG – Negative Coping score from COPE; CRACB – Caregiver Burden score from CRAS; SDSTRB – PSQI Sleep Disturbance Score.

Note: Whilst sample size varies for each assessment time-point, sample sizes are the same for all sleep variables because missing values were treated with mean substitution given the very low extent of missing data due to non-response.

Paired samples t-tests and Wilcoxon Signed Ranks tests were used to compare patients and caregivers on different predictor variables at each time point: $^{ns}p>.10$; $^{\dagger}p<.10$; $*p<.05$; $**p<.01$; $***p<.001$.

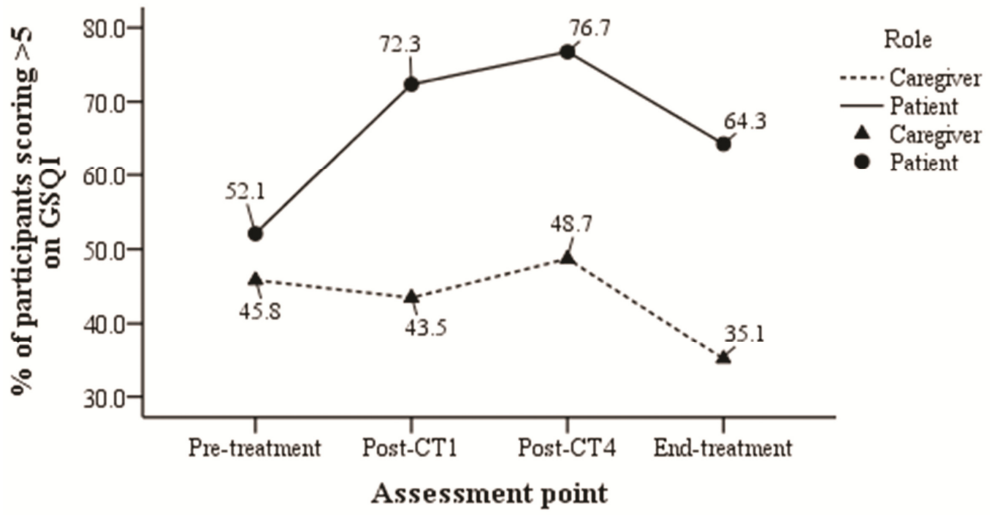

Figure 7-6. Percentages of patients and caregivers scoring above 5 on GSQI (indicating impaired sleep/wake patterns) at different time points throughout chemotherapy (*n*=36-48 dyads).

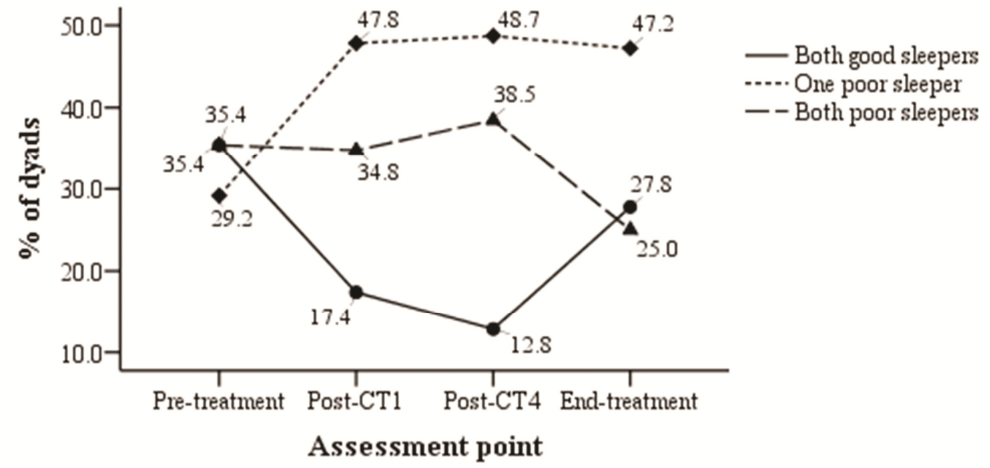

Figure 7-7. Percentages of patient-caregiver dyads with two good sleepers (both ≤5 on GSQI), one poor sleeper (one >5 and one ≤5 on GSQI), or two poor sleepers (both >5 on GSQI) at different time points throughout chemotherapy (*n*=36-48 dyads).

Mean habitual sleep efficiency was reported as lower than a cut-off score of 80% by patients and marginally above this score by caregivers, irrespective of timing of assessment; this was also true for mean sleep latency and mean sleep duration values, which were greater than 20 minutes and lower that 420 minutes, respectively, at all time-points for patients and caregivers (except for T1). Regardless of over-time fluctuations, on average, patients were awake during the night for at least one-and-a-half hour, with caregivers being awake for at least one hour.

Evidence of disrupted sleep patterns was further corroborated by reports of frequency of nocturnal awakenings, which for 35.4-51.1% of patients and 30.4-39.6% of caregivers exceeded 3 per night throughout the study; reports of early morning awakenings, where 16.7–27.9% of patients and 13.0-30.8% of caregivers awoke early and could not go back to sleep; and feelings of being only a little bit or not at all rested upon waking up in the morning in 39.6-57.1% of patients and 29.7-39.6% of caregivers. Yet, only 7.1-23.3% of patients and 5.4-10.9% of caregivers reported the use of sleep aids during the study. These included the benzodiazepine agent lorazepam, the non-benzodiazepine agents zolpidem and zopiclone, and the antidepressant drugs fluoxetine and citalopram.

The degree of sleepiness was only moderate with 10.4-30.3% of patients and 8.1-15.4% of caregivers feeling quite a bit or very sleepy during the day. However, the need for napping in the daytime was prominent for both groups (patients 50.0-76.7%; caregivers 41.7-56.8%). Mean duration of daytime naps exceeded 20 and 15 minutes for patients and caregivers, respectively. Of note, duration of daytime naps was reported to be greater than 30 minutes by 23.9-44.2% of patients and 10.4-18.9% of caregivers throughout the study.

At least half of the patients (58.3%) and the caregivers (50%) had experienced some problem with their sleep in the past, which, however, did not lead to a formal diagnosis of a sleep disorder. Interestingly, 62.5% of the women indicated that their sleep had been affected by the diagnosis of breast cancer, whereas 40.4% (n=19) of caregivers also admitted so. In terms of their sleeping arrangements, 87.5% (n=42) of dyads indicated sharing the same house, and 77.1% (n=37) also shared the same bedroom.

Analysis of SH scores indicated that sleep hygiene behaviours of patients and caregivers were, on average, favourable of a good night's sleep. Using the third quartile of obtained baseline scores as the cut-off score, 16.3-25% of patients (SH>13.75) and 16.2-28.2% of caregivers (SH>14) were classified as with inadequate sleep hygiene. Trends of reduction in mean SH scores (i.e. less sleep disruptive behaviours) were also noted from baseline to T3 for both patients and caregivers. In contrast, patient SDSTRB scores increased steadily from

baseline to end of study, possibly following the manifestation of chemotherapy toxicities. Indeed, throughout the study, mean patient PHYS scores were relatively low, but increased steadily from T0 to T1 and from T1 to T2, only showing a slight reduction towards the end of the study (end of treatment). Conversely, caregiver SDTRB scores decreased steadily throughout the study despite the fact that mean caregiver burden (moderate in magnitude throughout the study) increased during treatment and restored back to baseline levels only towards the end of study. In a somewhat inverse fashion, mean dyad psychological burden, albeit fluctuating between mild and moderate, was reported as relatively high prior to treatment initiation with a reduction during treatment, which was steady for caregivers but not for patients: after an initial reduction at T1, patient psychological distress showed trends for constant increase at T2 and T3. Finally, use of maladaptive coping strategies was generally infrequent in this sample. However, patients endorsed more negative coping strategies at the beginning of the study, which were gradually diminished to levels similar to those of caregivers, for whom COPNEG scores showed no major fluctuations throughout the study.

7.5. Preliminary Bivariate Correlation Analyses

Preliminary inter-dyad correlational analyses yielded some significant, yet sporadic and modest, associations between patients' and caregivers' sleep/wake patterns across time. Relative to the outcome variables, at different time-points during the study, patient and caregiver SL (T0 .37; T2 .36), PSQf (T0 .30), DDISTf (T1 .37; T2 .36; T3 .49), WASO (T2 –.24), GSQI (T0 .27), WAKETM (T0 .30; T3 .32), MORNFEEL (T0 .32), SLPNSS (T0 .30), and SAU (T2 .37) were also found to be linearly related. Bedtime was the only variable where patient and caregiver patterns were consistently correlated throughout the study (.35-.41).

When relationships between patient and caregiver predictor variables were examined, further positive, yet moderate, correlations were found. Dyads' sleep hygiene scores (.21-.37) were moderately associated throughout the study. Associations between dyads' psychological distress were also low-to-moderate and emerged at the second half of the study (T2 .21; T3 .37). At T1 (.22) and T2 (.25), positive between groups correlations were observed for SDSTRB. Lastly, positive associations between dyads' maladaptive coping strategies were recorded from T1 until the end of the study (.23-.41). Despite their limited number, to a certain extent these significant results (or trends towards significance) suggest the presence of non-independence in the dyads' outcome and predictor variables, thus supporting use of dyadic data analyses.

Intra-group correlation analyses revealed the presence of consistent and moderate-to-strong associations between time-points of assessment for the majority of repeatedly-measured outcome and predictor variables. Moderately to highly stable over-time sleep constructs included caregiver BEDTM (.68-.85) and WAKETM (.70-.76), caregiver SLPNSS (.53-.75), patient SAU (.57-.76), patient SH (.50-.69), and caregiver COPNEG (.52-.57). Low to moderate stability was found for patient SDSTRB (.21-.54), caregiver DDISTf (.10-.73), patient NAPTIME (.17-.44) and NAPNEED (.06-.40), patient SLPNSS (.16-.50), NOCAW (.03-.38) and EARLAW (.09-.58), caregiver SAU (.06-.47), and patient PSYCH (.22-.55). Stability of all other variables was at least moderate (coefficients >.30) at all assessment points.

Preliminary within-patient and within-caregiver correlational analysis revealed overall low to moderate associations between outcome and predictor variables (**Table 7.5**). However, in general, outcome and predictor variables were adequately related, yet they were sufficiently distinct to consider variables as distinct constructs, a fact that further supported the use of growth curve analyses with these data. When inter-correlations between outcome and demographic/clinical covariates were examined, only some modest associations were found (**Table 19-A2**). Irrespective of participant group, the most consistent associations between covariates and outcome variables were recorded for age, type of relationship, duration of relationship, presence of comorbidities and performance status, and past sleep history and sleep affected by cancer diagnosis with affected individuals reporting greater sleep impairment. Of note, physical activity, patient menopausal status and whether dyads were sharing the same house/bedroom were not or hardly correlated with any of the outcome variables. Finally, in terms of collinearity evaluation, no correlation coefficients exceeded the selected cut-off score of .85; indeed, in their majority inter-correlations among predictors, demographic/clinical covariates and their combinations were low to moderate.

Table 7.5. Within-patient and within caregiver associations between outcome and predictor variables.

Predictor variables		Outcome variables							
		PSQf	**DDISTf**	**NAPTIME**	**TST**	**SL**	**HSE**	**WASO**	**GSQI**
		Patients							
Patients	SH	.26*	.23*	.23*	$.01^{ns}$	$.16^{ns}$	$-.13^{ns}$	$.10^{ns}$	.31*
	PHYS	.29**	.47***	.22*	$-.15^{ns}$	.21*	$-.17^{\dagger}$	$.12^{ns}$	.52***
	PSYCH	.29**	.41***	$.10^{ns}$	$-.08^{ns}$	$.18^{\dagger}$	$-.10^{ns}$	$.05^{ns}$	.37**
	COPNEG	.23*	.35**	$.03^{ns}$	$.01^{ns}$	$.11^{ns}$	$-.01^{ns}$	$-.03^{ns}$	.33*
	SDSTRB	.39***	NA	$.19^{\dagger}$	$-.17^{\dagger}$	.23*	–.22*	$.19^{\dagger}$	NA
		Caregivers							
Carers	SH	.24*	.40***	$.02^{ns}$	$.01^{ns}$	$.13^{ns}$	$.06^{ns}$	$-.12^{ns}$	.30*
	CRACB	.20*	.37***	$.17^{\dagger}$	$-.07^{ns}$	$.05^{ns}$	$.09^{ns}$	$.05^{ns}$	.45**
	PSYCH	.29**	.55***	.28**	$.04^{ns}$	$.14^{ns}$	$-.06^{ns}$	$-.04^{ns}$	.48***
	COPNEG	.25*	.47***	$.18^{\dagger}$	$.10^{ns}$	$.08^{ns}$	$.04^{ns}$	$-.09^{ns}$	.44**
	SDSTRB	.35**	NA	$.19^{\dagger}$	$-.13^{ns}$	$.12^{ns}$	–.32**	.31**	NA

Abbreviations: PSQf – Perceived Sleep Quality factor from PSQI; DDISTf – Daily Disturbances factor from PSQI; NAPTIME – Daytime napping duration (minutes); TST – Total Sleep Time (minutes); SL – self-reported Sleep Latency (minutes); HSE – self-reported Habitual Sleep Efficiency (%); WASO – Wakefulness after sleep onset (minutes); GSQI – Global Sleep Quality Index score (denotes overall sleep/wake impairment); NA – Non applicable.

Notes: $^{ns}p>.10$; $^{\dagger}p<.10$; $*p<.05$; $**p<.01$; $***p<.001$; Kendall's tau-b correlation coefficients. Coefficients in bold denote predictor variables that were entered into each separate multivariate model.

7.6. Multilevel Modelling of Over-Time Changes in the Sleep/Wake Patterns of Care Dyads

Eight baseline (unconditional) MHLMs assessing the effect of time in a linear and curvilinear pattern were estimated for each sleep parameter/outcome variable (**Table 7.6**). Comparative analyses provided support for modelling the effect of time using the quadratic model for PSQf, NAPTIME, SL, SE, WASO, and GSQI, whereas for DDISTf the linear model was found to be a better fit to the data and was adopted as the baseline model. Of note, for TST, neither the linear nor the quadratic models were a significantly better fit to data than the means-only model. Unavoidably, this result limited examination of over-time changes in the dyads' total sleep time to a descriptive analysis only.

Based on estimation of variance components in the means-only models, intraclass correlation coefficients (ICC) were calculated for each outcome variable and participant group. For the patient variables, ICCs were as follows: $ICC_{PSQf}=.60$; $ICC_{DDISTf}=.38$; $ICC_{NAPTIME}=.57$;

ICC_{TST}=.55; ICC_{SL}=.48; ICC_{HSE}=.59; ICC_{WASO}=.59; and ICC_{GSQI}=.61. The respective ICCs for the caregiver variables were as follows: ICC_{PSQf}=.43; ICC_{DDISTf}=.48; $ICC_{NAPTIME}$=.42; ICC_{TST}=.62; ICC_{SL}=.38; ICC_{HSE}=.53; ICC_{WASO}=.42; and ICC_{GSQI}=.56. Given that all patient and caregiver intercept components were statistically significant (all p<.001), ICCs were also significant, indicating that MHLMs were both appropriate and needed for these data [516]. In addition, the overall moderate magnitude of the ICCs suggested that not only group means were different but also that there was enough variation within each group.

Table 7.6. Deviance statistics and comparison tests for the selection of baseline MHLMs

Outcome variable	Means-only	Linear model		Quadratic model	
	Deviance Statistic	Deviance Statistic	$\chi^{2,a}$	Deviance Statistic	$\chi^{2,b}$
PSQf	1317.8	1316.4	1.46^{ns}	**1275.5**	42.30**
					40.85***
DDISTf	955.9	**921.3**	34.67***	906.01	27.46*
					15.29^{ns}
NAPTIME	3385.7	3369.3	16.49†	**3278.5**	107.22***
					90.73***
TST	**3978.6**	3975.9	2.69^{ns}	3962.9	15.64^{ns}
					12.95^{ns}
SL	3065.4	3051.2	14.18^{ns}	**3015.3**	50.05***
					35.88***
HSE	2661.8	2658.9	2.89^{ns}	**2639.0**	22.75*
					20.13*
WASO	3809.9	3802.4	7.53^{ns}	**3770.6**	39.31*
					31.42**
GSQI	1787.5	1780.9	6.49^{ns}	**1744.8**	42.65**
					36.15***

Abbreviations: PSQf – Perceived Sleep Quality factor from PSQI; DDISTf – Daily Disturbances factor from PSQI; NAPTIME – Daytime napping duration (minutes); TST – Total Sleep Time (minutes); SL – self-reported Sleep Latency (minutes); HSE – self-reported Habitual Sleep Efficiency (%); WASO – Wakefulness after sleep onset (minutes); GSQI – Global Sleep Quality Index score (denotes overall sleep/wake impairment); MHLM – Multivariate Hierarchical Linear Model.

Notes: [a]Comparison test with means-only model (df=9); [b]Comparison test with means-only model is presented first (df=22), and with linear model second (df=13). Deviance statistics in bold indicate selected baseline (un-conditional) MHLMs for each outcome variable. ^{ns}p>.10; $^{\dagger}p$<.10; *p<.05; **p<.01; ***p<.001

Table 7.7 presents the FML parameter estimates and standard errors of the fixed and random effects for the MHLMs that were fit to the data for each sleep/wake parameter and for both members of the dyads.

Table 7.7. Estimates of intercepts, linear change, quadratic change, and variance in dyads' sleep/wake parameters

		Fixed Effects				Random Effects Variance	
Parameter	**Effects**	***b***	**SE**	***t* (47)**	r_{ES}	**VC**	χ^2 **(39)**
PSQf	PT intercept, β_{10}	2.73	.31	8.82***		3.58	155.74***
	CG intercept, β_{20}	2.03	.23	8.75***		1.68	85.21***
	PT linear, β_{30}	.97	.38	2.58*	.35	4.03	88.28***
	CG linear, β_{40}	.20	.23	.86^{ns}	.12	.61	30.40^{ns}
	PT quadratic, β_{50}	–.34	.11	–3.03**	.40	.32	78.32***
	CG quadratic, β_{60}	–.07	.07	–.97^{ns}	.14	.05	29.21^{ns}
	Level-1 residual					1.10	
DDISTf	PT intercept, β_{10}	1.96	.13	15.63***		.41	104.49***
	CG intercept, β_{20}	1.97	.15	12.73***		.80	129.54***
	PT linear, β_{30}	.25	.06	4.30***	.53	.06	74.65**
	CG linear, β_{40}	.04	.07	.58^{ns}	.08	.08	81.21**
	Level-1 residual						
NAPTIME	PT intercept, β_{10}	21.16	4.41	4.80***		683.94	146.04***
	CG intercept, β_{20}	11.63	2.90	4.02***		247.70	69.61**
	PT linear, β_{30}	21.78	8.34	2.61*	.36	2584.90	211.98***
	CG linear, β_{40}	7.37	3.91	1.88†	.26	363.74	28.57^{ns}
	PT quadratic, β_{50}	–5.49	2.72	–2.02*	.28	271.92	225.85***
	CG quadratic, β_{60}	–1.85	1.24	–1.49^{ns}	.21	35.58	20.72^{ns}
	Level-1 residual					262.41	
TST	PT intercept, β_{10}	404.87	9.82	41.22***		3782.33	257.30***
	CG intercept, β_{20}	408.04	11.21	36.39***		5103.32	332.17**
	Level-1 residual					3089.78	

		Fixed Effects				Random Effects Variance	
Parameter	**Effects**	***b***	**SE**	***t* (47)**	r_{ES}	**VC**	χ^2 **(39)**
SL	PT intercept, β_{10}	26.16	2.55	10.25***		169.48	49.13^{ns}
	CG intercept, β_{20}	19.42	1.91	10.18***		26.87	26.87^{ns}
	PT linear, β_{30}	8.39	3.25	2.57*	.35	157.80	59.48*
	CG linear, β_{40}	3.87	4.39	.88^{ns}	.13	478.77	48.29^{ns}
	PT quadratic, β_{50}	–2.87	1.06	–2.72**	.37	17.71	62.69*
	CG quadratic, β_{60}	–.90	1.27	–.71^{ns}	.10	37.78	38.60^{ns}
	Level-1 residual					203.35	
HSE	PT intercept, β_{10}	75.82	1.97	38.48***		130.30	124.04***
	CG intercept, β_{20}	82.17	1.84	44.70***		106.43	86.40***
	PT linear, β_{30}	–6.59	2.37	–2.78**	.38	112.82	78.01***
	CG linear, β_{40}	–1.16	1.78	–.65^{ns}	.09	11.46	32.12^{ns}
	PT quadratic, β_{50}	2.09	.75	2.78**	.38	10.74	77.67***
	CG quadratic, β_{60}	.30	.53	.57^{ns}	.08	.89	29.81^{ns}
	Level-1 residual					59.32	
WASO	PT intercept, β_{10}	106.15	10.65	9.97***		4207.04	188.63***
	CG intercept, β_{20}	68.05	7.26	9.38***		1538.01	73.28***
	PT linear, β_{30}	33.09	13.12	2.52*	.35	4771.87	107.57***
	CG linear, β_{40}	2.95	8.08	.37^{ns}	.05	317.85	38.14^{ns}
	PT quadratic, β_{50}	–10.43	4.12	–2.53*	.35	445.28	99.97***
	CG quadratic, β_{60}	–.64	2.62	–.24^{ns}	.03	33.91	39.99^{ns}
	Level-1 residual					1299.05	

		Fixed Effects				Random Effects Variance	
Parameter	**Effects**	***b***	**SE**	***t* (47)**	r_{ES}	**VC**	χ^2 **(39)**
GSQI	PT intercept, β_{10}	6.58	.60	10.98***		13.31	154.43***
	CG intercept, β_{20}	5.52	.51	10.93***		8.63	101.37***
	PT linear, β_{30}	2.55	.68	3.77***	.48	11.31	84.99***
	CG linear, β_{40}	.55	.42	1.31^{ns}	.19	1.34	30.90^{ns}
	PT quadratic, β_{50}	–.76	.20	–3.81***	.49	.82	74.21***
	CG quadratic, β_{60}	–.18	.12	-1.49^{ns}	.21	.05	26.65^{ns}
	Level-1 residual					4.13	

Abbreviations: PSQf – Perceived Sleep Quality factor from PSQI; DDISTf – Daily Disturbances factor from PSQI; NAPTIME – Daytime napping duration (minutes); TST – Total Sleep Time (minutes); SL – self-reported Sleep Latency (minutes); HSE – self-reported Habitual Sleep Efficiency (%); WASO – Wakefulness after sleep onset (minutes); GSQI – Global Sleep Quality Index score (denotes overall sleep/wake impairment); SE – Standard error; PT – Patient; CG – Caregiver; r_{ES} – Effect Size; VC – Variance component.
Notes: $^{ns}p > .10$; $^{\dagger}p < .10$; $^{*}p < .05$; $^{**}p < .01$; $^{***}p < .001$.

Presentation of findings in the following sections is in line with research hypotheses posed in Chapter 6 (Section 6.1) as part of the primary research question for this study. Hence, each of these sleep/wake parameter-specific sections aims to provide evidence with regard to whether (a) similarities in the shape of trajectories of patients and carers were recorded; (b) whether at least moderate correlations in average and change patterns emerged within dyads; and (c) whether the sleep/wake impairments reported in these care dyads were of comparable magnitude between dyad members.

Perceived Sleep Quality (PSQf)

A curvilinear pattern of change was evident for patient-perceived sleep quality, supported by a significant positive linear (β_{30}=.97) and a significant negative quadratic slope over time (β_{50}=–.34). Patient PSQf scores showed steady increase from prior to treatment to mid-treatment (indicated by an increase in mean scores from 2.73 to 3.32 and 3.26), with restoration to levels close to baseline towards the end of the study (three weeks post-treatment). In contrast, there was no significant linear or quadratic trend for caregivers, thus suggesting that, on average, caregiver PSQf scores showed no particular change over time. Despite non-significance, a trend for slight deterioration in caregiver-perceived sleep quality may be postulated at mid-treatment (T2) (**Figure 7-8**).

A multivariate hypothesis test indicated that average curves for the dyad members were significantly different (χ^2=15.50, *df*=3, *n*=48; *p*=.002), with patient-perceived sleep quality more affected than that of caregivers. More specifically, at baseline, average perceived sleep quality was worse for patients than for caregivers (χ^2=4.75, *df*=1, *n*=48; *p*=.027). Acceleration in deterioration of perceived sleep quality was greater for patients than for caregivers (linear trends: χ^2=5.01, *df*=1, *n*=48; *p*=.024), whereas deceleration was also significantly different towards the end of the study (quadratic trends: χ^2=5.91, *df*=1, *n*=48; *p*=.014).

However, random effects tau correlations indicated a modest association between average baseline patient and caregiver perceived sleep quality (.42; 95% CI [.15, .63]), and strong correlations between the linear and quadratic rates of change (.91; [.84, .95] and .82; [.69, .89], respectively) for patient- and caregiver-perceived sleep quality. Hence, within the same dyads, members' average perceptions of their sleep quality and especially changes in their sleep quality were closely related.

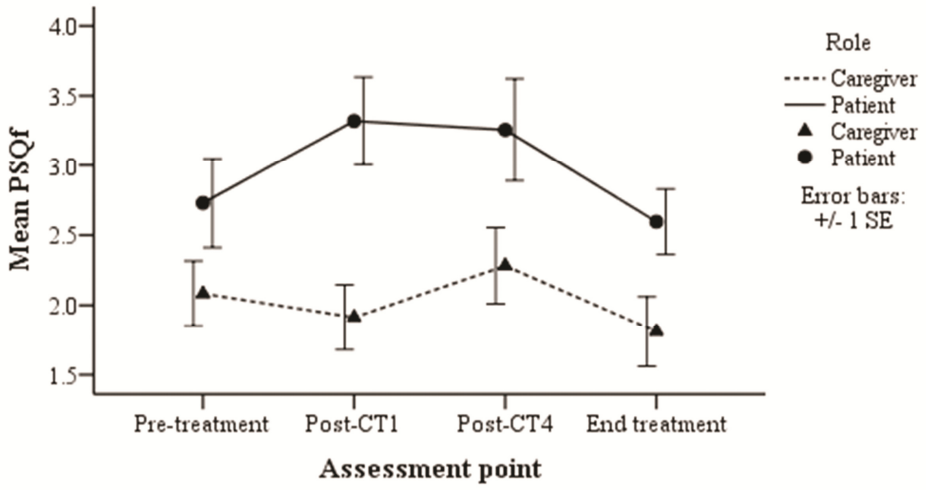

Figure 7-8. Average perceived sleep quality trajectories for patients and caregivers over the chemotherapy treatment period (*n*=36-48 dyads). Higher scores indicate worse perceived sleep quality with a possible range of 0-9.

Daily Disturbance (DDISTf)

A linear pattern of change in patients' daily disturbance scores was evident, which was supported by a significant positive, yet modest, linear slope over time (β_{30}=.25). In contrast, there was no linear trend for caregivers (β_{40}=.04). **Figure 7-9** shows that although patients reported increasingly more daily disruption during treatment (mean scores of 1.90 at baseline to 2.23 at T1, 2.63 at T2, and 2.57 at T3), caregivers' own daily disruption remained generally unaffected.

Overall, average DDISTf curves for patients and caregivers were significantly different (χ^2=12.77, *df*=2, *n*=48; *p*=.002). However, prior to treatment initiation average daily disturbance was similar for patients and caregivers (χ^2=.00, *df*=1, *n*=48; *p*>.05) (**Figure 7-9**). Yet, the linear trends were significantly different between patients and carers (χ^2=6.52, *df*=1, *n*=48; *p*=.01), indicating greater acceleration rates (increasing frequency of daily disturbances) for women than for caregivers. **Figure 7-9** clearly illustrates patient and caregiver curves fanning out from T1 through T2 to T3.

Within the same dyad, members' average perceptions of and changes in daily disruption were somewhat, yet not closely, related to each other. Random effects tau correlations indicated a modest association between average baseline patient and caregiver DDISTf scores

(.37; 95% CI [.10, .59]), but only a weak and non-significant relationship between the linear rates of change (.21; [–.08, .47]).

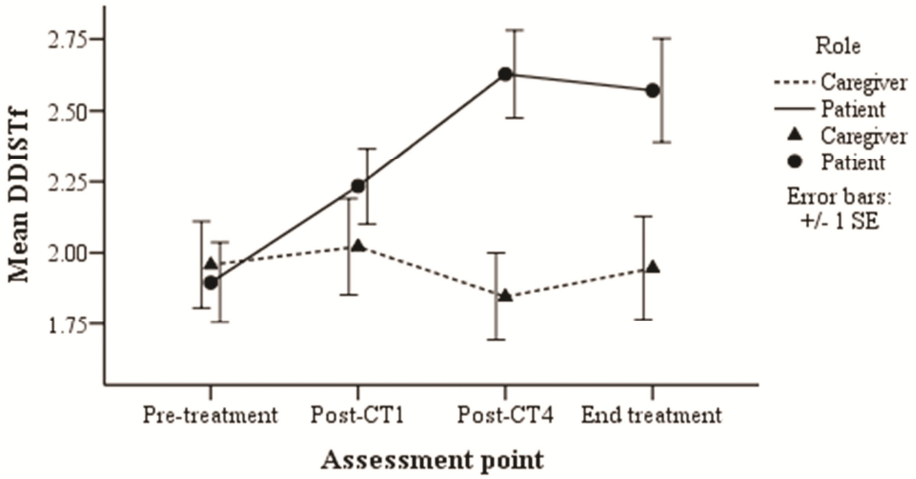

Figure 7-9. Average daily disturbance trajectories for patients and caregivers over the chemotherapy treatment period (*n*=36-48 dyads). Higher scores indicate greater daily disruption with a possible range of 0-6.

Daytime Napping Duration (NAPTIME)

A curvilinear pattern of change was evident for patient daytime napping duration, which was supported by a significant positive linear slope over time (β_{30}=21.78) and a significant negative quadratic slope over time (β_{50}=–5.49) (**Figure 7-10**). On average, patient napping duration increased by at least 10 and 20 minutes at T1 and T2, respectively, and despite some degree of restoration remained close to these levels even at the end of the study. In conjunction with similar evidence on daily disturbance, it can be inferred that considerable daytime dysfunction was evident for women even after the end of chemotherapy treatment. Caregiver average trajectories were not very dissimilar from patients'. Average napping during the day increased after CThC1 and reached a maximum after CThC4, with restoration to baseline levels at the end of chemotherapy (**Figure 7-10**). However, albeit marginally, neither the linear nor the quadratic trend for caregivers reached statistical significance.

Average curves for patients and caregivers were significantly different (χ^2=10.32, *df*=3, *n*=48; *p*=.016), with patients spending more time napping in the daytime throughout the

study. However, although from a clinical point of view patients spent more time napping during the day than caregivers, on average, both dyad members were similarly affected by demands posed during the treatment period. Indeed, neither the average (χ^2=2.71, *df*=1, *n*=48; *p*=.095) nor the linear (χ^2=2.43, *df*=1, *n*=48; *p*=.115), nor the quadratic trends (χ^2=1.54, *df*=1, *n*=48; *p*=.212) trends of daytime napping duration were significantly different between patients and caregivers.

Random effects tau correlations indicated a modest, yet negative, association between average patient and caregiver napping duration (–.30; 95% CI [–.54, –.02]), and only very weak and non-significant associations between the linear and quadratic rates of change (.00; [–.28, .29] and .07; [–.22, .35], respectively) between patients and caregivers. Seen together, these results are indicative of major discrepancies in the napping duration of dyad members; within the same dyad, duration of time in napping of patients remained practically unrelated to that of caregivers.

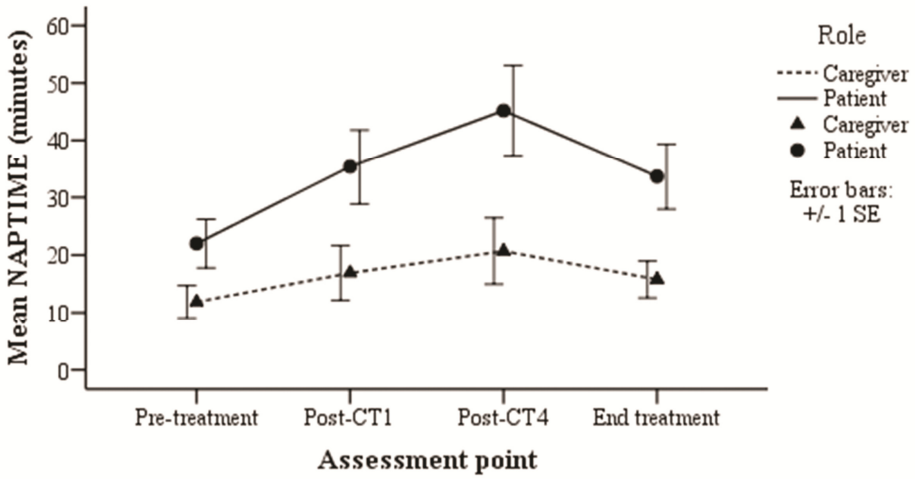

Figure 7-10. Average daytime napping duration trajectories for patients and caregivers over the chemotherapy treatment period (*n*=36-48 dyads).

Total Sleep Time (TST)

Throughout the study, no particular pattern of change in either patients' or caregivers' total sleep time at night was found. In addition, at baseline, there was no statistical or clinical difference in average reported total sleep time between patients and carers (χ^2=.05, *df*=1, *n*=48;

p>.05). A two-way repeated measures analysis of variance also confirmed this absence of over-time change patterns. Due possibly to the presence of wide variability in individual TST reports for both patients and caregivers, univariate within-subjects effects of time were also non-significant (trajectories plotted in **Figure 7-11**). In agreement with univariate paired *t*-tests presented in **Table 7.3**, significant over-time differences between the two groups (patients v. caregivers) were also absent (Wilks' Lambda=.97, *F*=1.108, *df*=3; *p*=.35). Nevertheless, 38% and 28% of patients, and 35% and 26% of caregivers experienced reduction in their total sleep time at T1 and T2, respectively, compared to baseline. At the same time-points, 50% and 49% of dyads included one or both members, whose actual sleep time during the night had been adversely affected. Interestingly, total sleep time of patients dropped by an average of 12 minutes the weeks following administration of CThC1 compared to baseline, whereas for caregivers an inverse trend was apparent (average increase in TST by 16 minutes).

A rather weak and not significant, positive tau correlation between average patient and caregiver reports of total sleep time emerged (.13; 95% CI [–.16, .40]). Whilst within some dyads average patient TST may have been positively and linearly linked to caregiver TST, and vice versa, on the whole one member's lower TST only minimally was followed by a respective reduction in the other's TST.

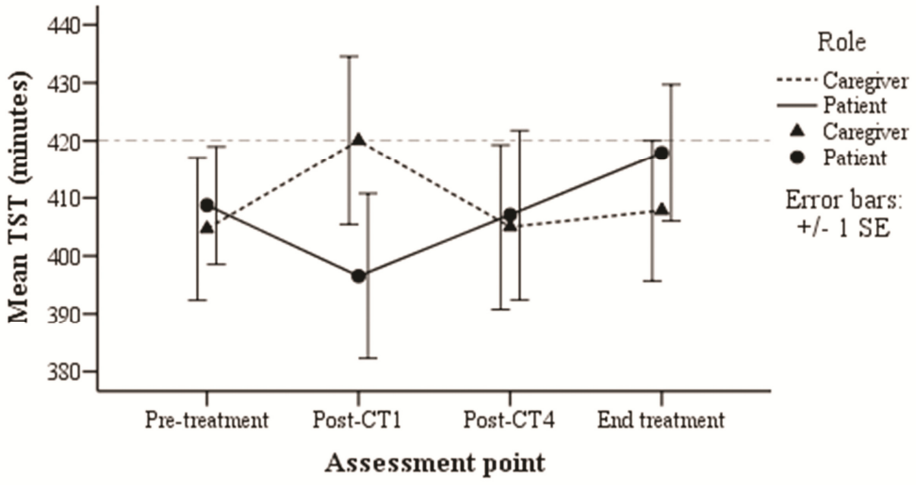

Figure 7-11. Average daily disturbance trajectories for patients and caregivers over the chemotherapy treatment period (*n*=36-48 dyads). A reference (faint dotted) line indicates the minimum normal TST of 420 minutes (≥7 hours) for healthy adult individuals.

Sleep Latency (SL)

As with perceived sleep quality, a curvilinear pattern of change was evident for patient sleep latency (**Table 7.7**). Increase in patient sleep latency from baseline to mid-treatment (indicated by increases in mean sleep latency from 26 to 32 and 30 minutes) was evident, which levelled off with restoration to levels close to, but slightly lower than, baseline towards the end of the study (25 minutes). In contrast, whereas a somewhat similar pattern was observed (**Figure 7-12**), there was no significant linear or quadratic trend for caregiver sleep latency. On average, caregivers required approximately the same time to fall asleep at all assessment points throughout the study.

Multivariate hypothesis testing indicated that average curves for patients and caregivers were significantly different (χ^2=9.70, *df*=3, *n*=48; *p*=.021). Indeed, on average, patients spent more time until falling asleep than caregivers did (χ^2=6.24, *df*=1, *n*=48; *p*=.012). However, no difference emerged for either the linear (χ^2=1.27, *df*=1, *n*=48; *p*=.259) or the quadratic (χ^2=2.62, *df*=1, *n*=48; *p*=.102) trends. These findings are in agreement with OLS results for matched groups presented in **Table 7.3**, where no between-groups differences in mean sleep latency were found at T2 and T3. From a clinical point of view, at T2 (mid-treatment) prolongation of average caregiver sleep latency to levels close to those reported from patients at the same time-point (29 v. 32 minutes) – and certainly higher than previous own (29 v. 20 v. 19 minutes) – was evident. Whereas early in the course of treatment dyad members' sleep latency was greater for patients than caregivers, as time elapsed (post-CThC1 to end treatment), differences in sleep latency patterns started to fade out; caregivers found falling asleep increasingly more difficult, thus assimilating patients' own difficulty. From T2 to end of study, dyad sleep latency curves became parallel, showing somewhat similar patterns of deceleration and restoration of sleep latency to pre-treatment levels.

Random effects correlations indicated a modest association between average patient and caregiver sleep latency (.36; 95% CI [.08, .58]). Yet, correlations between the linear and quadratic rates of change were particularly strong (.77; [.62, .86] and .80; [.67, .88], respectively), thus suggesting that within the same dyad, patient and caregiver changes in their sleep latency were positively and closely related.

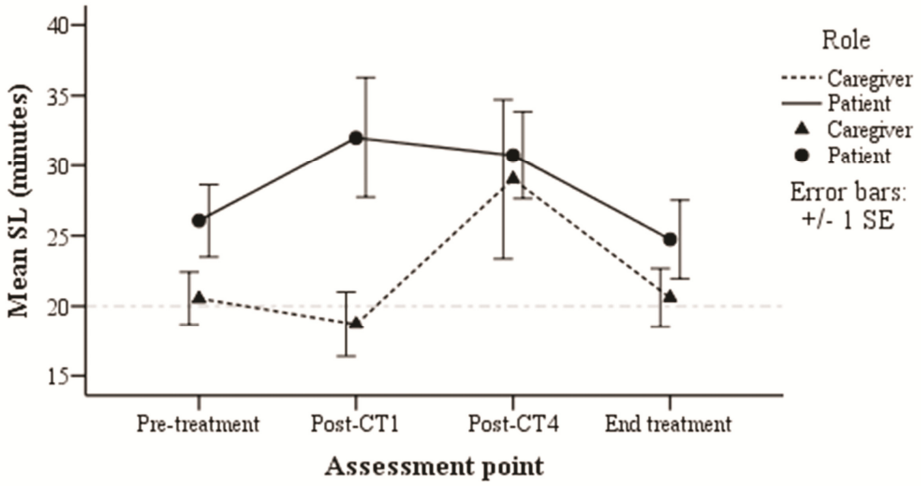

Figure 7-12. Average sleep latency trajectories for patients and caregivers over the chemotherapy treatment period (n=36-48 dyads). A reference (faint dotted) line indicates the minimum normal SL of 20 minutes for healthy adult individuals.

Habitual Sleep Efficiency (HSE)

As with other sleep parameters, a curvilinear pattern of change was evident for patient habitual sleep efficiency as well (**Table 7.7**). Average patient HSE declined from baseline to mid-treatment (indicated by a steady decrease in mean sleep efficiency percentages from 78% to 71% and 72%), with restoration to levels close to baseline three weeks after the end of chemotherapy. In contrast, caregiver linear (β_{40}=–1.16) and quadratic (β_{60}=.30) trends of habitual sleep efficiency fell short of significance, thus suggesting absence of a particular pattern of change in average HSE in this sample of caregivers. However, a trend for slight deterioration in caregiver HSE from 82% at treatment initiation to 80% at mid-treatment is shown in **Figure 7-13**.

Multivariate hypothesis testing suggested that average HSE curves for patients and caregivers were significantly different (χ^2=17.31, df=3, n=48; p<.001); patients' HSE was more affected than that of caregivers throughout the study. Indeed, baseline average HSE was worse for patients than for caregivers (χ^2=6.40, df=1, n=48; p=.011). Although no statistically significant difference was found between either linear (χ^2=3.11, df=1, n=48; p=.074) or quadratic (χ^2=3.52, df=1, n=48; p=.057) patient and caregiver trends, rates of decrease and acceleration in patient HSE were also consistently greater than those for the caregivers.

The random effects associated with the quadratic growth model for HSE revealed the extent to which patients' trajectory of change was related to that of their caregivers. A weak tau correlation coefficient for initial HSE status was found (.19; 95% CI [–.10, .45]). This dissociation in dyads' HSE was further confirmed by modest, but negative, correlations for linear (–.38; [–.60, –.11]) and quadratic change (–.48; [–.67, –.23]). Thus, within the same dyad, patient and caregiver reports of average HSE were found to be only weakly related, but more importantly, rates of change were found to be inversely related: steeper declines in a patient's HSE were correlated with steeper increases in caregiver HSE, and vice versa.

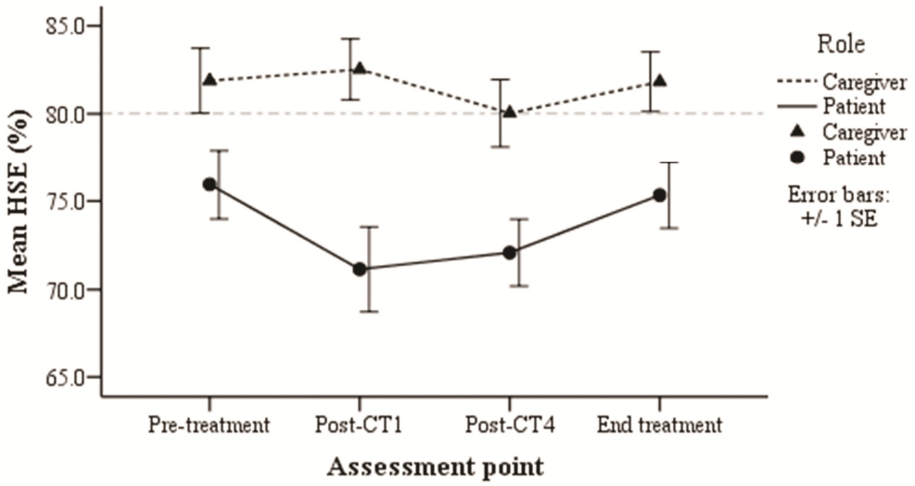

Figure 7-13. Average habitual sleep efficiency trajectories for patients and caregivers over the chemotherapy treatment period (n=36-48 dyads). A reference (faint dotted) line indicates the minimum normal HSE of 80% for healthy adult individuals.

Wakefulness After Sleep Onset (WASO)

A curvilinear pattern of change was also evident for patient wakefulness after sleep onset. Average patient WASO increased from baseline to mid-treatment (proposed by a steady increase in mean time in wakefulness from 105 minutes to 131 and 126 minutes), and then levelled off close to baseline three weeks after the end of chemotherapy. The effect sizes for the linear and quadratic trends were modest to large (.35 and –.35, respectively). As with other sleep parameters, caregiver linear (β_{40}=2.95) and quadratic (β_{60}=–.64) trends of WASO fell short of significance. Yet again, average dyad trajectories were indicative of a trend to-

wards slight deterioration in caregiver WASO by approximately 6 to 7 minutes on average baseline to mid-treatment (**Figure 7-14**).

The average WASO curve for patients was significantly different (greater) from caregivers' (χ^2=20.69, *df*=3, *n*=48; *p*<.001). Additional univariate tests revealed that baseline WASO was more prolonged for patients than for caregivers (χ^2=9.49, *df*=1, *n*=48; *p*=.002). No statistically significant differences were found between either linear (χ^2=3.21, *df*=1, *n*=48; *p*=.069) or quadratic (χ^2=3.44, *df*=1, *n*=48; *p*=.060) patient and caregiver trends; however, rates of increase and deceleration in patient WASO were again consistently greater than those for the caregivers.

Cross-dyad member tau correlations revealed a rather weak patient-caregiver association in baseline WASO (.12; 95% CI [–.17, .39]). As with dyads' HSE, dissociation in dyads' WASO was further confirmed by negative, yet strong, between groups correlations for linear and quadratic change (–.77; [–.86, –.62] and –.69; [–.81, –.50], respectively). Thus, within same dyads, patient and caregiver rates of change were found to be inversely related: steeper increases in a patient's WASO were correlated with steeper declines in caregiver WASO, and vice versa.

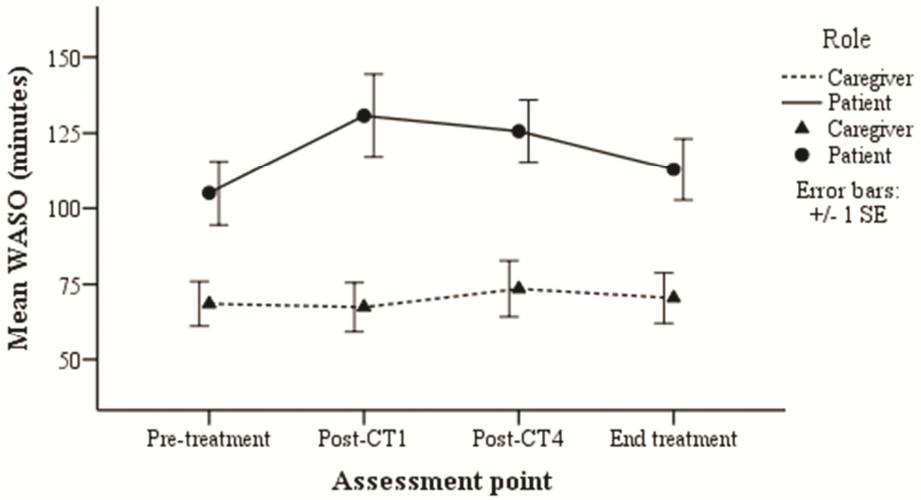

Figure 7-14. Average wakefulness after sleep onset trajectories for patients and caregivers over the chemotherapy treatment period (*n*=36-48 dyads).

Overall Sleep/Wake Impairment (GSQI)

A significant curvilinear pattern of change was evident for patients with large effect sizes for the linear and quadratic trends (.48 and –.49, respectively). Average patient GSQI scores increased from baseline (6.58 at T0) to mid-treatment (8.19 and 8.47 at T1 and T2, respectively), and then levelled off but remained higher than baseline three weeks after the end of chemotherapy. Consistent with previously reported findings, caregiver linear (β_{40}=.55) and quadratic (β_{60}=–.18) trends of overall sleep/wake impairment fell short of significance with small to medium size effects (.19 and –.21, respectively). However, the typical caregiver exceeded a cut-off GSQI score of 5 suggesting potential sleep/wake impairment. What is more, average dyad trajectories illustrated in **Figure 7-15** are indicative of a trend for slight deterioration in average caregiver sleep/wake patterns as dyads entered mid-treatment; in other words, average caregiver sleep/wake impairment reached its peak at the same time as patients'. As a result, dyads half way through the patient's chemotherapy treatment were more sleep-impaired than at any other point over this period.

Multivariate hypothesis testing revealed that the average sleep/wake impairment curve for patients was overall greater than for caregivers (χ^2=18.74, *df*=3, *n*=48; *p*<.001). On average however, dyad members about to enter the experience of chemotherapy treatment were simultaneously sleep-impaired (χ^2=2.64, *df*=1, *n*=48; *p*=.100). In contrast, as treatment progressed, care dyad members' sleep/wake patterns were affected differently. Rates of increase (χ^2=8.12, *df*=1, *n*=48; *p*=.005) and deceleration (χ^2=7.06, *df*=1, *n*=48; *p*=.008) in patient sleep/wake impairment were consistently greater than those for the caregivers.

Cross-dyad member tau correlations revealed a moderate patient-caregiver association in baseline overall sleep/wake impairment (.42; 95% CI [.15, .63]). This finding was supported by fairly strong correlations for linear (.76; [.61, .86]) and quadratic change (.84; [.73, .91]). In all, within same dyads, not only was average sleep/wake disruption found to be linearly related between a woman and her caregiver, but more importantly, rates of change were found to be positively and strongly related: steeper increases in a patient's sleep/wake impairment were correlated with steeper increases in their caregiver's own sleep/wake impairment, and vice versa. In other words, despite the differences in the magnitude of sleep impairment, within care dyads, deterioration or amelioration (i.e. change) in dyad members' sleep/wake impairment was very similar.

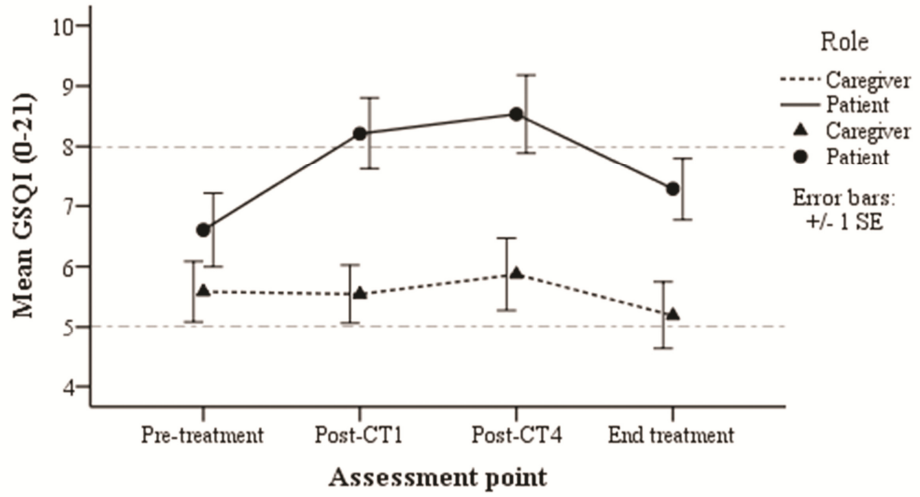

Figure 7-15. Average sleep/wake impairment trajectories for patients and caregivers over the chemotherapy treatment period (*n*=36-48 dyads). Two reference (faint dotted) lines indicate established cut-off scores of >5 and >8 for possible sleep/wake impairment.

7.7. Multilevel Modelling of the Effects of Sleep–Impairing Factors

Inclusion of time-varying and time-invariant predictors led to the formation of separate conditional MHLMs for each of the outcome variables, which were adjusted for the effects of additional covariates. Significant variation around the average and/or linear and/or quadratic patient and caregiver trajectories of sleep/wake parameters indicated whether it was appropriate to examine predictors at Level 2 (**Table 7.7**).

As previously, presentation of findings in the following sections is in line with research hypotheses posed in Chapter 6 (Section 6.1) as part of the secondary research question for this study. Hence, each of these sleep/wake parameter-specific sections aims to provide evidence with regard to the (a) average (enduring) and change-related (contextual) effects of the selected predictors on patients' own sleep/wake parameters, such that greater burden is associated with poorer sleep/wake outcomes; (b) average (enduring) and change-related (contextual) effects of the selected predictors on caregivers' own sleep/wake parameters, such that greater burden is associated with poorer sleep/wake outcomes; and (c) average (enduring) and change-related (contextual) cross-partner effects of the selected predictors, such that

greater burden on the patient's part is associated with poorer caregiver sleep/wake outcomes, and vice versa.

Perceived Sleep Quality (PSQf)

Both enduring and contextual effects of nocturnal disturbance were found. Indeed, own mean nocturnal disturbance significantly predicted own mean perceived sleep quality for both patients (γ_{111}=.15, SE=.07, p=.03; r_{ES}=.36) and caregivers (γ_{29}=.09, SE=.04, p=.019; r_{ES}=.37) (**Table 20-A2**). Moreover, increases in own nocturnal disturbances were followed by increases in reports of poor sleep quality for both patients (γ_{70}=.18, SE=.04, p<.001; r_{ES}=.46) and caregivers (γ_{80}=.12, SE=.05, p = .01; r_{ES}=.27). Additional important associations emerged: increase in own psychological distress was related to worse perceived sleep quality for women (γ_{120}=.45, SE=.21, p=.032; r_{ES}=.23), while increase in caregiving burden was associated with worse perceived sleep quality for caregivers (γ_{111}=.08, SE=.03, p=.005; r_{ES}=.30). Quite surprisingly, more frequent use of negative coping strategies by caregivers was found to be associated with better perceived sleep quality (γ_{111}=–.13, SE=.05, p=.007; r_{ES}=–.28) (**Figure 7-16**).

Some interesting cross-partner effects were also found flowing predominantly from patients to caregivers. More specifically, patients' mean physical distress (γ_{24}=1.57, SE=.55, p=.007; r_{ES}=.45), mean psychological distress (γ_{26}=.75, SE=.30, p=.019; r_{ES}=.40), mean negative coping strategies (γ_{211}=.14, SE=.06, p=.03; r_{ES}=.37), and mean nocturnal disturbance (γ_{213}=.14, SE=.05, p=.014; r_{ES}=.41) were associated with worse mean PSQf scores in the caregivers. Interestingly, increase in patients' psychological distress was also associated with positive change (worsening) in caregivers' perceived sleep quality (γ_{190}=.42, SE=.18, p=.023; r_{ES}=.26). In addition, increase in caregiver burden throughout treatment was found to be related not only to own decline (γ_{250}=.06, SE=.03, p=.003; r_{ES}=.23), but also to decline in patients' perceived sleep quality (γ_{260}=.09, SE=.03, p=.041; r_{ES}=.33).

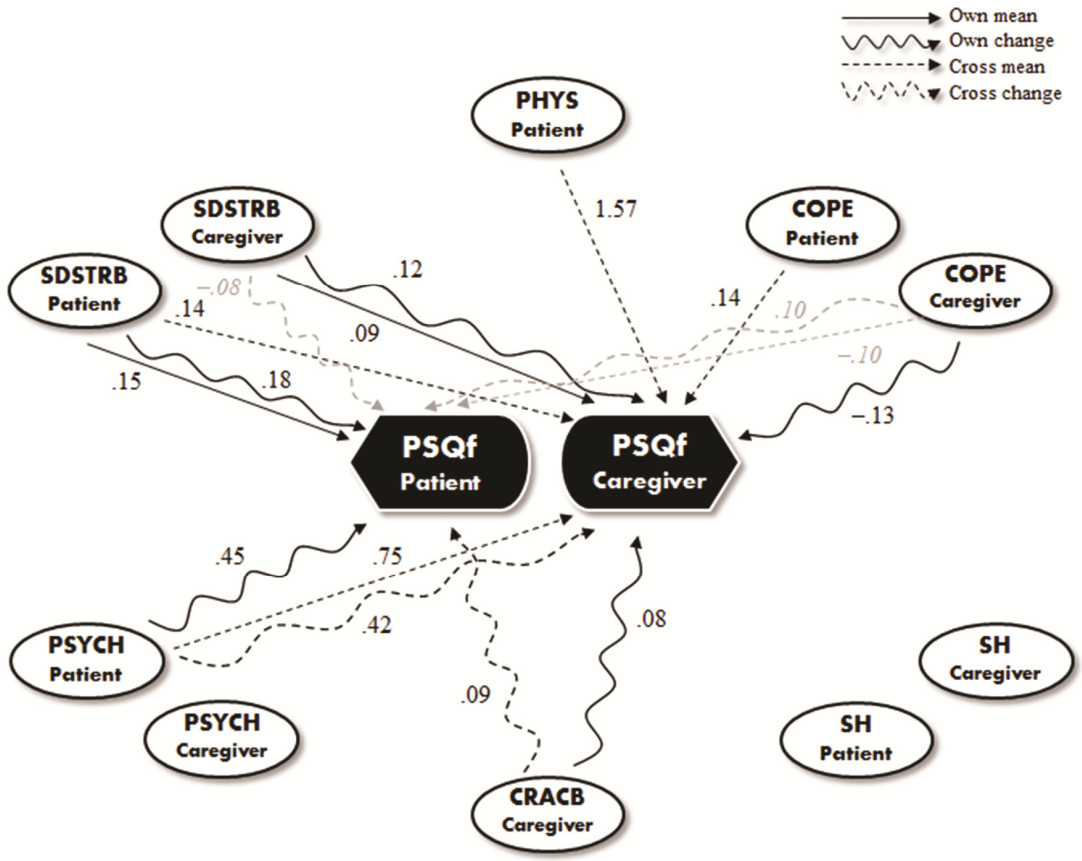

Figure 7-16. Statistically significant (p<.05) enduring (mean) and contextual (change) own and cross-partner effects of the sleep-impairing factors examined on patients' and caregivers' perceived sleep quality (PSQf). Faint arrows indicate associations where trends towards significance emerged (.10>p≥.05). All models were controlled for the effects of SLPAST, SLCA, AGE, RELATDUR, CMRBDT, PS, and BCSTAGE for patients; and SLPAST, SLCA, AGE, and RELATDUR for caregivers. Where no arrows are shown, no statistically significant associations (or trends towards significance) emerged. Numbers next to arrows denote the MHLM parameter estimates (coefficients) for each predictor variable; negative values indicate an inverse relationship between predictor and outcome variable (see **Table 20-A2**).

Daily Disturbance (DDISTf)

Significant enduring effects of own mean patient physical burden/caregiver burden on own mean daily disturbance for both patients (γ_{14}=.96, SE=.28, p=.002; r_{ES}=.49) and caregivers were found (γ_{24}=.04, SE=.02, p=.036; r_{ES}=.34) (**Table 21-A2**). In addition, mean caregiver psychological distress was positively associated with mean daily disturbance (γ_{25}=.37, SE=.15, p=.016; r_{ES}=.39). In terms of change, increase in own use of poor sleep behaviours

was significantly associated with more daily disruption for both patients (γ_{50}=.05, SE=.02, p=.012; r_{ES}=.39) and caregivers (γ_{60}=.04, SE=.02, p=.009; r_{ES}=.40). Additional important associations emerged: increase in own physical distress (γ_{70}=.74, SE=.19, p<.001; r_{ES}=.54) and more frequent use of maladaptive coping strategies (γ_{100}=.06, SE=.03, p=.037; r_{ES}=.33) was related to more daily disruption for patients. Moreover, increase in caregiver burden was found to be associated with increased own daily disturbance (γ_{120}=.05, SE=.02, p=.006; r_{ES}=.42). Overall, results suggest that the effects of the predictors tested on daily disturbance were primarily contextual for both dyad members (**Figure 7-17**).

In further analyses, only an enduring cross-partner effect emerged: poorer caregiver sleep hygiene was associated with increased patient daily disruption (γ_{19}=.04, SE=.02, p=.042; r_{ES}=.35), after controlling for potential own effects. It can be inferred that one's own daily disturbance in this sample was primarily influenced by own sleep-impairing factors. Nevertheless, a hint of intra-dyad influence suggested that sleep disruptive behaviours on the caregivers' part may have triggered patient restlessness during the night and subsequent disruption in the daytime.

Daytime Napping Duration (NAPTIME)

Two significant and positive own enduring effects were found for patients, with mean physical distress (γ_{14}=31.63, SE=14.63, p=.038; r_{ES}=.35) and disruptive sleep hygiene (γ_{16}=2.75, SE=1.03, p=.012; r_{ES}=.42) predicting prolonged own mean napping duration (**Table 22-A2**). In addition, mean caregiver psychological distress was positively associated with own mean daytime napping duration (γ_{25}=15.94, SE=6.08, p=.013; r_{ES}=.41). In terms of contextual predictor effects, increase in caregiver frequency of nocturnal disturbances was associated with more time spent in napping (γ_{80}=1.47, SE=.67, p=.032; r_{ES}=.23). For patients, increase in own psychological distress was related to increase in daytime napping (γ_{120}=11.74, SE=4.05, p=.005; r_{ES}=.30) (**Figure 7-18**).

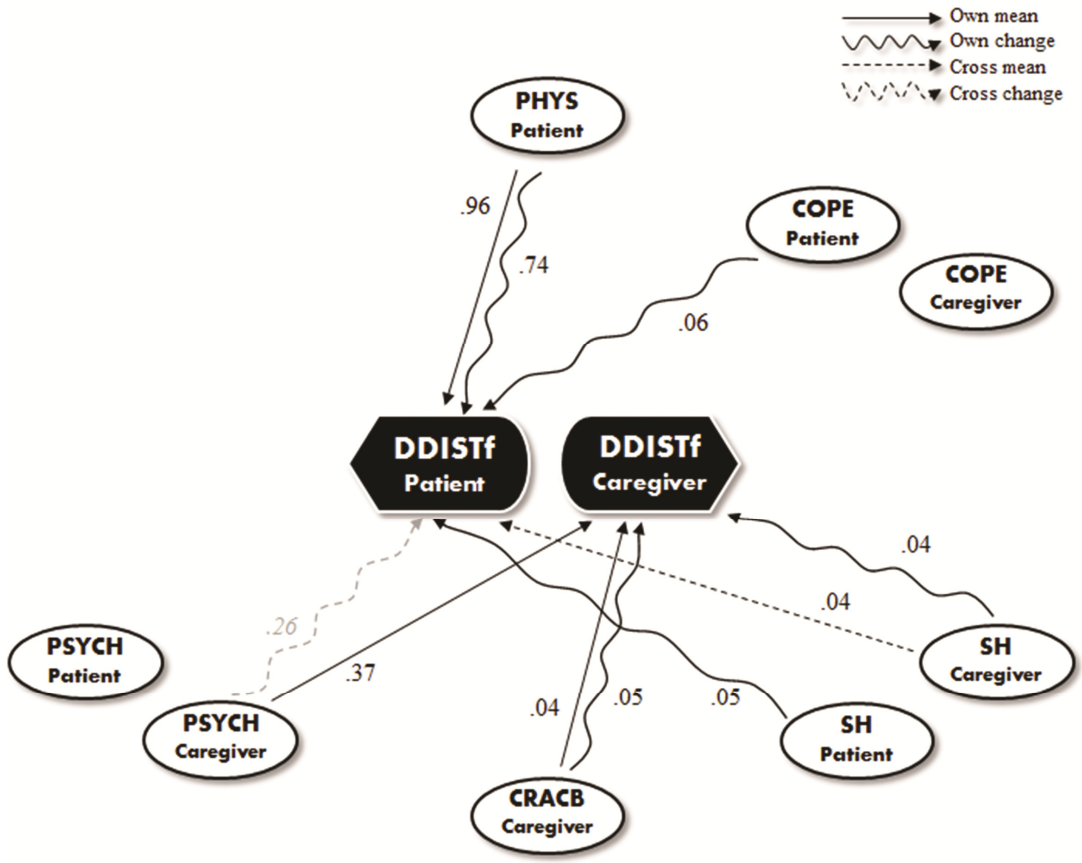

Figure 7-17. Statistically significant (p<.05) enduring (mean) and contextual (change) own and cross-partner effects of the sleep-impairing factors examined on patients' and caregivers' daily disturbance (DDISTf). Faint arrows indicate associations where trends towards significance emerged (.10>p≥.05). All models were controlled for the effects of SLPAST, SLCA, AGE, RELATDUR, CMRBDT, PS, and BCSTAGE for patients; and SLPAST, SLCA, AGE, and RELATUR for caregivers. Where no arrows are shown, no statistically significant associations (or trends towards significance) emerged. Numbers next to arrows denote the MHLM parameter estimates (coefficients) for each predictor variable; negative values indicate an inverse relationship between predictor and outcome variable (see **Table 21-A2**). The SDSTRB predictor variable was removed from this model as data used to create it were also used to create the DDISTf outcome variable.

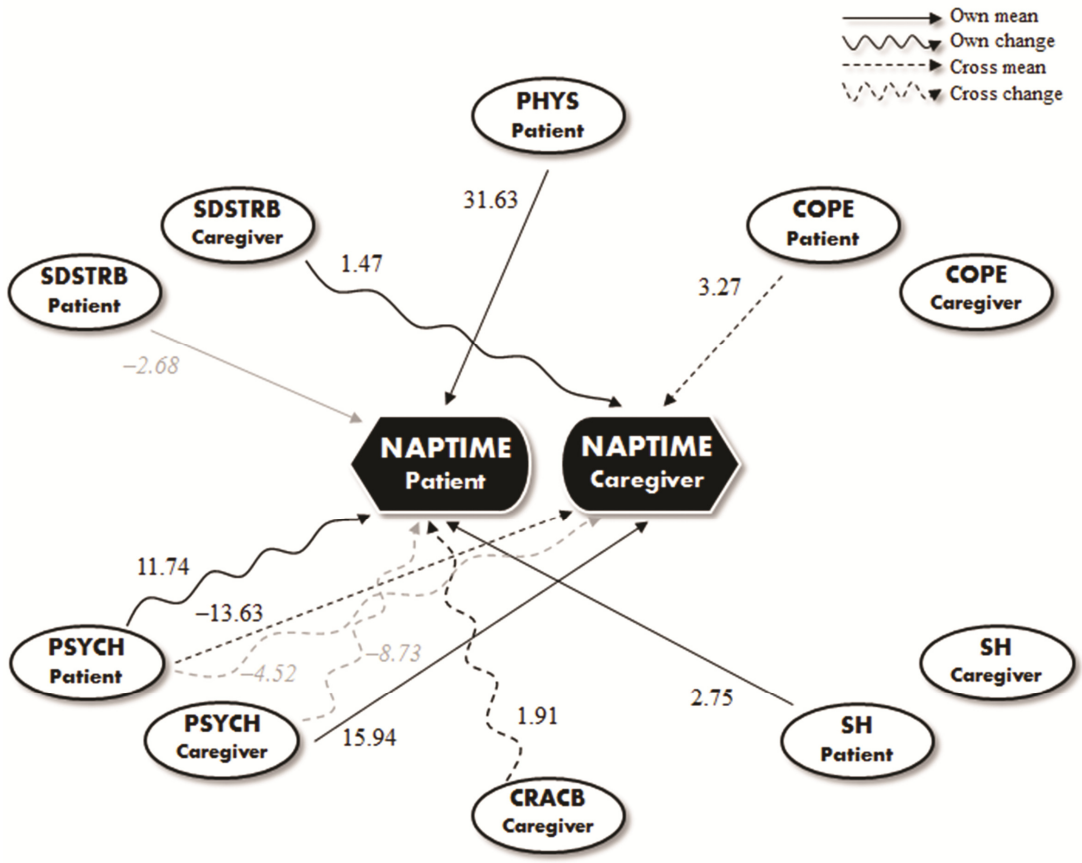

Figure 7-18. Statistically significant (p<.05) enduring (mean) and contextual (average) own and cross-partner effects of the sleep-impairing factors examined on patients' and caregivers' daytime napping duration (NAPTIME). Faint arrows indicate associations where trends towards significance emerged (.10>p≥.05). All models were controlled for the effects of SLSROOM, SLSHOUS, AGE, RELDYAD, RELATDUR, PS, and BMI for patients; and SLSROOM, SLSHOUS, RELDYAD, RELATUR, and SEXCG for caregivers. Where no arrows are shown, no statistically significant associations (or trends towards significance) emerged. Numbers next to arrows denote the MHLM parameter estimates (coefficients) for each predictor variable; negative values indicate an inverse relationship between predictor and outcome variable (see **Table 22-A2**).

Two enduring cross-partner effects flowing from patients to caregivers were also revealed (**Figure 7-18**). First, greater patient psychological distress was associated with shorter caregiver napping (γ_{26}=–13.63, SE=5.94, p=.029; r_{ES}=–.39). Second, increased patient use of negative coping strategies was associated with lengthier caregiver napping (γ_{213}=3.27, SE=1.41, p=.028; r_{ES}=.39). In terms of contextual cross-partner effects, increases in caregiver burden were significantly associated with an increase in patient napping over the study

duration (γ_{260}=1.91, SE=.60, p=.002; r_{ES}=.34). In a counteracting fashion and albeit marginally non-significant, increases in dyad members' psychological distress were linked to decline in the other party's napping duration. Yet, as previously identified, increases in patients' psychological distress were still significantly associated with increases, rather than decreases, in own daytime napping after controlling for potential cross-partner effects (γ_{170}=10.49, SE=4.30, p=.017; r_{ES}=.27). A similar own-effects association for caregivers fell short of statistical significance. These results may nevertheless be suggestive of a link between mood and napping, the direction of which may depend on the point of view from which it is examined, namely own (positive) or cross-partner (negative) effects.

Total Sleep Time (TST)

No significant own effects were found for either patients or carers except that a trend towards lengthier actual sleep at night was found for those caregivers whose own nocturnal disturbance was, on average, lower (γ_{27}=–5.33, SE=2.86, p=.070; r_{ES}=–.28). Although similarly expected, the respective association for patients fell short of significance (γ_{110}=–2.98, SE=2.72, p=.281) (**Table 23-A2**).

Own and cross-partner effects analyses revealed only a trend towards an enduring cross-partner effect flowing from caregivers to patients: greater caregiver burden was linked to shorter patient total sleep time (γ_{14}=–3.80, SE=2.10, p=.080; r_{ES}=–.31) (**Figure 7-19**). Together with a similar (in both direction and magnitude) trend emerging for caregiver burden effects on own TST (γ_{23}=–4.73, SE=2.61, p=.078; r_{ES}=–.29), it can be inferred that in dyads where caregivers felt more burdened, not only they themselves might have experienced sleep deprivation, but also patients' actual sleep duration might have been adversely affected, with caregiver burden equally related to dyad members' mean TST.

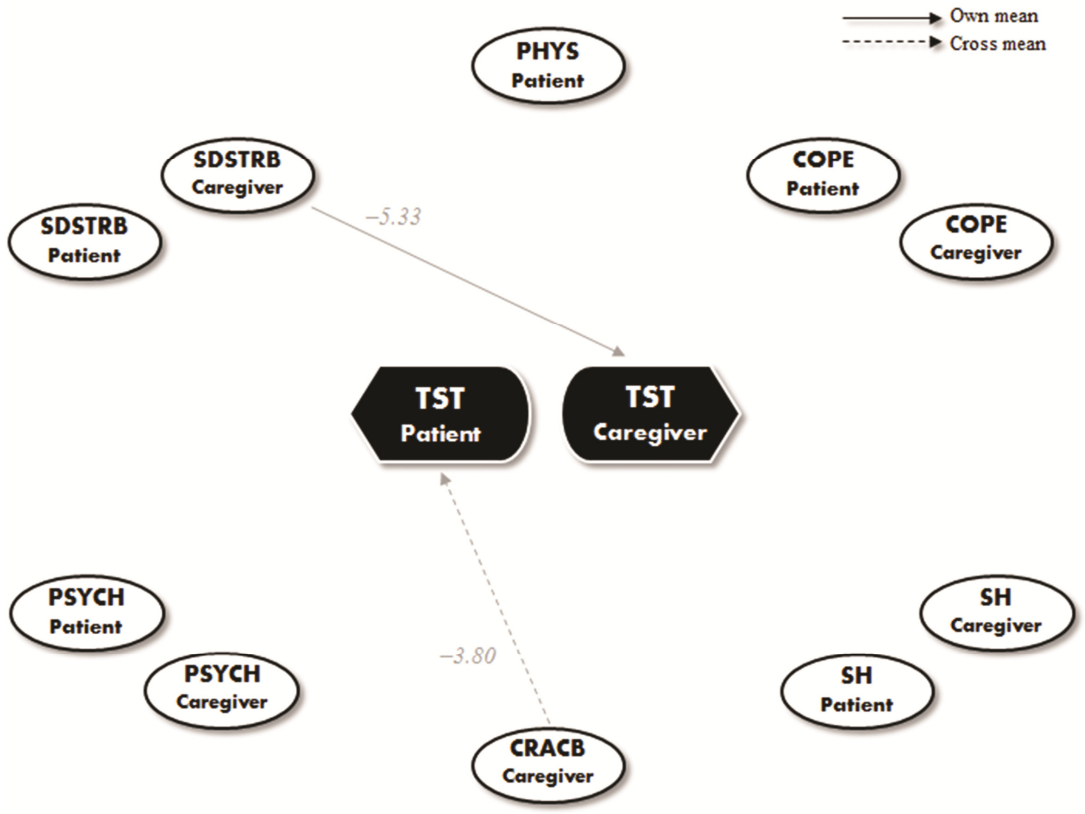

Figure 7-19. Statistically significant (p<.05) enduring (mean) own and cross-partner effects of the sleep-impairing factors examined on patients' and caregivers' total sleep time (TST). No contextual (change) effects were investigated as the means-only model was found to be a better fit to the data. Faint arrows indicate associations where trends towards significance emerged (.10>p≥.05). All models were controlled for the effects of SLPAST, SLCA, RELDYAD, CMRBDT, PS, and ALCHL for patients; and SLPAST and RELDYAD for caregivers. Where no arrows are shown, no statistically significant associations (or trends towards significance) emerged. Numbers next to arrows denote the MHLM parameter estimates (coefficients) for each predictor variable; negative values indicate an inverse relationship between predictor and outcome variable (see **Table 23-A2**).

Sleep Latency (SL)

No significant associations between changes in any of the predictors and changes in sleep latency were found for either patients or carers; yet, contextual trends towards significance were recorded for two predictors (see **Table 24-A2**). First, increases in patient use of maladaptive sleep practices (i.e. declines in sleep hygiene) were linked with increases in own sleep latency (γ_{90}=.71, SE=.40, p=.082). The size of this effect was only small to medium (r_{ES}=.19). Second, change in caregiver burden was positively linked to own sleep latency

(γ_{160}=.43, SE=.24, p=.080; r_{ES}=.19) (**Figure 7-20**). Thus, as caregivers became increasingly burdened during the patients' treatment they were more likely to find difficulty in falling asleep at night.

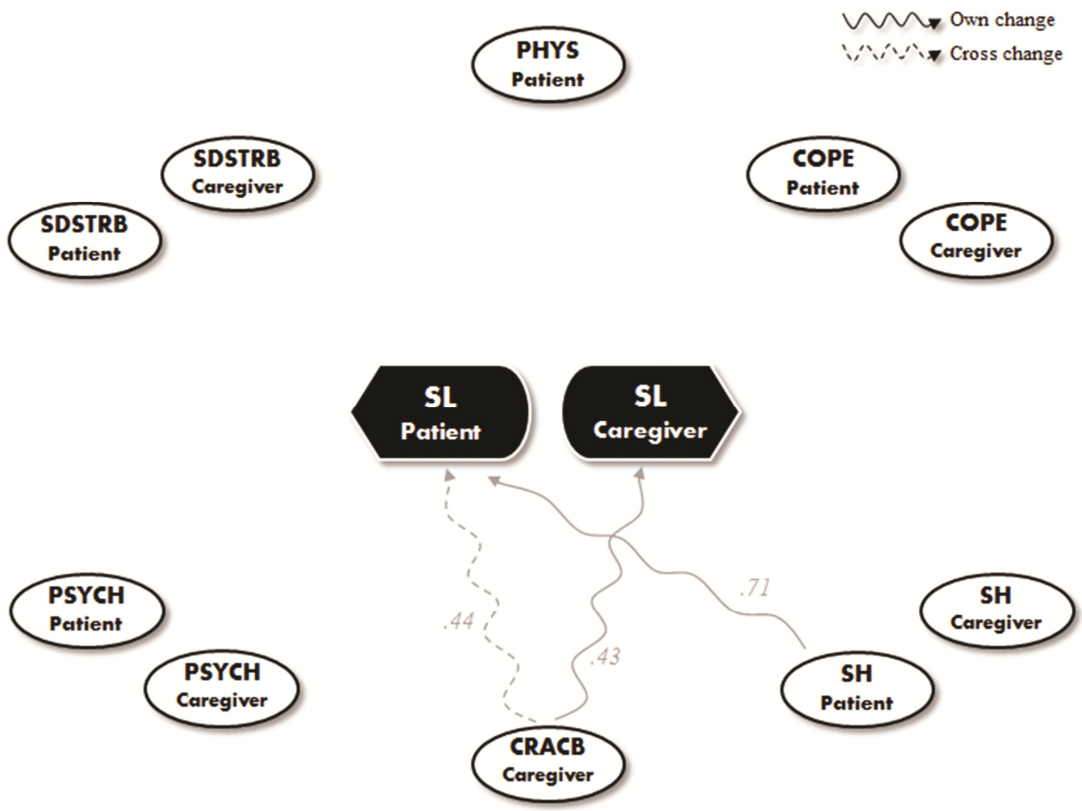

Figure 7-20. Statistically significant (p<.05) contextual (change) own and cross-partner effects of the sleep-impairing factors examined on patients' and caregivers' sleep latency (SL). No enduring (own) effects were investigated as not enough variability in the model's intercepts was found to allow inclusion of average effects. Faint arrows indicate associations where trends towards significance emerged (.10>p≥.05). All models were controlled for the effects of SLPAST, RELATDUR, CMRBDT, and BCSTAGE for patients; no covariates were entered for caregivers due to lack of significant variability. Where no arrows are shown, no statistically significant associations (or trends towards significance) emerged. Numbers next to arrows denote the MHLM parameter estimates (coefficients) for each predictor variable; negative values indicate an inverse relationship between predictor and outcome variable (see **Table 24-A2**).

As with own effects, no significant cross-partner effects emerged (**Figure 7-20**). Nevertheless, increases in caregiver burden were linked to increase in patient sleep latency over the study duration (γ_{260}=.44, SE=.24, p=.068; r_{ES}=.21). At the same time, as previously identified, increase in caregiver burden was still linked to worsening sleep latency after controlling for potential cross-partner effects (γ_{250}=.90, SE=.53, p=.092; r_{ES}=.19). Multivariate hypothesis testing suggested that the effects of increasing caregiver burden on the dyads' changes in sleep latency were somewhat different, as patients seemed to become more affected than caregivers themselves (χ^2=6.94, df=1; p=.029).

Habitual Sleep Efficiency (HSE)

A trend towards worse patient HSE with greater nocturnal disturbance was recorded (γ_{19}=–.69, SE=.36, p=.060; r_{ES}=–.30). Quite unexpectedly, a positive association was also found between patient mean negative coping and own mean HSE (γ_{18}=1.20, SE=.53, p=.030; r_{ES}=.43), suggesting that greater use of maladaptive strategies was related to better sleep during the night for patients. Conversely, mean caregiver burden was inversely associated with own mean HSE (γ_{23}=–.97, SE=.30, p=.002; r_{ES}=–.54), as was own mean nocturnal disturbance (γ_{28}=–.88, SE=.31, p=.007; r_{ES}=–.42), and own mean sleep hygiene (γ_{25}=–.63, SE=.24, p=.013; r_{ES}=–.39). Consistent associations between changes in predictors and the outcome variable were found for patients only. More specifically, increases in patient nocturnal disturbance (γ_{70}=–.86, SE=.25, p<.001; r_{ES}=–.35), increases in patient disruptive sleep hygiene practices (γ_{90}=–.96, SE=.23, p<.001; r_{ES}=–.41), and increases in patient physical distress (γ_{110}=–4.61, SE=2.31, p=.049; r_{ES}=–.21) were independently related to declines in HSE during treatment. Medium effect sizes were found for both enduring and contextual effects for patients, with magnitude of contextual effect sizes greater than those of the enduring ones (**Table 25-A2**).

Investigation of this MHLM revealed a number of interesting cross-partner effects. Greater mean caregiver psychological distress was significantly associated with poorer patient HSE (γ_{15}=–5.09, SE=2.08, p=.020), an effect that was medium in size (r_{ES}=–.39). A trend towards worse patient HSE with greater mean caregiver burden (γ_{12}=–.51, SE=.26, p=.056; r_{ES}=–.33) also was evident. In addition, changes in caregiver nocturnal disturbance (γ_{100}=–.56, SE=.32, p=.083; r_{ES}=–.20), caregiver sleep hygiene behaviours (γ_{140}=–.39, SE=.18, p=.035; r_{ES}=–

.24), and caregiver burden (γ_{260}=–.37, SE=.20, p=.067; r_{ES}=–.21) were negatively linked to changes in patient habitual sleep efficiency over the study duration (**Figure 7-21**).

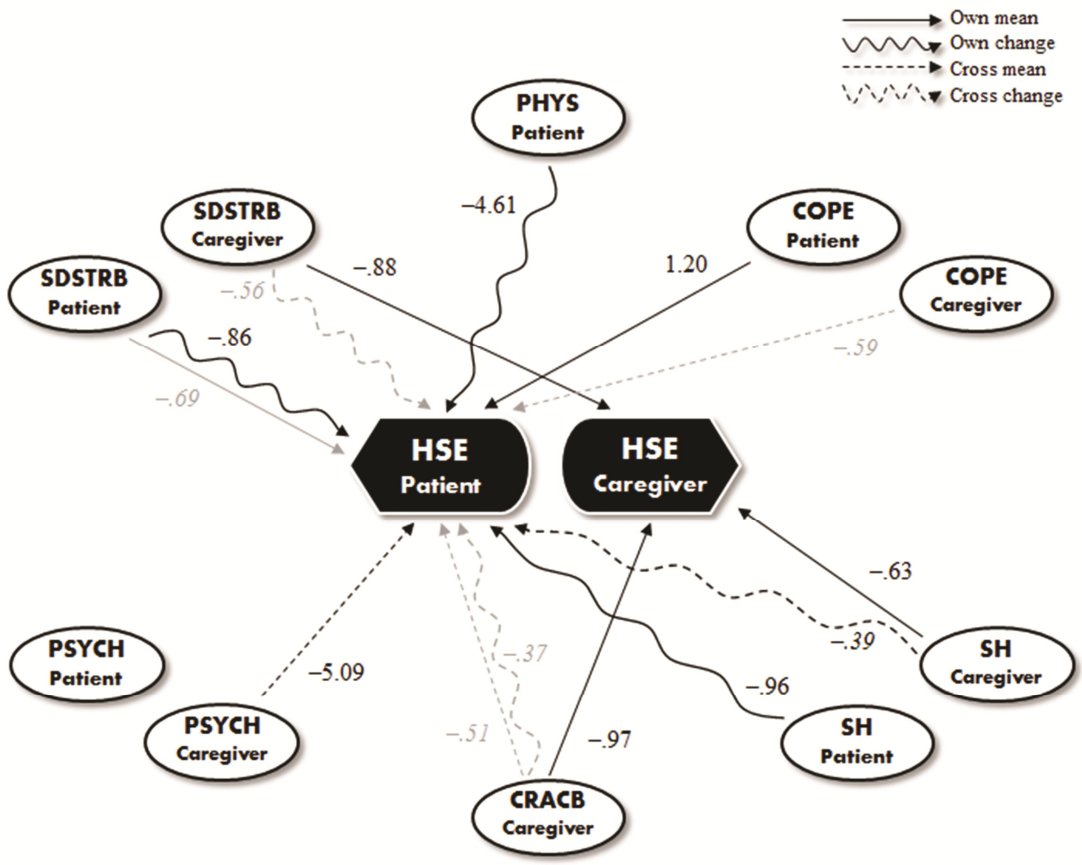

Figure 7-21. Statistically significant (p<.05) enduring (mean) and contextual (change) own and cross-partner effects of the sleep-impairing factors examined on patients' and caregivers' habitual sleep efficiency (HSE). Faint arrows indicate associations where trends towards significance emerged (.10>p≥.05). All models were controlled for the effects of SLPAST, RELATDUR, CMRBDT, and PS for patients; and SLPAST, SLCA, RELATUR, EDUCCG, and ALCHLCG for caregivers. Where no arrows are shown, no statistically significant associations (or trends towards significance) emerged. Numbers next to arrows denote the MHLM parameter estimates (coefficients) for each predictor variable; negative values indicate an inverse relationship between predictor and outcome variable (see **Table 25-A2**).

Wakefulness After Sleep Onset (WASO)

A wealth of enduring own effects emerged (**Table 26-A2**). More frequent use of maladaptive coping strategies was related to greater WASO for patients (γ_{18}=6.05, SE=2.75, p=.034; r_{ES}=.34). More severe caregiving burden was positively related to prolonged time in wakefulness for caregivers (γ_{23}=3.12, SE=1.46, p=.038; r_{ES}=.33). For both patients and caregivers, poorer own sleep hygiene behaviours, and more nocturnal disturbance were independently associated with poorer own outcomes. Whereas enduring effects of own nocturnal disturbances were comparable in size (r_{ES}=.34 v. .35), enduring effects of own sleep hygiene on WASO were significantly greater for caregivers than for patients (χ^2=5.66, df=1; p=.033). Not only enduring, but also contextual effects of own sleep hygiene practices were recorded. Increases in the use of disruptive sleep practices was associated with prolongation in WASO for both patients (γ_{90}=3.47, SE=1.48, p=.021; r_{ES}=.24) and caregivers (γ_{100}=1.94, SE=.63, p=.003; r_{ES}=.31), although the size of these effects was again greater in magnitude for carers than for patients (r_{ES}=.31 v. .24). Similarly, as patients experienced more nocturnal disturbance during treatment, they spent more time awake during the night, and vice versa (γ_{70}=6.36, SE=1.70, p<.001; r_{ES}=.38) (**Figure 7-22**). These results suggest that accumulation of disruption caused by triggers acting at the early (sleep hygiene) and later phases (nocturnal disturbance) of sleep particularly increased the risk of both dyad members for a sleepless night during the patient's treatment.

Only a few, yet particularly interesting, mean and time-varying cross-partner effects that flowed from caregivers to patients also emerged. After controlling for own effects, caregiver mean psychological distress was significantly, but negatively, associated with increased patient WASO (γ_{15}=–30.76, SE=13.48, p=.029; r_{ES}=–.37), thus indicating that women, whose caregivers were, on average, less emotionally affected, spent more time awake at night during the treatment period. Increases in caregiver nocturnal disturbance throughout the study period were significantly associated with increases in patient WASO (γ_{100}=4.98, SE=1.83, p=.008; r_{ES}=.30), after controlling for own effects. Seen in conjunction with own effects, patients spent more time in wakefulness, not only as a result of their own nocturnal disturbance, but also as a result of their caregivers'. Yet, own effects (r_{ES}=.41) had a greater impact on patient WASO than the cross-partner ones (r_{ES}=.30). In addition, a contextual cross-partner effect from caregiver sleep hygiene practices to patient WASO was also apparent (γ_{140}=3.39, SE=1.00, p=.001; r_{ES}=.36). In this case, however, multivariate hypothesis testing indicated that the emerging significant difference was in favour of the cross-partner effects; that is, after controlling for own effects, patients were impacted more by the caregivers' disruptive sleep hygiene behaviours than by their own (χ^2=6.88, df=1; p=.017).

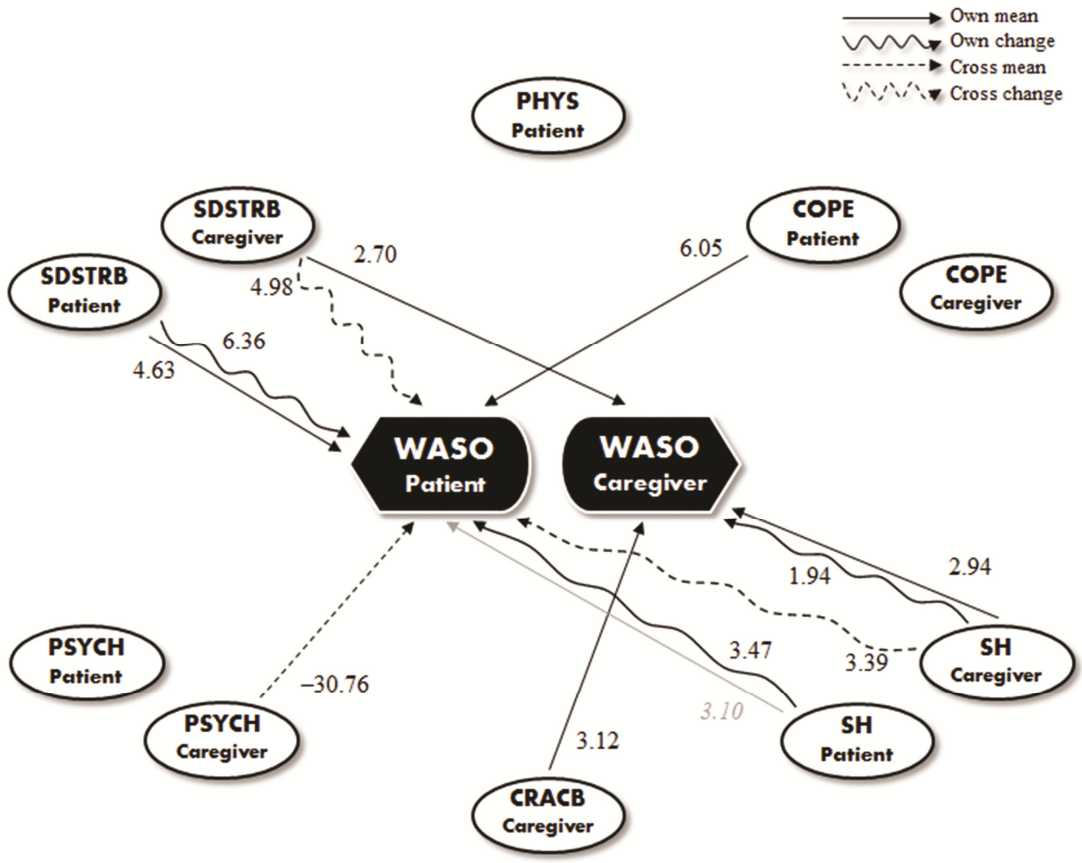

Figure 7-22. Statistically significant (p<.05) enduring (mean) and contextual (change) own and cross-partner effects of the sleep-impairing factors examined on patients' and caregivers' wakefulness after sleep onset (WASO). Faint arrows indicate associations where trends towards significance emerged (.10>p≥.05). All models were controlled for the effects of SLPAST, CMRBDT, and PS for patients; and SLPAST, SLCA, and EDUC for caregivers. Where no arrows are shown, no statistically significant associations (or trends towards significance) emerged. Numbers next to arrows denote the MHLM parameter estimates (coefficients) for each predictor variable; negative values indicate an inverse relationship between predictor and outcome variable (see **Table 26-A2**).

Overall Sleep/Wake Impairment (GSQI)

A few enduring effects were contemplated by significant contextual effects in this MHLM (**Table 27-A2**). Mean caregiving burden was positively and significantly associated with own sleep/wake impairment for caregivers (γ_{24}=.18, SE=.08, p=.04; r_{ES}=.30), and mean physical distress was linked to greater own sleep impairment for patients (γ_{14}=3.17, SE=1.43, p=.032; r_{ES}=.34). Deterioration in patient physical distress (γ_{90}=2.80, SE=.67, p<.001; r_{ES}=.42) and in caregiving burden (γ_{140}=.12, SE=.05, p=.026; r_{ES}=.30) was also related to

worsening in overall sleep/wake patterns for both dyad members (**Figure 7-23**). Moreover, confirming previous findings, changes in own sleep hygiene practices were also positively related to changes in sleep/wake patterns for both patients (γ_{70}=.32, SE=.08, p<.001; r_{ES}=.41) and caregivers (γ_{80}=.09, SE=.03, p=.002; r_{ES}=.28). Effect sizes were significantly larger for patients than for caregivers (χ^2=16.12, df=1; p<.001), thus suggesting that during the chemotherapy period patients' sleep/wake patterns were more susceptible to deterioration due to own disruptive sleep behaviours than those of caregivers.

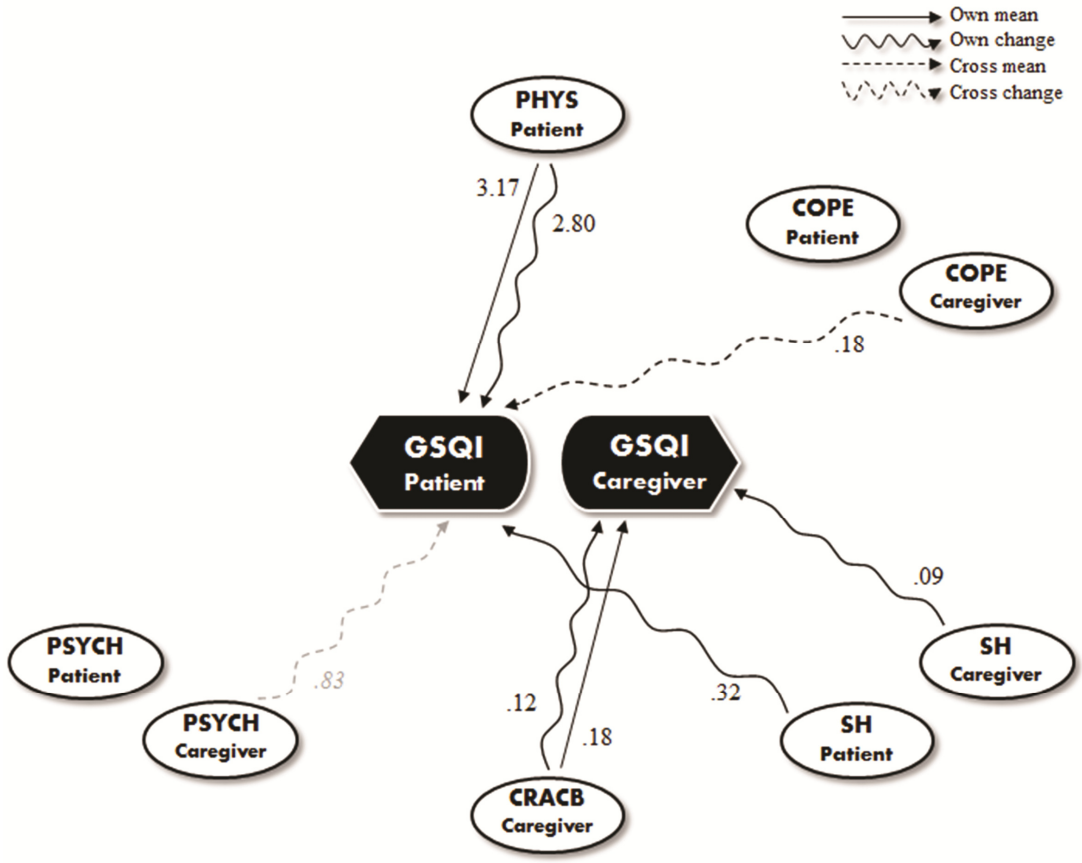

Figure 7-23. Statistically significant (p<.05) enduring (mean) and contextual (change) own and cross-partner effects of the sleep-impairing factors examined on patients' and caregivers' overall sleep/wake impairment (GSQI). Faint arrows indicate associations where trends towards significance emerged (.10>p≥.05). All models were controlled for the effects of SLPAST, SLCA, AGE, RELATDUR, CMRBDT, and PS for patients; and SLPAST, SLCA, AGE, RELATDUR, and EDUC for caregivers. Where no arrows are shown, no statistically significant associations (or trends towards significance) emerged. Numbers next to arrows denote the MHLM parameter estimates (coefficients) for each predictor variable; negative values indicate an inverse relationship between predictor and outcome variable (see **Table 27-A2**). The SDSTRB predictor variable was removed from this model as data used to create it were also used to create the DDISTf outcome variable.

Finally, investigation of this MHLM revealed the potential for only one contextual cross-partner effect: changes in use of negative coping on the caregivers' part were significantly and positively related to changes in patients' overall sleep/wake impairment (γ_{200}=.18, SE=.09, p=.042; r_{ES}=.22) (**Figure 7-23**). Interestingly, changes in patients' sleep were more likely to be predicted by caregivers' change in negative coping rather than their own fluctuation. Conversely, patients' negative coping remained unrelated to either own or partner sleep impairment as no cross-partner effect emerged.

CHAPTER 8.
Discussion and Future Implications

8.1. Overall Appraisal of Findings

The present study implemented a longitudinal, dyadic approach to explore sleep/wake patterns of patient-caregiver care dyads in the context of adjuvant chemotherapy for early stage breast cancer. In order to operationalize the generic term of 'sleep/wake patterns', this study specifically focussed on a number of distinct sleep/wake parameters as these have been identified in the literature [49]. Eight sleep/wake parameters (perceived sleep quality, habitual sleep efficiency, sleep latency, total sleep time, wakefulness after sleep onset, daily disturbance, daytime napping duration, and overall sleep/wake impairment) served as outcome variables throughout all analyses. By collecting and examining additional data on dyads' nocturnal and early morning awakenings, restless legs episodes, feelings of restfulness upon morning awakening, daytime sleepiness, and need for daytime napping it is believed that a comprehensive sleep assessment has taken place.

Two main research questions were addressed in the current study. The first research question examined trajectories of change in patients' and caregivers' sleep parameters, as well as relationships, similarities and interdependence in these parameters across the care dyads. Three hypotheses were posed and investigated. As discussed in the following paragraphs, results provided partial confirmation to these hypotheses in that whereas overall trajectories of change for patient sleep/wake patterns followed a significant curvilinear pattern (a linear pattern in the case of daytime disturbance), carers' perceptions of their own sleep did not follow this same pattern, or this was clinically important for some parameters only, such as daytime napping duration, or overall sleep/wake impairment (Hypothesis 1). However, at pre-treatment, wake variables, total sleep time, and overall sleep/wake impairment were not significantly different between members of dyads; after CThC4, there was a similar pattern for total sleep time and sleep latency, possibly suggesting that then both patients and carers had diminished sleep duration and had similar difficulty to fall asleep (Hypothesis 3). In terms of interdependence, analyses showed that changes in perceived sleep quality, sleep latency and overall sleep/wake impairment in the women were followed closely by similar in direction changes in their caregivers. Daytime wake variables remained uncoupled. Quite

interestingly, an inverse relationship was found for sleep efficiency, total sleep time and wakefulness after sleep onset: increases in patients were followed by decreases in caregivers, and vice versa (Hypothesis 2).

As with previous research [119, 518], women represented a highly sleep-deprived group of individuals even before initiation of chemotherapy treatment: over half of the sample were classified as with altered sleep at baseline. With at least 60% of women possibly reporting waking up in the middle of the night or early in the morning [7], this finding confirms previous research. Hence, any further disruption in sleep architecture seems to only lead to the accumulation of already existing sleep problems. In fact, at post-treatment, 65% of the women still complained of poor sleep based on PSQI cut-off scores. Possibly adding to this finding, daily disturbance in this patient group showed a linear trend of positive change (worsening) throughout the duration of chemotherapy treatment [518], remaining high in prevalence even at post-treatment. Previous research has also revealed that the initial period (first 2 days to 2 weeks) after intravenous chemotherapy for breast cancer may be characterised by sleep fragmentation that disrupts the maintenance of habitual sleep/wake patterns [7, 126-128]. At mid-treatment (CThC3 and CThC4), the cumulative discomfort reaches a peak [128, 518] and the impact on a woman's sleep is exacerbated. Indeed, current results revealed statistically significant curvilinear patterns of change for most of the patient sleep/wake parameters throughout chemotherapy. Although objective sleep data might not corroborate these findings [120, 518], perceived sleep quality, sleep latency, habitual sleep efficiency, WASO, daytime napping duration, and overall sleep/wake impairment showed a pattern of increase/worsening from pre-treatment to post-CThC1; reached a peak after administration of CThC4; and returned to (or close to) pre-treatment levels 30 days after the end of chemotherapy. Effect sizes were generally modest to large (.35 to .48), thus indicating at least moderate clinical changes on average. Nevertheless, frequency of sleep aid use remained low, close to pre- (14-20%) and mid-treatment rates (23-32%) reported in previous studies [136, 137]. Whether this result reflects reluctance on the women's part to receive hypnotic treatment, or failure on the clinicians' part to adequately manage such problems, can only be hypothesised. In this patient sample, habitual sleep efficiency was below normal limits, and this stands in contrast with previous findings [119]. Habitual sleep efficiency is the ratio of total actual sleep time divided by the total time spent in bed [3]; therefore, reductions in total sleep time can offer a possible explanation for this discrepancy. However, as a group, patients manifested no particular pattern of change in their total sleep time. Kotronoulas et al. [119] concluded with a similar absence of a pattern in this context. An alternative explanation could be that women increased their time spent in bed. Indeed, during chemotherapy, patients reported earlier bedtimes and later wake times. Thus, on average,

whereas time asleep remained the same, time awake while lying on the bed increased, and this was translated into a decrease in HSE.

The current study was among the first to longitudinally explore sleep/wake patterns of informal caregivers in relation to patient health transition phases [366, 519], and the first to do so in the context of cancer care. A considerable proportion of caregivers were identified with sleep problems (35-49%), which is in agreement with past research revealing sleep/wake impairment in at least 4 out of 10 carers of patients with cancer irrespective of type or phase of disease [182]. In a different cultural context that might have increased caregiving demands, eight out of ten family caregivers of newly diagnosed women with early stage breast cancer reported poor sleep quality [30]. Current findings are similar to studies among individuals providing informal care prior to [520], during [30, 521] and after [522] chemotherapy: sleep latency and duration, nocturnal disturbance and WASO, daytime dysfunction were those areas most greatly affected. Unlike patients, however, caregiver sleep/wake parameters did not significantly change during and after chemotherapy, thus suggesting that overall caregiver self-reported sleep quality and quantity was not considerably affected as patients progressed through chemotherapy. Given the effects of caregiving on sleep documented in previous studies [182, 523], this might seem as a striking finding. Another possible way to interpret this result would be to acknowledge the fact that in this caregiver group, already established sleep problems showed no trend towards improvement, either. For instance, caregiver overall sleep/wake impairment, total sleep time, and WASO remained adversely affected throughout treatment. In spite of the absence of major significant change, a consistent slight trend towards worsening in caregiver-perceived sleep quality, habitual sleep efficiency, WASO, and overall sleep/wake impairment was apparent at mid-treatment (post-CThC4), possibly suggesting accumulation of the disruptive effects of caregiving at that time point. In contrast with nocturnal sleep, a borderline significant upward linear trend in daytime napping duration did emerge, which was extended until mid-treatment. Seen in conjunction with a similar increase in need for daytime napping reports, it can be inferred that caregivers' wake patterns were particularly affected by the demands posed to them during chemotherapy. Current results confirmed caregiver reluctance to use sleep medications, as documented in previous studies [23, 27, 30, 244, 521-523]. A possible explanation for this outcome relates to caregiver concerns about the potential side effects of these medications that might interfere with a carer's ability to timely respond to patient need at night or in the daytime [182]. Another explanation could relate to caregivers' perceived temporality of sleep/wake impairment, which might have prevented them from seeking help in the hope that once the intense treatment period was over, so would be their sleep problems.

From a dyadic point of view, comparability in frequencies of poor self-reported sleep between patients and caregivers has been suggested [233, 242, 244, 251, 524], but was only confirmed for pre-treatment data in this study. Importantly, current results also revealed alarming percentages of dyads of at least one poor sleeper that reached 65% even before chemotherapy initiation. These further increased as patient treatment progressed. Indeed, at mid-treatment, approximately 49% and 39% of this dyad sample consisted of one or two poor sleepers, respectively. Baseline findings are somewhat comparable to previous research. Over a one-week period of observation of 60 patients with advanced cancer and their family caregivers, Gibbins et al. [244] reported that in 23% of the dyads, both members reported not sleeping well, whilst in an additional 45%, either the patient or the carer complained about poor sleep. Discrepancy in the prevalence rates reported in this and in previous studies may well be due to contextual effects of ever changing demands posed during chemotherapy continuation; conversely, the Gibbins et al. study offered a snapshot of the experience of care dyads attending cancer clinics for follow-up purposes [244].

The use of longitudinal multilevel modelling techniques in this study allowed for a simultaneous account of dyad members' sleep/wake parameters. Except for total sleep time, the significant differences in average curves of all outcome variables were indicative of a generally greater impact on patients' rather than caregivers' sleep during the chemotherapy period, which persisted into the initial post-chemotherapy period. Similar overall results were yielded among 23 dyads of chronically (9.3±6.0 years) ill individuals with Parkinson's disease and their primary caregiver [285]; yet, in a recent bright light trial, only sleep efficiency was negatively affected in memory-impaired individuals than in their caregivers [525]. What is more, rates of acceleration in the deterioration of perceived sleep quality, habitual sleep efficiency, WASO, daily disturbance, and overall sleep/wake impairment were consistently steeper for patients during the administration of chemotherapy cycles as suggested by between-groups differences in their linear and quadratic trends. These findings were not only complemented by a consistent clinical difference in the frequency of sleep aid use, nocturnal awakenings, daytime sleepiness, and need for napping in the daytime between the two groups, but also by evident differences in the shape of average trajectories: whereas patients' sleep/wake parameters changed in a significant curvilinear fashion during chemotherapy, for the most part, caregiver parameters did not follow. Prospective studies in the context of dementia [363] and cancer care [244] have also suggested greater problems with sleep maintenance [363] and daytime functioning [244] for patients than for caregivers. Gibbins et al. [244] found that activity levels were consistently higher for caregivers and time immobile in the daytime was greater for patients. In the current study, however, physical activity levels were, overall, similar between dyad members. Therefore, patient-caregiver differences in

napping duration do not seem to be due simply to differences in activity; it is more possible that nocturnal sleep loss and physical symptom burden urged women for more prolonged napping in the daytime.

Additional diverse perspectives can be examined to interpret the afore-mentioned between-groups differences. As women with breast cancer constitute a highly independent patient population, over-night caregiving demands might have been kept to a minimum. In contrast, caregivers of people with advanced cancer or with different types of cancer may be required to actively respond to patients' needs at night and become more sleep deprived [28, 182, 277, 520, 526]. In other studies, co-habiting caregivers changed their sleeping arrangements so that nocturnal alertness on the patients' part left them unaffected [368]. Yet, a recent systematic review of studies conducted with care recipient-caregiver dyads, irrespective of health context, concluded with only partial evidence suggesting nocturnal interactions between the dyad members [366]. Conversely, caregivers in the current study went to sleep at night an average of 4-18 minutes later than patients and woke up in the morning an average of 39-50 minutes earlier throughout the study period. This finding is consistent with previous dyadic studies in which, irrespective of context of illness, caregivers had generally later bedtimes and earlier awakening times, possibly in an attempt to organise their sleep routines around the patient [242, 247, 367]. In the current study, an alternative explanation of this trend might be that, due possibly to adverse chemotherapy effects, women simply felt the need to rest earlier than usually, and also extended the time they spent lying on the bed, even if they were not actually sleeping.

Despite these differences, at specific time points and for certain variables, dyad members' sleep patterns tended also to converge. At baseline, daily disturbance, daytime napping duration, total sleep time, and overall sleep/wake impairment were no different between patients and caregivers. In preliminary analyses, no differences also emerged for bedtime, restless legs, nocturnal and early morning awakenings, feelings of restfulness upon morning awakening, sleepiness, and need for daytime napping, thus suggesting that to a certain extent dyads shared similar degrees of sleep/wake impairment at pre-treatment. With the exception of nocturnal awakenings, these results confirm similar evidence reported by Carney et al. [242] in a sample of 102 patient-caregiver dyads one week prior to primary or adjuvant radiation therapy for diverse non-metastatic cancers. Among the unique findings of this study stands the fact that over treatment continuation, rates of change in sleep latency and duration of daytime napping were not significantly different between patients and caregivers, with respective increases in the dyad members' sleep latency (indicating more difficulty in falling asleep) and napping duration (indicating the need for more rest in the daytime). Especially

with regard to sleep latency, average patient and caregiver trajectories almost coincided at mid-treatment, where difficulty to fall asleep became equivalent for both dyad members (patients, 31 minutes versus caregivers, 29 minutes). However, one of the most clinically important observations in this study was that deterioration in caregiver sleep/wake variables reached its highest as dyads reached mid-treatment, a time point where patient sleep/wake impairment also peaked. Even though severity of impairments may not have been comparable, this trend gives credence to the hypothesis that not only patients with breast cancer [9] but also caregivers show progressive impairments in their sleep/wake patterns, which can be translated in dyad members concurrently manifesting sleep deficits at specific time points.

In agreement with the concept of patients and caregivers living in a close relationship [366], multilevel modelling techniques also supported examination of the notion that a caregiver's sleep can be a function of the patient's sleep, and vice versa. Even in the presence of non-cohabiting dyads in this sample (n=6), moderate positive correlations emerged between patient and caregiver perceived sleep quality, sleep latency, daily disturbance, and overall sleep/wake impairment at pre-treatment. Two cross-sectional studies conducted with dyads in the context of cancer [242] and Parkinson's disease [285] reported relationships of a similar magnitude in the dyad members' perceived sleep quality. Of note, patterns of change in these variables were strongly correlated between dyad members throughout the study, thus indicating that deterioration in patient sleep parameters was followed by a similar worsening in the respective caregiver variables, and vice versa. Preliminary correlational analysis also suggested close synchronisation of patient and caregiver bedtimes and wake times throughout the study, in agreement with past research [366]. This finding underpins the notion of dyadic 'sleep rituals' [369], which might be more common in dyads similar to the ones participated here: spouses/partners in well-established relationships. In addition, a few moderate correlations between patient and caregiver feelings of restfulness upon morning awakening and daytime sleepiness at baseline were found, which, however, faded out over treatment continuation. Similarly to Carney et al. [242], nocturnal disturbance at pre-treatment remained unrelated in the dyads, although weak correlations did emerge during treatment. Moreover, analyses in the models indicated only minimal, or even inverse, relationships between average patient and caregiver total sleep time, habitual sleep efficiency, and WASO curves; this finding stands in contrast with existing evidence suggesting moderate-to-strong positive relationships depending on objective recordings [242, 247, 367], but also supports similar weak associations based on self-reports [242]. It can certainly be hypothesised that these results reflect differing degrees of burden posed to dyad members during chemotherapy that have ultimately blurred or weakened such relationships. Whether, however, this might also be the result of limitations in self-report sleep assessments is an equally valid

question, as external influences and variability might have affected accuracy (see below); in any case, this remains to be answered in future studies. Finally, it is noteworthy that trajectories of daytime behaviours (i.e. need for daytime napping and daytime napping duration) of members of the dyads remained widely uncoupled throughout this study, as also has been shown in the past [242, 278, 285, 367, 368]. The reason for this outcome can possibly be because of differences in daytime schedules in this sample of young and employed dyads, compared to older adults who may share their daytime activities more closely.

The second research question examined whether changes in patients' physical burden, caregivers' burden, and dyads' sleep hygiene, nocturnal disturbance, psychological burden, and maladaptive coping strategies were associated with own changes in sleep/wake impairment. In addition, the potential for more complex interrelations within a dyad's sleep patterns was explored, as suggested by the presence of additional cross-partner effects. Briefly, analyses revealed that increased physical burden, greater use of sleep disruptive behaviours and more nocturnal sleep disturbances were the variables that most consistently predicted poorer outcomes in the patients' own sleep/wake patterns (Hypothesis 4). Similarly, increased caregiving burden, more nocturnal sleep disturbances, and poorer sleep hygiene were the variables that most consistently predicted poorer outcomes in the caregivers' own sleep/wake patterns (Hypothesis 5). Evidence for cross-partner effects most frequently emerged with regard to the dyads' psychological burden, as well as for caregiving burden, although some additional links might be suggested for own poor sleep hygiene and worse partner outcomes on daytime functioning, sleep efficiency, or WASO (Hypothesis 6).

Inadequate sleep hygiene can be an important predisposing and/or perpetuating factor for impaired sleep patterns [65]. In the current study, dyads who exercised more sleep inhibitory practices during the chemotherapy period spent more time awake at night, reported less efficient sleep, and experienced more dysfunction in the daytime. According to Lee's model (**Figure 1-1**) [62], it can be thus postulated that sleep hygiene of dyad members was related mainly to sleep deprivation and secondarily to sleep disruption. Using a daily process approach, Rumble et al. [527] prospectively investigated sleep/wake patterns in 41 survivors of early stage breast cancer who complained of insomnia post-completion of primary treatment. Sleep inhibitory behaviours in the previous day and night significantly predicted poorer sleep quality and less efficient sleep the same night [527], a finding that was partly replicated in this study. Indeed, whereas no significant associations with perceived sleep quality were found for either patients or caregivers, increases in the frequency of sleep impairing behaviours did predict decreases in patients' sleep efficiency. In addition, carers with poorer

sleep hygiene at pre-treatment reported significantly less efficient sleep on average. Whether similar results for patients' mean and contextual effects were also present for caregivers could not be established in this study due to a lack of significant variability in this sample's reports. An at least moderate (r_{ES}=.39) association is nevertheless proposed here, which stands in contrast with qualitative findings derived from a cross-sectional study of 90 caregivers of patients with cancer during active chemotherapy treatment: only a very small part of respondents consciously recognised poor sleep hygiene as a contributing factor to their overall poor sleep quality [521]. Interestingly, the only cross-partner effects that emerged were uni-directional flowing from caregivers to patients; this finding may strike one as odd because sleep hygiene practices were not significantly different between dyad members at any time point. However, in dyads comprised of caregivers with poor and fluctuating sleep hygiene behaviours, patients remained sleepless for longer at night (decreased HSE, increased WASO), and experienced greater disturbance in the daytime. Moreover, cross-partner effects were at least comparable in size with own effects. What this result suggests is that in a highly susceptible to sleep deprivation patient population, not only own poor sleep hygiene but also (and possibly equally) that of carers living in close relationship can be held responsible and perpetuate problems with sleep maintenance and daytime dysfunction once these arise. These findings partly confirm previous hypotheses for the existence of complex interrelationships [366] and can potentially be of importance in clinical practice.

Similarly to sleep hygiene, own nocturnal sleep disturbance in the form of night time awakenings, the need to use the bathroom, feeling hot/cold, snoring, nightmares, and other potential disrupting events, consistently and significantly predicted poorer outcomes in own perceived sleep quality, habitual sleep efficiency, and WASO for both patients and caregivers. Dyads who were more affected by sleep disrupting events at night reported poorer sleep quality and more problems with sleep maintenance as suggested by more time spent in sleeplessness at night. What is more, increases in patients' own nocturnal sleep disturbance also predicted lengthier naps in the daytime, possibly in an attempt to compensate for the previous night's poor sleep. Seen in conjunction, nocturnal sleep disturbances in this dyad sample were related to both sleep restriction and fragmentation [62]. These results give support to past cross-sectional and longitudinal research demonstrating a relationship of sleep to hot flashes in patients with breast cancer [148, 172, 528], as well as to findings from studies where nocturnal awakenings, toilet use, occurrence of bad dreams, and snoring were self-reported as reasons for sleep difficulty by patients [7, 529] and caregivers [23, 237, 521]. Utilising similar methodology and instrumentation, Sanford et al. [529] longitudinally assessed sleep quality of 80 women before, during (CThC4), and approximately 6 months after adjuvant chemotherapy for breast cancer. Although changes in snoring, having to get up to

use the bathroom, and feeling too hot were not consistent with over-time changes in the sleep/wake parameters investigated [529], patterns of change were similar to the current study. Importantly, bidirectional cross-partner effects were found in this study, which, despite their limited number, support the existence of nocturnal interactions between patients and caregivers [368]. In agreement with a study conducted among patients with Parkinson's disease and their partners [233], average patient nocturnal sleep disturbance predicted worse perceived sleep quality in their caregivers. In a similar population, greater patient sleep disturbance was related to diminished caregiver sleep duration [285]; yet, this finding was not replicated in the current study. Albeit smaller in magnitude than the respective own effects, significant reverse cross-partner effects were also apparent, especially with regard to sleep maintenance. In the Happe et al. study, such effects fell short of significance [233], but this discrepancy may be attributed to differences in clinical characteristics and the nature of the disease between the two study samples.

A wealth of evidence exists with regard to the effects of chemotherapy-related physical symptoms on sleep/wake patterns of women with breast cancer [134, 145, 146, 530]. Past research has confirmed that pain, fatigue, shortness of breath, and gastrointestinal symptoms can be adversely related to disruptions in sleep architecture and subsequent sleep deprivation [104, 120, 123, 125-127, 129, 143, 147, 148, 165, 172]. In the current study, frequency, severity and associated distress of 14 physical symptoms were taken into consideration in an attempt to estimate overall physical symptom burden for patients. As with past research [531, 532], preliminary analyses indicated moderate burden that increased from baseline to mid-treatment and remained elevated even 30 days post-chemotherapy. Nevertheless, in the current study no associations were found between patient physical symptom burden and own perceived sleep quality, sleep latency, total sleep time, or WASO; thus, no evidence for sleep fragmentation in this dyad sample emerged [62]. This is a hard to explain finding, which might possibly be a function of the actual method of physical symptom measurement, that is to say, the use of a generic rather than symptom-specific measure. Yet, sleep restriction was evident. More severely affected patients were found with poorer sleep efficiency and greater overall sleep/wake impairment, with changes in physical burden being followed by modest changes in these sleep variables throughout the study. In addition, patient physical burden was consistently, significantly and strongly associated with greater daytime dysfunction. Despite their small sample size, Kuo et al. [129] concluded with a similar, yet even stronger, relationship. One explanation might be that as chemotherapy progresses and patient distress peaks, the link between physical burden and daytime sleepiness/dysfunction becomes even more apparent. Indeed, in Kuo et al.'s study, patients were evaluated at mid-treatment, between CThC 3 and CThC4, which, as previously stated, are key time points

where sleep/wake impairment reaches a peak [119, 128]. Conversely, absence of cross-partner effects was noted in the current study. It can be postulated that, despite a hypothesised association of caregiver sleep/wake impairment to patient physical burden, there seems to be no direct link between the two concepts. One alternative explanation could be that whatever link might have existed between the two variables was blurred by the inclusion of both cohabiting and non-cohabiting dyads. Yet, preliminary analyses showed that no effect of cohabitation for the majority of sleep variables arose, whereas multilevel modelling analyses were adjusted to partial out this confounding. Therefore, unless patient symptoms literally disrupt caregiver sleep (e.g. constant and heavy patient coughing in cohabiting dyads), it can be hypothesised that patient physical symptom only mediates the path between caregiving burden and subsequent caregiver sleep deprivation, or between patient sleep disturbance and caregiver sleep quality. Such hypotheses warrant replication in future studies through adequate analytic techniques (see below). The only exception to the afore-mentioned findings pertains to a significant relationship between patient physical burden and caregiver perceived sleep quality: in dyads comprised of patients severely affected by chemotherapy-related symptoms, their caregivers perceived their own quality of sleep as poor. In the context of dementia, McCurry et al. [363] also reported that where patient physical functioning was poor and affected the caregiving situation, dyads were more likely to consist of concurrently poor sleepers.

The current study examined another yet unexplored territory by evaluating caregiving burden as a potential predictive factor of poor sleep in the patient-caregiver dyads [366]. With existing cross-sectional literature offering only ambiguous evidence [182, 519, 523], the emergence of consistent moderate-to-strong associations (r_{ES} ranging from .20 to .56) between subjective caregiving burden and the majority of caregiver sleep/wake parameters is an intriguing finding, especially since adjustment for potentially even stronger triggers such as psychological burden also took place. Similarly, two prospective studies among caregivers of memory-impaired individuals concluded with caregiving burden being one of the strongest predictors of sleep problems in the long run [274, 519]; however, in these studies caregivers' objective rather than subjective burden was considered, which was assessed at baseline only. Through repeatedly evaluating caregiving burden, the current study goes a step further by proposing that fluctuations in caregiving burden can be consistently related to analogous fluctuations in caregiver sleep initiation and maintenance, as well as daytime functioning, thus reinforcing the links between caregiving burden and sleep disruption (primarily) and deprivation (secondarily) [62]. Somewhat differently, significant cross-partner effects were limited to associations with patient perceived sleep quality, total sleep time, and daytime napping duration. Additional cross-partner effects only marginally fell short of sig-

nificance possibly due to sample size limitations. Overall, in dyads where caregivers were more burdened with deficits in their own health and disruption in their schedule, patients suffered additional negative impact from fluctuations in the caregivers' burden, and reported greater sleep/wake impairment. As with patient physical burden, the exploratory nature of this study dictates that these results are viewed with caution. Nevertheless, these analyses suggest that examining the effects of caregiving burden – mainly those contextual ones – offers increased understanding of its impact on dyads' sleep/wake patterns during the intense period of chemotherapy treatment, and therefore have important clinical implications.

Psychological/emotional distress has long been recognised as a contributing factor for sleep/wake impairment in people with cancer [1, 3, 533], their informal caregivers [182, 520, 524, 534], and patient-caregiver dyads [366]. Existing evidence suggests that anxiety and depressed mood are the strongest predictors of alterations in self-reported sleep/wake patterns of women receiving adjuvant treatment for breast cancer, with effect sizes ranging from .28 to .44 [7, 121, 123, 131, 136, 143, 144, 165], and from .36 to .52 [7, 8, 120, 121, 123, 125, 131, 136, 143-147, 165, 166], respectively. On the other hand, caregiver psychological burden – especially depressive mood – has been associated with poor sleep quality, decreased total sleep time and sleep efficiency, and increased daytime dysfunction irrespective of health care context [27, 28, 232, 237, 265, 266, 270, 274, 276, 285, 519, 521]. Hence, in the current study, the almost absolute absence of significant own effects of psychological burden on the dyad members' nocturnal sleep patterns stands as a striking finding, which renders relevant effects on sleep deprivation and/or disruption unclear [62]. A possible explanation, yet not the only one (see below), could be that, overall, dyads' psychological burden levels were only low-to-moderate, also following a downward trend from baseline to end of treatment, which, when coupled with low variability in responses, might have precluded the emergence of statistical significance in this small sample. Among the very few notable own effects, fluctuations in patients' mood throughout treatment did predict similar changes in their perceived sleep quality, whereas a trend for poorer habitual sleep efficiency in caregivers reporting more psychological burden was also recorded; both of these findings are in agreement with existing literature [8, 27, 120, 144, 166, 237]. Similarly, only a few inconsistent cross-partner effects relating to perceived sleep quality, habitual sleep efficiency, and WASO also emerged, which, however, warrant additional future research. Conversely, more consistent associations of psychological burden with daytime functioning were found for both dyad members, thus suggesting that, prior to and during chemotherapy treatment, psychologically burdened dyad members were more likely to report spending more time napping and greater dysfunction in the daytime. These results were complemented by a few additional bidirectional cross-partner effects, showing that, as psychological burden

peaked, dyad members' wake patterns were increasingly and mutually affected. Although a link between depressive mood and increased daytime dysfunction has been proposed in the literature [535], it has only been minimally investigated in previous dyadic studies with evidence being unclear [285, 366]; this fact renders the particular finding unique and calls for replication in future research.

Coping strategies are described as a person's cognitive or behavioural efforts to manage the demands of a situation that is appraised as stressful, such as breast cancer or treatment [536], and changes in response to these stressors have been proposed [537]. In that sense, maladaptive coping strategies can interfere with effective stress management and affect an individual's sleep. Whether maladaptive coping processes were associated with alterations in sleep/wake trajectories of patient-caregiver dyads was another novel concept that the current study aimed to investigate [366]. Existing literature is limited to a few cross-sectional studies of individual samples of women with breast cancer during primary treatment [110, 133, 538] or informal caregivers [238], which, nevertheless, have reported on preliminary findings suggestive of a link between increased use of negative coping strategies and poorer sleep/wake outcomes in either population group. In that sense, the fact that in the current study, more dysfunctional coping on the patients' part was associated with greater own sleep/wake impairment, further supports past sleep research [110, 133, 538], and also confirms that avoidance coping is predictive of poor psychological adjustment in patients with chronic illness [539]. The findings of this study however were unsupportive of a similar existing link in informal caregivers. In fact, the only significant association related to increases in use of maladaptive coping strategies predicting the perception of better, rather than worse, sleep quality. Maladaptive coping strategies might yield a protective effect, but only in the short term [540, 541]. Whether avoidance/denial, substance use, venting or behavioural disengagement practices were seen by caregivers as an alternative means to let some steam off and be distracted from worries during a highly demanding period that subsequently led to better sleep at night, can only be hypothesised for now and possibly explored in future research employing both quantitative and qualitative methodologies. Seen under the prism of Lee's model [62], maladaptive coping strategies in this dyad sample were linked to sleep fragmentation – but not restriction – for patients, whereas no such links became apparent for caregivers. What is more, despite the fact that cross-partner effects were kept to a minimum, the potential for interactions pertinent to sleep between dyad members due to maladaptive coping does exist. Interestingly, whereas own coping was practically unrelated to own sleep/wake trajectories, not only caregivers' sleep quality and daytime napping was affected by the patients' own ways of coping, but also, increased use of own negative coping adversely impacted on patients' sleep. Although the effects of dyadic coping on psychological

well-being have been discussed [542], no similar evidence exists in the relevant literature [366], thus urging for additional dedicated sleep research; the implications for clinicians are nonetheless very important.

The present study acknowledged the potential effects of various patient, caregiver and dyad demographic and clinical covariates on sleep, and appropriately controlled for these in explanatory models. Explicit investigation of each covariate goes beyond the purposes of this study. However, it can be noted that past history of sleep problems, presence of comorbid illnesses, poor performance status, and short relationship duration were the covariates most consistently related with sleep/wake impairment in the dyad members during chemotherapy. The current study is one of the few sleep studies in the context of cancer care [136, 244] where past sleep history was formally assessed as well as examined as a potential covariate in adjusted models. Six out of ten patients and four out of ten caregivers reported troubled sleep in the past; to a similar extent, participants also linked sleep problems to the diagnosis of breast cancer. Earlier, Gibbins et al. [244] reported comparable prevalence rates in patients (42%) with incurable advanced cancer and their family caregivers (38%). What is more, the presence of comorbid illnesses and lower physical functioning were also related to the dyads' sleep, thus confirming existing positive findings [144, 248, 521] and hypotheses [366]. Novel in this area, results on the effects of relationship duration and, less consistently, the effects of the type of dyadic relationship on the dyads' nocturnal sleep patterns, are particularly intriguing. Several efforts have been made to establish a link between reported or observed sleep/wake disturbances and relationship functioning or quality [350-352] and attachment behaviours [353-355] in healthy couples. Although evidence is mainly based on either cross-sectional dyadic studies [352, 353] or single-arm studies [350, 351, 354, 355], a positive unidirectional association has been reported. What can be proposed here is that, aside from the dyad's quality of relationship, the length and stability of the relationship itself can (both independently and in conjunction) exert protective effects on the dyad's sleep/wake patterns, even during intense/challenging periods such as the one of chemotherapy treatment. Patient-caregiver cohabitation and room sharing has received some attention in the context of dementia care [278, 363, 367, 368], but as yet findings are discrepant; thus, clarification in future studies is still pending. If such a relationship does exist, it seems to be more related to patients', rather than to caregivers', sleep/wake patterns [367]; this might suggest that sleep/wake impairment in informal caregivers possibly goes beyond the mere distinction that sleeping arrangements pose. Alternatively, whether cohabitation/room sharing actually plays a role in patients' sleep patterns might also be a matter of gender. In a sample of heterosexual couples without sleep disorders, Pankhurst and Horne [346] observed more movements in men than in women, with women reporting that their sleep was

affected by their partners' sleep more than did men. Men are also more often loud snorers [347], and the sound of snoring can be a major disturbing factor of the sleep of their bed/room-partner, who might report symptoms of insomnia, morning headache, daytime sleepiness and fatigue [348]. In any case, no associations between the dyad members' own sleep/wake patterns and caregiver gender, employment status, time since diagnosis/surgery, type of surgery, patient menopausal status, and physical activity were found, which are consistent with past ambiguous evidence for patients with breast cancer [7, 121, 123, 125-127, 131, 136, 137, 143, 144, 146-148] and informal caregivers [23, 27, 30, 234, 235, 237, 240, 246-252, 284, 521].

8.2. Study Strengths and Limitations

This study has a number of strengths. First, the current study employed a dyadic methodology, thus introducing a unique and novel way to examine sleep/wake disturbances in the context of cancer care, and advancing existing research in the field [242, 244]. Previous sleep research in cancer care has been characterised as predominantly individualistic [209, 366], an approach rather secluded and unable to reveal sleep-related processes and sources/triggers of sleep problems in patients and their carers who, due to cancer-related circumstances – but not exclusively because of them – live in a close relationship and are co-affected within and because of it. Conversely, the dyadic methodology utilised here acknowledges the potential for interrelations in the sleep of cancer care dyads, and allows for a simultaneous investigation of sleep/wake parameters of individuals, however, seen within the context of their unique relationship. Second, this sleep study employed a longitudinal, repeated measures design, along with the assessment of concurrent changes in sleep-impairing factors; this design has long been recommended in relevant literature as a highly sought-after way of prospectively exploring trajectories of sleep/wake parameters and establishing (direction of) relationships between sleep and sleep-impairing factors [3, 10, 49]. In conjunction with the aforementioned methodological approach, this study provides unique findings, whose application in clinical practice goes beyond individuals. As Rumble et al. [527] argue, such knowledge can be instrumental to the development of future sleep interventions for patients with breast cancer and their caregivers. Third, the selection of assessment points in the current study was informed by previous longitudinal research in women receiving neo-/adjuvant chemotherapy for breast cancer [119], therefore is in line with and further extends relevant literature. Yet, this study makes a significant addition in regard to our knowledge of

sleep/wake patterns/disturbances of caregivers of patients with cancer. Indeed, the need for systematic longitudinal research so that the previously documented disruption in caregivers' sleep/wake patterns is more consistently and thoroughly explored has been highlighted in previous key papers [3, 10, 534]. Knowledge derived from this study can usefully inform sleep interventions in cancer caregiver populations (see below). Fourth, careful and systematic procedures for the selection of sleep and behavioural measures were pursued in an attempt to increase methodological rigour, while at the same time preserving comparability with existing literature. In addition, measures used in this study adopted similar time frames in order to avoid the attenuation of relationships between sleep and predictor variables. Last, the current study utilised sophisticated multilevel modelling techniques to analyse data [376], an approach that, to the best of the researcher's knowledge, has only recently been employed in past sleep research with patients with breast cancer [146, 518, 527], but never used in previous sleep studies with informal caregivers or care dyads in the context of cancer care.

This study also has several limitations. From a statistical standpoint, a definite disadvantage of the current study is its small sample size, which may have reduced statistical power, compromised inferences, and affected generalisability to similar populations. With a sample size of 48 dyads, a post-hoc power analysis revealed a power ranging from < 50% (WASO) to 80% (GSQI scores) to detect small-to-medium effect sizes of non-independence (tau correlation coefficients ranging from .12 to .42) in patient and caregiver pre-treatment sleep/wake parameters [293]. Similarly, power to detect a significant difference between overall sleep/wake impairment of patients and caregivers ranged from 50% to > 80% (effect sizes ranging from d = .42 to 1.15) [293]. Therefore, caution is necessary when interpreting results of this exploratory study. This is especially true for findings pertinent to potential predictors of sleep/wake impairment in the dyads. Since *a priori*, no formal sample size estimation analysis was undertaken, it is sensible to hypothesise that power to detect significant relationships may have been low. Hence, current findings can only be viewed as preliminary and requiring replication in future studies. Of note, multiple statistical analyses with this small sample have elevated the statistical error Type I rate for the study overall. An effective way to deal with this problem is to reduce the level where statistical significance is assumed [513]. As this was an exploratory study, it was decided to keep α at the .05 level to include as many emergent relationships as possible. However, by testing effects within the MHLMs, the number of p values that were computed per dependent variable was kept to a minimum; to a certain extent, this method outbalanced the potential for type I errors. What is more, moderate attrition rates in this study created an unbalanced dataset. Attrition-related missing data were effectively managed during multilevel modelling analyses under the assumption of

MAR [508]. As it was shown, there was reliable evidence that the MAR assumption held and systematic bias did not interfere with the current study; nevertheless, Schafer and Graham [543] argue that, in general, there is no way to prospectively test whether MAR holds in a dataset, and that in most cases departures from MAR should be expected [543]. In any case, the fact that current findings converge with those of previous studies using self-report measures suggests that they are not spurious.

The decision to rely on subjective sleep measures for the collection of sleep data in the current study warrants commenting. As previously discussed, current recommendations for measuring sleep-wake patterns in people affected by cancer are to consider combining self-reported and objectively recorded sleep data [49]. In line with these guidelines, initial planning of this study did include the use of wrist actigraphs to complement data gathered through sleep questionnaires. To accommodate simultaneous use with twenty dyads participating at any time during the study, forty actigraphs were estimated as a necessary requirement for the purposes of this project. However, an unforeseen cut-back in the study's funding rendered purchase of these devices practically impossible, whereas restrictions in the PhD timeline prevented further funding from being sought. In view of these events, a decision was made to proceed with inclusion of self-report sleep measures only. Although a valid and reliable sleep measure was used, absence of objective evaluation to corroborate self-reports in itself constitutes a limitation of this study. In addition, due to their retrospective nature, self-reported sleep measures are subject to introducing recall bias [366], which, when combined with arguments posing that "patients are notoriously bad at estimating the duration of sleep and wakefulness, particularly when they have a problem with sleep" (p. 868) [244], may have affected measurement accuracy in the current study. An example could well be an inability to test trajectories in the dyads' changes in total sleep time: despite wide variation between individuals being present (**Figure 7-11**), within-individuals variability was limited, which may suggest that participants were not able to retrospectively report changes in their sleep duration on PSQI during the study, even if these actually took place. In an attempt to deal with the potential of recall bias, the time frame for recall in all sleep-related measures was reduced to the previous 15 days, which, it is believed that to a certain extent, reduced the magnitude of measurement inaccuracies. It can certainly be argued that relying on sleep diaries instead of sleep questionnaires could have diminished the magnitude of the aforementioned issues. Although there is some truth in this statement [544], as it will be argued further below, use of diaries/logs in sleep research is not always feasible or even advisable for several reasons; for instance, in the current study, prolonged use of sleep diaries could have possibly led to participants becoming overburdened and potentially increased attrition.

The absence of consistent associations between physical burden and sleep/wake patterns, as well as between psychological burden and sleep in this sample, was a somewhat unexpected finding, and inadequate statistical power in this study may have been a contributing factor that is readily acknowledgeable. Measurement issues, however, may have also played a role. Increased physical burden in women receiving chemotherapy for breast cancer may be the result of several individual physical symptoms such as pain, fatigue, nausea, and breathlessness among the most frequently cited in the relevant literature [90, 531, 545]. Critically, such symptoms may be experienced simultaneously [545-547]. Therefore, it was decided that for the purposes of this study, a cumulative index of physical burden (i.e. MSAS-PHYS) would offer a more comprehensive measure of a range of potentially concurrently manifested physical symptoms with sleep-disruptive properties. Unavoidably, this decision led to the inclusion of symptoms of differing individual magnitudes of prevalence/frequency, severity, distress and relationship to sleep, which might have blurred overall correlation to sleep/wake patterns. Presumably, relying on symptom-specific measures of selected physical symptoms (e.g. use of the Brief Pain Inventory [548] to test the relationship of pain severity to sleep latency) could have allowed for more consistent and/or larger in magnitude associations to be obtained. For reasons already explained (see Chapter 5), measurement of the dyads' psychological burden was conducted via the use of a global cumulative, yet non-specific, index (i.e. MSAS-PSYCH) to avoid increase in the participants' reporting burden. It can certainly be argued that psychological burden was not optimally measured in this study and that inclusion of anxiety- (e.g. State-Trait Anxiety Inventory [430]) and/or depression-dedicated (e.g. CES-Depression [431]) self-reported measures might have resulted in less unwanted variability/noise, greater specificity, and perhaps more and stronger associations with sleep/wake patterns.

Despite current limited evidence [265], it has been hypothesised that as patient needs increase, primary informal caregivers are expected to undertake several activities and provide intensive care, which allows only for minimal periods for rest and sleep [182]. Whereas in the current study caregiving burden was measured as disruption in schedule and impact on personal health status, this may have been more about how carers perceived their being affected by living closely with a woman receiving chemotherapy treatment. No specific assessment of objective burden was undertaken with regard to whether carers were actually involved in patients' care, for how long, and what the number and nature of caring activities might have been. In addition, as the current sample involved highly independent women with breast cancer, there is the possibility that caring activities might have been infrequent; nevertheless, subjective caregiving burden was far from negligible in this study.

Although assessments of type and duration of relationship were employed, dyads' relationship quality, either compromised or empowered during treatment for breast cancer [218, 549], was not measured in the current study. As a fundamental attachment behaviour [338], sleep may be regulated within and affected by close human relationships in the sense that the closer/better the relationship, the greater the odds of a good night's sleep, and vice versa [209, 338, 366]. It has been argued that caregivers who, regardless of their actual caregiving tasks, value their role as important to them and the patient they care for, might be more affectionate towards the patient, thus leading to patients feeling more secure in their relationship and sleeping better [209, 366]. Fluctuations in relationship quality may be predictive of changes in the sleep quality and quantity, as well as daytime dysfunction of patient-caregiver dyads and future longitudinal research is warranted.

Sleeping arrangements in the form of dyads sharing the same house/bedroom were assessed only at pre-treatment. With dyads exhibiting dissimilar changes in their sleep trajectories and sleep impairment of differing magnitude during and after treatment, the possibility cannot be ruled out that, once patient symptom severity increased and nocturnal disturbances manifested themselves, some of the dyads changed their sleeping arrangements as well. This may have led to patients and caregivers spending more (e.g. if children caring for mothers had to move into the patient's home) or less time together at night (e.g. if caregivers stopped sharing the same bedroom with the patient). Consequently, the extent to which such practices may have influenced inferences relating to comparisons between patient and caregiver changes in sleep patterns, as well as to the effects of sleeping arrangements themselves remains unknown. Along these lines, dysfunctional thoughts about sleep may constitute another potentially important predictive factor for disturbance [527]; hence, the fact that no such evaluation in this study was undertaken must be regarded as an additional limitation.

Demographic/clinical homogeneity of the sample population studied may limit the generalisability of the current findings in relation to a number of domains. The patient sample in this study consisted of female individuals only. Although breast cancer incidence in men is extremely low (1% of all breast cancer cases), treatment is similar to that for women [550]. Whether sleep/wake patterns in this very small population during chemotherapy treatment bare any resemblance to those of women reported here and elsewhere [119] is unknown. The same is true for this caregiver sample, which, in its majority (90%), consisted of male caregivers. Past research has mainly focused on examining sleep patterns of predominantly female caregiver populations [182]; therefore, discrepancies are to be expected. Indeed, it has been argued that with caregiver samples included in previous studies involving women over a mean age of 55, reports of sleep disturbance incidence may be associated with menopausal

symptoms, hyperarousability or past sleep problems, rather than just the caregiving experience itself or patient sleep patterns [250]. Perhaps the inclusion of predominantly or exclusively male caregivers can result in different associations [209]. In addition, given that all participants in the current study were white Caucasian, and almost all Scottish, findings may not apply to patient-caregiver dyads of different racial/ethnic background. What is more, with the majority of dyads consisting of spouses/long-term partners, current findings seem applicable to such dyad populations only. Along these lines, generalisability to other cancer populations and/or other cancer treatments should be considered similarly low.

Data collection in the current study spanned over a 16-week period, where patients and their caregivers provided information at four clinically important time points throughout chemotherapy treatment. Whereas this prospective design facilitated the investigation of outcomes on different occasions, it still constitutes only a snapshot of the whole experience of patient-caregiver dyads dealing with a diagnosis of early stage breast cancer. It should be thus acknowledged that since no assessments took place at the period following diagnosis and before and after primary surgery, it still remains unknown how such processes may have impacted on the dyads' sleep/wake processes and adjustment mechanisms before they entered this study. In the past, anxiety and intrusive thoughts about surgery were linked to diminished sleep duration the night prior to primary breast surgery [551]. Also, patients with higher preoperative levels of sleep disturbance have been identified as being at increased risk for persistent breast pain following breast cancer surgery [552], and which can further interfere with own sleep architecture, and increase caregiving demands. The same is true for the period after chemotherapy, given the absence of long-term assessment as patients and dyads may go through radiation or hormone therapy, or into survivorship, in more general terms. Berger et al. [122, 131] investigated the effects of a behavioural therapy intervention with a similar sample of patients with breast cancer up to one year after administration of the first CThC. Global sleep quality considerably improved in both the intervention and control groups; baseline higher fatigue, higher anxiety and better educational background were still associated with poorer sleep at one year [131].

Of note, whereas patients and carers were asked to complete study questionnaires independently from each other, it is unclear whether this actually happened in all of the cases. Therefore, the possibility cannot be ruled out that some dyads discussed their responses, and this might have affected the way they responded in subsequent assessment points. In addition, carers were not excluded from the study if they were providing additional care to other family members. It can be hypothesised that in those carers who were parents of young children, sleep impairments might have been magnified by their increased parenting responsibil-

ities as well. Moreover, in the current study, no standardised diagnostic interviews to determine if patients met eligibility criteria in terms of sleep and psychiatric disorders were employed [553, 554]. Local collaborators – all of them clinicians with over 15 years of clinical/research experience – were instructed to exclude patients with a prior history of such medical issues, based on careful examination of medical case notes and confirmation by the patient herself; however, the potential that women manifesting such symptoms but never being formally diagnosed cannot be confidently ruled out. In addition, exclusion of informal caregivers for the same reasons was based on self-reports only, therefore reliability of this caregiver sample's characterisation can be questioned.

Finally, the use of demographic/clinical data from patients who were approached but refused to take part in the study warrants comment. Although only limited non-identifiable data were collected under the clinical collaborators' supervision (i.e. age, but not date of birth; breast cancer stage; type of surgery), regarded as confidential and stored anonymously and securely based on the principles stated in Chapter 6, no formal ethics approval was sought, which in itself constitutes a limitation of this study. It is, however, acknowledged that for such procedures specific Caldicott Guardian Approval is required following ethical approval of a research project to improve the way the NHS handles and protects patient information [555].

8.3. Implications for Future Research

Future (dyadic) sleep research among diverse cancer populations could be enhanced by considering inclusion of (a) longitudinal study designs spanning over health/treatment transition phases; (b) repeated measures of sleep/wake parameters, ideally continuous or daily; (c) combinations of objective and self-reported sleep measures [49, 556], which (d) are validated and realistically selected; and (e) careful consideration of measures of sleep-impairing factors and/or health outcomes. These should be complemented by (a) robust diagnostic/eligibility methods; (b) sophisticated data analysis techniques; (c) systematic procedures to minimise attrition; and (d) novel methods to test already established interventions to manage sleep/wake problems in patients with cancer and their carers [366]. Thus, it is to be expected that the goals of future dyadic sleep research – also reflected on the current study – are met (**Table 8.1**) [209, 366].

First and foremost, replication of the current findings in future research should be regarded as an absolute priority. Future studies will be required to re-examine associations between

patients' and caregivers' sleep, confirm similarities (e.g. perceived sleep quality, sleep latency) and dissimilarities (e.g. daytime napping duration, daily disturbance), and resolve ambiguity (e.g. total sleep time, WASO) with regard to dyads' sleep/wake trajectories, as well as re-investigate the magnitude of dyads' sleep/wake impairment during treatment for breast cancer in the long-run. How are these associations/patterns affected by differences in the type/stage of cancer, phase of illness/treatment, or the caregiver's or dyad's circumstances? Perhaps with more rigorous and comprehensive measurement of sleep/wake patterns, investigation of whether changes in sleep/wake parameters of women with breast cancer can predict changes in those of caregivers, and vice versa, could shed more light to possible interdependencies. What may be the effects of additional sleep/wake parameters of clinical interest such as daytime sleepiness, feelings of restfulness upon awakening in the morning, restless legs, or early awakenings? The presence of only unilateral cross-partner effects, such as the effects of caregiver poor sleep hygiene on women's sleep maintenance, but not vice versa, also deserves additional investigation. Is this a population-specific effect? Women are known to be susceptible to sleep loss [557, 558], especially distressed women receiving chemotherapy for breast cancer, whereas caregivers (in their majority, males) might remain unaffected in this regard. Sleep research in the context of prostate cancer, where patients are men but caregivers are mainly women, could possibly allow examination of whether this cross-partner effect takes place in a reverse order. Similarly, the absence of cross-partner effects with regard to sleep initiation (i.e. sleep latency) that was apparent in the current study is puzzling and requires further exploration.

Table 8.1. Summary of Important Associations Yet to Be Explored in the Sleep/wake Patterns of Care Recipient-Caregiver Dyads [366]

- Longitudinal effects of the dyad's psychological and/or physical distress on the dyad's sleep/wake patterns.
- Longitudinal effects of historical relationship quality on the dyad's sleep quality.
- Longitudinal effects of sleep hygiene practices and/or past history of poor sleep on the dyad's sleep quality.
- Longitudinal effects of the dyad's poor sleep on the dyad's health-related quality of life and functioning.
- Longitudinal measurement of daytime/night-time blood pressure and diurnal cortisol rhythms to understand the effects of sleep deficits on the dyads physical health.
- Salient neurobiological mechanisms or pathways that mediate development of poor sleep in the dyads.
- Differences in sleep/wake patterns/problems between dyads of female care recipients/male caregivers versus dyads of male care recipients/female caregivers.

To date, and for methodological/practical reasons that are perfectly understandable, sleep research in patients with breast cancer has been limited to longitudinal investigation of snapshots only of the illness/treatment experience [119]. Admittedly, considerable knowledge has been gained with regard to sleep/wake trajectories of women during breast surgery [528, 551, 552, 559], chemotherapy [7, 8, 104, 120, 121, 123, 125-129, 133, 136, 137, 143-148, 165, 166, 172], radiotherapy [110, 153, 560-563], or survivorship [33, 100, 527, 564-572]. However, and in conjunction with a striking absence of similar longitudinal data for informal cancer caregivers, there is still a pressing need for long-term sleep studies that follow individuals/dyads through major health/treatment transitions, and bring together different phases to provide a unified perspective of the breast cancer experience. One might question feasibility and acceptability of such studies especially at long periods, where patients and caregivers may be considerably burdened. However, previous research has confirmed feasibility with acceptable attrition rates [131, 528, 573], whereas alternative ways to paper-and-pencil data collection may improve participant acceptability and adherence/retention to the study (see below).

The combined use of objective and self-reported sleep measures has been advocated as necessary for the comprehensive investigation of sleep/wake impairments [49]. Yet, inherent conceptual differences have rendered comparison of objective and subjective sleep data frustratingly difficult in studies, where both the aforementioned sleep assessment methods were employed [49, 574-576]. These difficulties suggest that data of a different nature be treated in a way that acknowledges inherent differences, accounts for disadvantages, and co-visualises rather than synthesises deriving information. With their ability to record continuously, objective sleep measures can provide more abundant data on several sleep variables, including sleep latency, sleep duration, nocturnal awakenings, WASO, and circadian rhythms than subjective measures do [577]. Polysomnography remains the ‘gold standard’ for the detection of specific sleep and wake states [49, 364, 578], especially with the latest advances of ambulatory devices [49]. Apart from its obvious advantage of being less expensive than its laboratory counterpart, in-home polysomnography has also facilitated recording of sleep in the individual’s habitual sleeping environment [579, 580], even for patients with advanced disease [581]. In addition, actigraphy has been implemented in various studies [120, 121, 126, 127, 131, 159, 577, 582] as a relatively inexpensive, ambulatory method of objective sleep assessment. Actigraphy has been shown to be particularly good in the evaluation of circadian rhythm disorders too [577], and can be useful in examining dyads’ habitual sleep patterns in their naturalistic environments for long periods of time [338]. On the other hand, self-reported research instruments measure perceptions [49]; hence, they can provide data on the more qualitative features of sleep such as sleep quality, feelings of rest-

fulness upon arising, or daytime sleepiness and dysfunction [583]. Psychometrically sufficient instruments include the Insomnia Severity Index, the Pittsburgh Sleep Quality Index, the Sleep Assessment Questionnaire, and the Athens Insomnia Scale [3, 399, 402, 403, 584] (see **Table 16-A2**), whereas the Pittsburgh Sleep Diary can allow prospective monitoring of sleep parameters in longitudinal studies [584]. In addition, subjective sleep data may correlate more strongly with self-reports of health-related outcomes, thus allowing for intra- and inter-personal relationships to be more thoroughly examined. In any case, specific research hypotheses rather than a priori assumptions of a technique's superiority over another should guide selection of the methods to assess sleep in care recipient-caregiver dyads [338].

Although it is true that having more sleep interaction data over time would increase the power for looking at care recipient-caregiver sleep relationships (and correlates), some considerable challenges in collecting such data should nevertheless be acknowledged. For instance, given their retrospective nature, self-reported sleep measures are prone to introducing recall bias, which, when combined with their being influenced by the respondent's situational mood, can affect accurate interpretation of a person's – let alone a dyad's – sleep patterns [49]. In addition, not all self-report sleep measures have been extensively tested in all patient/caregiver populations, while even fewer are suitable for use as outcome measures given an absence of data to prove their ability/sensitivity to detect significant/meaningful changes in sleep patterns. Similar comments could be made about daily sleep logs/diaries. Sleep diaries have been regarded as the 'gold standard' for subjective sleep assessments in the clinical practice [544]; however, they are not always standardised and they are much harder to keep for prolonged periods than is generally acknowledged in the literature. New attempts have been made to develop and validate core sleep questionnaires based on cutting-edge validation techniques [585, 586], and standardise prospective sleep self-monitoring through development of the Consensus Sleep Diary [544]; yet, additional research is required to confirm their psychometric properties. Objective measurement of sleep can be similarly challenging. While wrist actigraphy is considered a relatively easy to implement and adhere to method, some patients and/or caregivers cannot tolerate wearing the devices for prolonged periods of time, hence the risk for missing data increases [364]. With in-home polysomnography, participant burden can increase even more [364]. Equipment failures are not insignificant either. Furthermore, simple collection of more data might not completely solve the problem since there are no gold standards for which actigraph type to use, or which data collection or scoring protocols to follow [577]. Given that actigraphy works by detecting movement, it may be unable to differentiate between a patient who is asleep and a patient who is awake but not moving [587]. Therefore, it is likely to overestimate levels of sleep efficiency and total sleep time [579, 583, 587], and has a low ability to pick up wakefulness in sleep-disordered indi-

viduals [587], possibly leading to an overestimation of daily napping as previously evidenced in a study of patients with advance cancer and their family caregivers [244]. When sleep interaction data are considered, the aforementioned issues can be of particular importance so as to enhance accuracy in sleep measurement, promote adherence to sleep assessment methods, and prevent unnecessary burden to the dyad. Such issues also pose several implications for care dyads in the context of advanced cancer, possibly elder ones, and/or stressed by requirements of active anti-cancer treatment and everyday living.

The investigation of correlates of co-occurring sleep problems in care recipient-caregiver dyads is both intriguing and challenging. In a recent review of the literature, this area emerged as a rather under-studied one [366]. Yet, current available findings can be usefully employed to form a model of complex interrelationships between sleep and sleep-correlates. This model suggests that a dyad's sleep is a dynamic field of interference of several compounding and interacting variables, which affect and are affected by sleep so that an infinite loop of chronic sleep loss and dysfunction can be established as the dyad moves in time and across health transitions. Whilst the mediating effects of co-habitation and bedroom-sharing remain to be explicitly established, a dyad's sleep quality seems to be largely compromised by how parties are co-affected once sleep disturbances are manifested in one or both of them. Hence, frequency and severity of one's sleep deficits can be potentially strong correlates of the other's, possibly influenced by the effects of a history of poor sleep or of an inadequate sleep hygiene. In dyads then where physical functioning and/or psychological well-being are also compromised, sleep/wake patterns can be further impacted. Disease severity and chronicity, aging, caregiver burden, dysfunctional coping strategies, and unavailability of external support can pave the way towards this direction by interfering with sleep either directly or through their physical and psychological impact. Albeit unexplored in this context, historical relationship quality, as influenced by the degree of attachment, the dyad's age, and the impact of a demanding health situation, can possibly affect (and be affected by) the dyad's sleep. A number of psychological, behavioural, and neurobiological mechanisms have been also suggested to mediate this relationship in married couples [338], which may be similar for dyads of care recipients and caregiving spouses, but warrant further exploration.

However comprehensive the quest for identification of potential sleep-affecting factors may be, it is true that additional triggers may exist. Arousability, or hyperarousal, and decreased homeostatic sleep drive are among the predisposing factors most often hypothesised for insomnia [60, 99]. Combined with a pre-existing homeostatically altered regulation of sleep, these manifestations might render individuals susceptible to disordered sleep during cancer

experience [99]. Dupont et al. [156] found that although intrusive thoughts and hyperarousal predicted worse sleep adequacy post-completion of breast cancer treatment, the effects vanished 12 months later; thus further research is warranted to confirm the magnitude of such associations. Moreover, conditions perpetuating sleep problems may be maladaptive or dysfunctional beliefs and wrong attitudes towards sleep and insomnia that an individual develops at the onset of sleep disorders and to which likes to refer later on [409]. In patients with cancer, such dysfunctional thoughts may include concerns of relapse or recurrence of cancer (or pain) due to lack of sleep, or beliefs that malfunctioning sleep will prevent treatment or even control of the disease [155, 409]. The positive results of cognitive-behavioural therapy interventions for insomnia in women with non-metastatic breast cancer [122, 131, 161, 588-590] suggest that this population is prone to developing such dysfunctional attitudes. Quite reasonably, similar dysfunctional thoughts can adversely impact caregivers' sleep too.

Reversely, the effects of a dyad's nocturnal sleep loss on daytime wakefulness/fatigue, functional ability and work presenteeism/productivity, especially when this becomes a constant situation, are not insignificant, and may be selected as outcomes for evaluation in other research. In the long run, perpetuated sleep deprivation can lead to deficits in care dyads' quality of relationship and subsequently quality of life. In long-term survivors of breast cancer complaining of insomnia, poorer sleep quality the previous day predicted increased pain, fatigue and hot flashes the next day, and less efficient sleep was related to increased fatigue and hot flashes, and lower levels of positive mood the next day [527]. Quality of life can also be put at risk [518]. During treatment for breast cancer, symptoms of insomnia predict greater cognitive impairments [591, 592], which may further impact on daily functioning and return to work [593]. A longitudinal study among caregivers of people with advanced cancer also revealed that prospective sleep disturbance had analogous negative effects on their functional status and quality of life [28]. Links to lowered immune function have also been proposed [594, 595]. It is obviously intriguing to investigate the unilateral or bilateral effects of prolonged sleep loss in patient-caregiver dyads on important health outcomes, in an attempt to better understand inter-linked processes, identify important endpoints and primary outcomes, and plan sleep promoting interventions that target the care dyad. This quest needs to include not only care dyads during survivorship from (breast) cancer, whose health outcomes might be compromised by prolonged sleep loss [244], but also care dyads during health transitions and/or during the patient's active cancer treatment when stress peaks [242] and situational sleep deprivation might interfere with a host of dyad members' health outcomes.

As argued above, to date, data regarding correlates of co-occurring sleep problems in care-recipient/caregiver dyads remain scarce and at times discrepant. The same is true when the reverse of this relationship is investigated: the question about what health outcome measures would be most appropriate is still pending. Of relevance to the latter, wide variability (or otherwise, inconsistency) in the use of measures of sleep-correlates has been reported in the literature pertinent to dyadic sleep research [366]. For instance, Kotronoulas et al. [366] found that five different instruments were used across the studies reviewed to assess for the sleep-impairing effects of depression. Conversely, other constructs were only partially (e.g., burden, coping) or not at all (e.g., attachment) investigated [366]. This lack of standardisation in the measurement of key constructs can be seen as a confounding factor that hinders comparability of relevant outcomes. On a closely related matter, psychometric insufficiency of some instruments may result in compromised findings. Clearly, there is a need for concrete evidence- and research-based guidelines for the use of psychosocial assessment measures in this context. To this end, the Patient-Reported Outcomes Measurement Information System (PROMIS) Network has been funded to establish a publicly available resource of standardised, accurate and efficient outcome measures for clinical research [596]. A wealth of comprehensive literature reviews also exists that can assist researchers to select the most sound measures to assess outcomes related to or affected by sleep/wake deficits in patient-caregiver dyads living with cancer [435, 597-604]. Importantly, researchers will need to rely on instruments with proven psychometric properties, preferably those for which responsiveness (otherwise, sensitivity to change over-time) has also been established. Examination of measures' psychometric properties should lead to a rational approach to selecting those appropriate as well as promote consistency in their use. This common language will allow for comparable, reproducible and wide in scope data to be collected.

Attrition rates reported in the current study should also be taken into consideration. The mail-based data collection system utilised served as a basic means to send and receive questionnaires in paper format. This system can be useful for low-budget and/or cross-sectional studies, but it cannot efficiently manage data collection that occurs in multiple waves. For instance, it is unclear whether some missing data were due to failures to the mail system alone, or because participants simply forgot to return completed questionnaires. To enhance participant adherence and retention in similar sleep studies, implementation of more effective data collection systems is required, complemented by additional methods such as personal telephone contact and/or home visits. The use of technology can be a particularly useful adjunct to that end. Rumble et al. [527] used an automated telephone-based system for the daily collection of sleep log data from women with breast cancer. Moreover, electronic systems such as handheld computers, mobile phones or web-based platforms could prove

useful to automatically generate alerts/reminders for participants at each assessment point, and also to securely store self-reported and objectively recorded sleep data. With current efforts to produce and validate electronic versions of already existing paper-and-pencil sleep [585] and health outcome questionnaires [605], data collection and retention in future sleep studies are expected to improve considerably [606].

Whilst demographic/clinical diversity of the study samples is to be sought to increase representativeness and, consequently, generalisability of findings, bias introduced by including patients/caregivers with undiagnosed and/or uncontrolled sleep/wake and/or psychiatric disorders should be prevented. Standardised screening procedures, including structured diagnostic interviews for sleep/wake (e.g. the Duke Structured Interview for Sleep Disorders [607]) and current mood, anxiety, alcohol or substance abuse, or psychotic disorders (e.g. the Structured Clinical Interview for DSM-IV Axis I Disorders [608]), need always be considered in sleep research. In this way, sleep/wake impairment can be attributed to cancer experience alone. What is more, cognitive functioning evaluation of potential participants (possibly via the High Sensitivity Cognitive Screen [609]) can enhance self-report sleep data accuracy in the long run by excluding individuals with cognitive deficits. This is of particular importance for patients with cancer receiving chemotherapy treatment because recent evidence suggests cognitive disruption (referred to as ‘chemobrain’) associated with systemic administration of specific anti-cancer agents [610].

Longitudinal sleep studies that make use of predictive models of statistical associations are highly advisable [49]. Analysis of dyadic data on sleep/wake patterns, sleep-impairing covariates, and/or related health outcomes with sophisticated, state-of-the-art statistical models such as the multivariate two-level model for matched pairs’ data [371], or the Actor-Partner Interdependence Model [293], could permit adequate exploration of inter-dyad effects. Alternative types of dyadic MLM analyses for binary and/or ordinal data could further increase the scope of such investigations. Structural equation modelling (SEM) can also be used in dyadic research as an alternative data analytic strategy [293]. Albeit more complicated, SEM has been advocated as a particularly useful technique when dyads are distinguishable (e.g. dyads of patients and caregivers) [293]. Moreover, future use of latent class growth analysis [611] could facilitate identification of subgroups of dyads (e.g. both poor sleepers versus both good sleepers versus one poor sleeper) and allow a comparative investigation of over-time changes in sleep/wake patterns. Moreover, testing mediation in multilevel modelling could well answer some of the questions generated in this study: “is there a mediating effect of patient symptom burden in the relationship between caregiver burden and caregiver sleep disruption/restriction?” and “is there a mediating effect of coping strategies in the relation-

ship between depression/anxiety and own sleep problems?" According to the method proposed by Kenny et al. [293], in separate MLM analyses, effects of predictor variables on outcome variables, and of predictor variables on mediators are estimated first. Next, the effects of predictor and mediator variables are simultaneously estimated. Mediation is established when in this step mediators are significantly related with outcomes, whereas at the same time predictors are no longer associated with a given outcome variable [293]. Last but not least, mixed-methods studies integrating quantitative and qualitative data [612] could be particularly useful in the clarification of sleep behaviours and beliefs, as well as underlying mechanisms in the development of dyadic sleep disturbances. Such information could well inform future observational and intervention studies, also pointing at previously unearthed issues that could lead to better management in clinical practice.

The potential to move sleep research beyond the care dyad and consider wider 'family' networks is an intriguing one. According to the family systems perspective [613], an individual's behaviour cannot be investigated "apart from the interpersonal behavioural systems in which he or she is embedded" (p. 224) [293]. Sleep research in triads or wider groups including the patient, primary (e.g. spouse/partner) and secondary caregivers (e.g. friends), as well as additional care recipients (e.g. children or parents) is now feasible. One of the most comprehensive methods to investigate patterns and dynamics of such groups is the Social Relations Model (SRM) [293]. Based on the principles of SEM for data analysis, the SRM can be used to evaluate change over time and relationships at multiple levels of analysis, and measure reciprocity in the triad and group members [614].

Finally, although RCTs of hypnotic medication use for patients with cancer is "noticeably absent" [615], a considerable amount of work has been conducted since 2000 with regard to the efficacy of non-pharmacologic interventions for sleep/wake impairment in this population [616, 617]. Of note, to date, an assortment of interventions based on exercise or education, but mainly on CAM therapies and cognitive-behavioural therapy (CBT), have been tested in RCTs predominantly with women with breast cancer [616]. Conversely, only two similar intervention approaches have been reported for informal caregivers of people with cancer [29, 618]. Even worse, the absence of interventions aimed at helping both the patient and the carer is striking [615, 616]. However, results of the current and previous studies [242, 244, 363, 367, 525] make explicit the need for future non-pharmacologic intervention studies that go beyond the individual, thus attempting to document sleep-promoting effects when interventions are jointly provided to care dyads [366, 616]. Designing a dyadic sleep intervention study is an intriguing and challenging task, which requires careful selection of the intervention component itself, as well as of the mode, dose and duration of delivery. Cur-

rent findings favour a behavioural therapy intervention (stimulus control, sleep restriction, relaxation and sleep hygiene) augmented by education on coping strategies/stress reduction/caregiver task planning (BTE) for patient-caregiver dyads in the context of adjuvant chemotherapy for breast cancer. Face-to-face delivery of this BTE intervention over at least 10-12 weeks (2 weeks per chemotherapy cycle) and with a weekly dose of at least 5 hours could be crucial first steps [616]. Importantly, such an intervention should not target dyads of poor sleepers only; the ability to show no deterioration in the sleep/wake patterns of dyads of good sleepers during treatment is equally important. Hence, a three-group pilot RCT (dyadic BTE intervention versus individualistic BTE intervention versus standard care) can be designed to document the added value of targeting dyads instead of individuals in order to improve sleep/wake impairment and associated health deficits.

8.4. Implications for Clinical Practice

Implications for clinical practice arising from this study are also numerous. With latest approaches to support patients and caregivers urging for early identification of and ongoing assessment for sleep disturbance [3, 49, 364], the finding that at least 25% to 48% of care dyads may at the same time meet criteria for sleep/wake impairment throughout chemotherapy treatment for early stage breast cancer clearly calls for a proactive management of sleep complaints in this population. Together with similar percentages of dyads with one poor sleeper, this renders the quest to simultaneously manage sleep/wake impairment in dyads of patients and caregivers even more compelling. One important message for clinicians is that even in dyads of one poor sleeper, good sleepers may represent a source of disturbance for the member prone to sleep deprivation, additional to potential own sleep-impairing factors. Even if this is not the case, dyads of both poor sleepers, particularly those closely interacting, may be at risk for ‘sleep distress’ when diminished sleep duration, multiple nocturnal awakenings, wakefulness after sleep onset, or daytime sleepiness co-occur.

With pressing requirements for improved psychosocial cancer care [184, 619-621], healthcare teams are now expected to view the patient-caregiver dyad as the unit of care [184] and provide support that meets concurrent and interdependent needs, and promotes the combined well-being of the dyad. With sleep/wake assessments in clinical practice still being infrequent and/or inadequate [622], engagement of health professionals is a crucial first step to implement dyadic sleep assessments. Communication of the findings of studies

as the present ones in open workshops and seminars, as well as inclusion health professionals in clinical educational programmes and research projects could well enhance their set of skills and the actual delivery of such assessments. Evaluation of sleep from a dyadic perspective also requires that clinicians engage in a systematic and ongoing investigation that goes beyond the individual: data are simultaneously taken into account, synthesised and contrasted to establish a dyad's levels of sleep quality. These will need to be complemented by additional information regarding past sleep problems, present sleeping arrangements, sleep hygiene behaviours, and current use of sleep aids that can help clinicians identify potentially vulnerable dyads for sleep problems. Incorporation of screening tools for organised sleep assessments in routine clinical practice is thus recommended. Screening tools for the detection of sleep-wake disturbances, such as the Insomnia Severity Index, the Clinical Sleep Assessment for Adults, the Medical Outcomes Study Sleep Scale, and the Epworth Sleepiness Scale, are recommended for use in clinical practice [49, 364, 402, 584].

Once problems are suspected and/or complaints are raised, evaluation of the onset, duration and severity of sleep deficits, as well as daytime dysfunction can reveal potentially evolving, co-occurring and/or interrelated problems. During assessment sessions clinicians need to explore in-depth the possibility of interactions that lead to sleep disturbance in the dyads by incorporating targeted questions such as "Would you say that your sleep is being influenced by that of your family member's/by symptoms or habits of your family member? If yes, in what way?" This is a key question in dyadic sleep assessment that prompts dyad members to consider another potential source of sleep disruption. Current research suggests that clinical assessment of cross-partner effects should not rely on patients'/caregivers' spontaneous reports only. Indeed, findings of this and previous studies [237, 244, 521] reveal that, when asked in general terms about potential sleep-impairing factors, only fewer than three out of ten patients/carers spontaneously admitted to have been disturbed by the other dyad member. Importantly, whether this assessment should be introduced to dyad members jointly (to allow discussion) or separately (to prevent conflict) is an issue that needs to be tailored to specific dyads. Nevertheless, a plan of practical suggestions to reduce disturbing nocturnal interactions of cohabiting dyads can be usefully devised, including use of twin beds or separate rooms for sleep, separation of sleeping quarters, the use of alarms, readjustment of the patient's caregiving routines, and synchronisation of positive sleep hygiene behaviours [368]. Such actions can prove instrumental in addressing the predisposing and perpetuating cross-partner effects of sleep hygiene, as well as the precipitating and perpetuating cross-partner effects of nocturnal disturbance, and patient physical and caregiver burden that the current study demonstrated during the chemotherapy period.

Moving beyond the dilemma of dyad co-habitation or not, clinicians are faced with the challenge to identify and treat triggers for sleep/wake impairment before treating sleep problems themselves. To a certain extent, this indirect approach may be enough to effectively deal with sleep/wake problems in patient-caregiver dyads in the cancer care context. Optimisations in patient symptom control and caregiver health deficits management can prove beneficial [364], especially when the shared needs of the dyads are taken into consideration. Women with breast cancer can benefit from the early assessment and management of cancer/chemotherapy-related physical symptoms such as pain, nausea/vomiting, loss of energy, mucositis, and hot flashes that can interfere with own sleep patterns. Nowadays, a wide range of effective pharmacologic and non-pharmacologic approaches to the management of chemotherapy toxicity are available for use in clinical practice [623-628]. Timely health screening for informal caregivers is equally important as it can prevent increase in burden and therefore alterations in sleep architecture [182]. Clinicians could usefully implement formal assessments for caregivers, including identification of pre-existing comorbidities; deterioration in symptomatology associated with known illnesses; confirmation of adherence to/efficacy of current treatment plan; and exploration of new symptoms, the onset of which may be associated with caregiving responsibilities. Moreover, psychosocial adjustment of couples/dyads to breast cancer and adjuvant treatment may be instrumental to the prevention of sleep deficits. Clinicians will need to plan comprehensive education assessments and offer tailored information to women and their carers. Results of the current study suggest that offering dyads more information about the prognosis of illness and clarifying what it is to be expected during chemotherapy could lead to alleviation of distress and fear, which in turn could help women to fall asleep more easily and have better quality sleep, and to carers enjoying less disrupted/restricted sleep during the night. In addition, dyadic evaluation of psychological well-being and coping throughout chemotherapy treatment could well identify dyad members/dyads in distress or susceptible to distress. Health professionals will also need to evaluate the dyad's support environment, and advise on the benefits for caregivers of carefully planning their everyday tasks to minimise disturbance, and of having a support person to share caregiving responsibilities with, whether this person is a family member or a hired attendant. The availability of respite care services should also be explored as it can lead to improvements in sleep quality of both the care recipient and their informal care provider [367]. Referrals to specialist health services could be a useful adjunct for dyads of poor sleepers, where relationship quality is compromised and complicated by dysfunctional coping and psychological distress [338, 339].

The pharmacologic treatment of sleep deficits in patient-caregiver dyads requires careful consideration of a number of issues. To begin with, necessity of pharmacotherapy should

always be confirmed. In the context of breast cancer treatment where sleep loss may be only temporal and restoration to normal may be achieved as dyads enter the survivorship phase, the gain from using hypnotic medications may be outbalanced by potential adverse effects. However, in cases where a history of past sleep problems is present and/or insomnia symptoms manifest early and persist over consecutive weeks, pharmacologic treatment may be advisable, particularly in dyads sharing the same bed/room and especially if all other indirect methods have failed. Yet, patients and caregivers may be reluctant to make use of pharmacological agents to help them sleep even if sleep deprivation is constant and/or causes considerable distress [27, 136, 137, 521]. This reluctance may be due to either avoidance ("I am already taking so many medications; I believe I can manage without another one") or fear of adverse effects ("I may be overly sleepy in the morning and cannot attend to the patients' needs"). Such concerns may be legitimate. In the context of cancer care/treatment, there is considerable uncertainty concerning the efficacy but mainly the safety of pharmacologic sleep agents [622, 629]. Indeed, to date, no randomised controlled trials of hypnotic therapy for sleep disturbance in patients with cancer exist [615, 622, 629]. Hence, valid concerns have been raised regarding the possibility that hypnotic agents might be hazardous for patients receiving systemic treatment due possibly to interference with the metabolism of chemotherapy agents. For instance, a melatonin receptor agonist, ramelteon, may be used for sleep-onset problems [630]; however, its pharmacokinetics in chemotherapy-treated individuals remain unknown. Another issue might be that pharmacologic agents (especially if used without proper consultation) may be accompanied by serious adverse effects that can do more harm than good in situational (rather than true) poor sleepers such as the majority of patients with cancer or their caregivers; indeed, hypersomnolence is a documented adverse effect of most sleep agents [4]. Even in the cases of sleep agents where half-life is short (e.g. zaleplon), thus suggesting less sustained hypnotic effects [631], daytime disruption may not be insignificant. The same is true for over the counter medications and supplements to treat insomnia symptoms, especially those including antihistamines as their major ingredients. In addition, variability in efficacy (e.g. melatonin) and risk for severe hepatotoxicity (e.g. Kava Kava) have been reported, which have led to these agents being regarded as not recommended for patients receiving chemotherapy [3, 632] and/or cautiously used depending on individual characteristics. Current basic principles call for the use of hypnotics in conjunction with non-pharmacologic interventions [3, 49, 622, 629]; consideration of the overall medical situation with particular focus on comorbid conditions that may influence the choice of agent; initiation with a low dose and titration; avoidance of long-term administration of benzodiazepines; consideration of past abuse history; and the initiation of a tapering schedule to prevent withdrawal insomnia when stopping the agent [632].

Consideration of efficacious non-pharmacologic sleep interventions for patients with cancer and informal caregivers as complementary or alternatives to the pharmacological treatment of sleep/wake problems is paramount. In the past two decades, over 20 RCTs have been published reporting on the effectiveness of non-pharmacologic interventions for women with breast cancer at various phases during the illness trajectory [49, 616]. CBT for insomnia symptoms has been the most widely implemented approach in this patient population; however, additional types have been investigated including exercise interventions, a wide range of complementary/alternative therapy (CAM) interventions, and education/information interventions [3, 49, 616, 629]. Overall, positive outcomes have been associated with CBT, but evidence regarding other types of non-pharmacologic interventions is less consistent [615]. CBT seems to be similarly effective for informal carers of patients with cancer [29], but relevant evidence is considerably limited [616]. Nevertheless, clinicians clearly have an array of available sleep interventions to choose from. What is important and proposed here is that the effectiveness of these non-pharmacologic interventions for sleep disturbances needs to be re-examined, this time at a dyadic level. Whereas therapeutic interventions such as CBT, home-based walking, education, mindfulness-based stress reduction, hypnosis, expressive writing, massage, or guided imagery have previously been shown to improve sleep and correlates in patients and informal caregivers [3, 49, 616, 633-637], concurrent delivery to dyads rather than merely individuals could be 'twice as effective' resulting in combined improvement in sleep [233] and other health outcomes. Davidson [615] and Langford et al. [616] argue in favour of an approach that looks at helping *both* the patient and the caregiver; since they may share a bed, "the sleep of one is bound to affect the sleep of the other". However, there is much more to it: even dyads that do not interact at night may manifest sleep/wake problems at the same time. Concurrent 'sleep distress' may put dyad members living in this close caring relationship at greater risk for concurrent health deficits, concurrent quality of life deficits, and inability to cope and function both independently and together. Joint provision of the aforementioned sleep interventions to patients and caregivers may have an additive effect to the benefit that they can gain from them as individuals. For instance, since CBT interventions for insomnia can be conducted either one-on-one or in groups of individuals (e.g. patients) [616], devising a plan to offer CBT to dyads should not be a difficult task to accomplish. Importantly, the target would be to produce components of CBT (usually, cognitive, behavioural, and educational) that promote individualised goal-setting for patients (possibly focusing more on restructuring maladaptive thoughts about sleep or exercising relaxation techniques, or avoiding maladaptive coping strategies) and caregivers (possibly focusing on planning caregiving tasks and on stimulus control), and for dyads by concentrating on a concurrent sleep hygiene plan to avoid disruptive behaviours/habits that may interfere with sleep [366].

8.5. Conclusions

As confirmed in the current study, alterations in the habitual sleep/wake patterns of women with breast cancer and their informal caregivers is a widely prevalent symptom, the pervasive and debilitating effects of which can severely affect health and quality of life [49]. However, it has been argued that patient sleep/wake problems during chemotherapy treatment still go unrecognised and under-treated [622]. For some, these might be secondary problems that women need to endure, and which will go away once treatment is over. Seldom is this the case. In addition, informal caregivers often experience sleep loss and daytime dysfunction that might not be readily visible to the healthcare team [182, 534]. For others, these might erroneously be seen as symptoms that carers are used to dealing with and know how to overcome. Complemented by the fact that whereas sleep not only is a biological [2] but also a social phenomenon [338], which however only rarely has been examined as such [366], it can be assumed that researchers' and healthcare providers' understanding of complex sleep interaction may often be inadequate and care may fall short.

The current study has taken dyadic sleep research a step forward by examining the interrelations in the sleep/wake patterns of women receiving chemotherapy for early stage breast cancer and their informal caregivers, and by acknowledging the individualistic and dyadic nature of sleep-impairing factors that should be addressed by future sleep interventions. Current results revealed alarming percentages of dyads consisting of at least one poor sleeper prior to chemotherapy initiation, which further increased as patient treatment progressed. However, for the majority of sleep/wake parameters, impairment was generally greater for patients rather than caregivers during the chemotherapy period, which persisted into the initial post-treatment period. Despite these differences, at baseline, daily disturbance, daytime napping duration, total sleep time, and overall sleep/wake impairment tended also to converge. In addition, over treatment, continuation rates of change in sleep latency and duration of daytime napping were not significantly different between patients and caregivers. Patterns of change in perceived sleep quality, sleep latency, daily disturbance, and overall sleep/wake impairment were strongly correlated between dyad members throughout the study. These findings suggest that deterioration in patient sleep parameters was followed by a similar worsening in the respective caregiver variables, and vice versa, and confirms interdependence. Further analyses revealed that increased poor sleep hygiene behaviours and nocturnal sleep disturbances, and caregiving burden were the variables that most consistently predicted poorer outcomes in the sleep/wake patterns of the dyads. Conversely, evidence for cross-partner effects most frequently emerged with regard to the dyads' psychological burden, as well as for caregiving burden. Whereas more dysfunctional coping on the patients' part was

associated with greater own sleep/wake impairment, caregiver use of maladaptive coping strategies was found to predict better, rather than worse, perceived sleep quality.

Nevertheless, research has only begun to gain an understanding of the bi-directional associations in the sleep/wake patterns of patients with cancer and their caregivers [366]. Unravelling the complex underlying pathways that lead to the development of sleep/wake impairments in these dyads and exploring how interventions can support people affected by cancer in every-day practice are questions that future researchers and clinicians will be required to give answers to in an attempt to find innovative and more effective ways to provide better care to patients and their caregivers.

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Appendix 1. Figures & Schematics

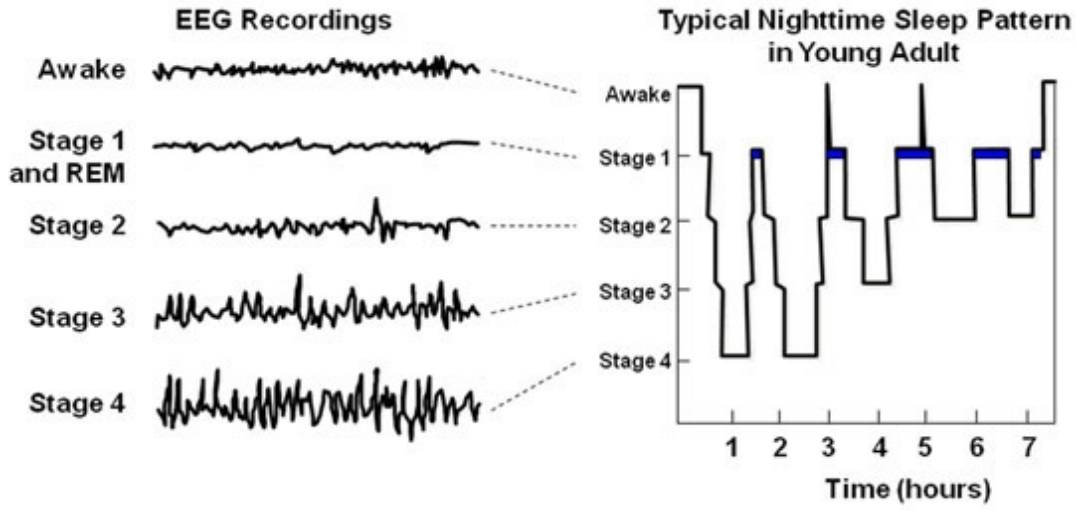


Figure 1-A1. Normal electroencephalographic (EEG) characteristics (left panel) and sleep architecture (right panel) in a young adult. *Source:* Kandel et al. (1991) [638].

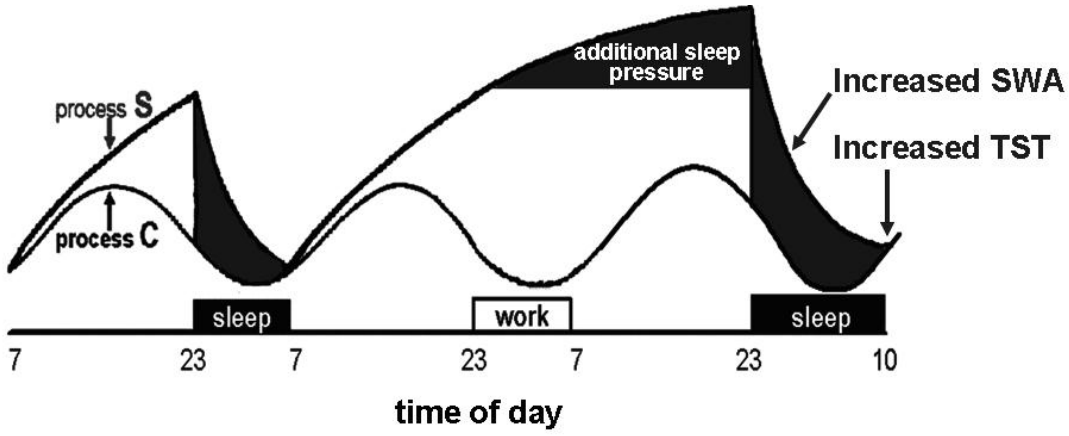


Figure 2-A1. The two process model of sleep regulation (SWA – Slow-wave activity; TST – Total sleep time). *Source:* Borbely (1982) [40]

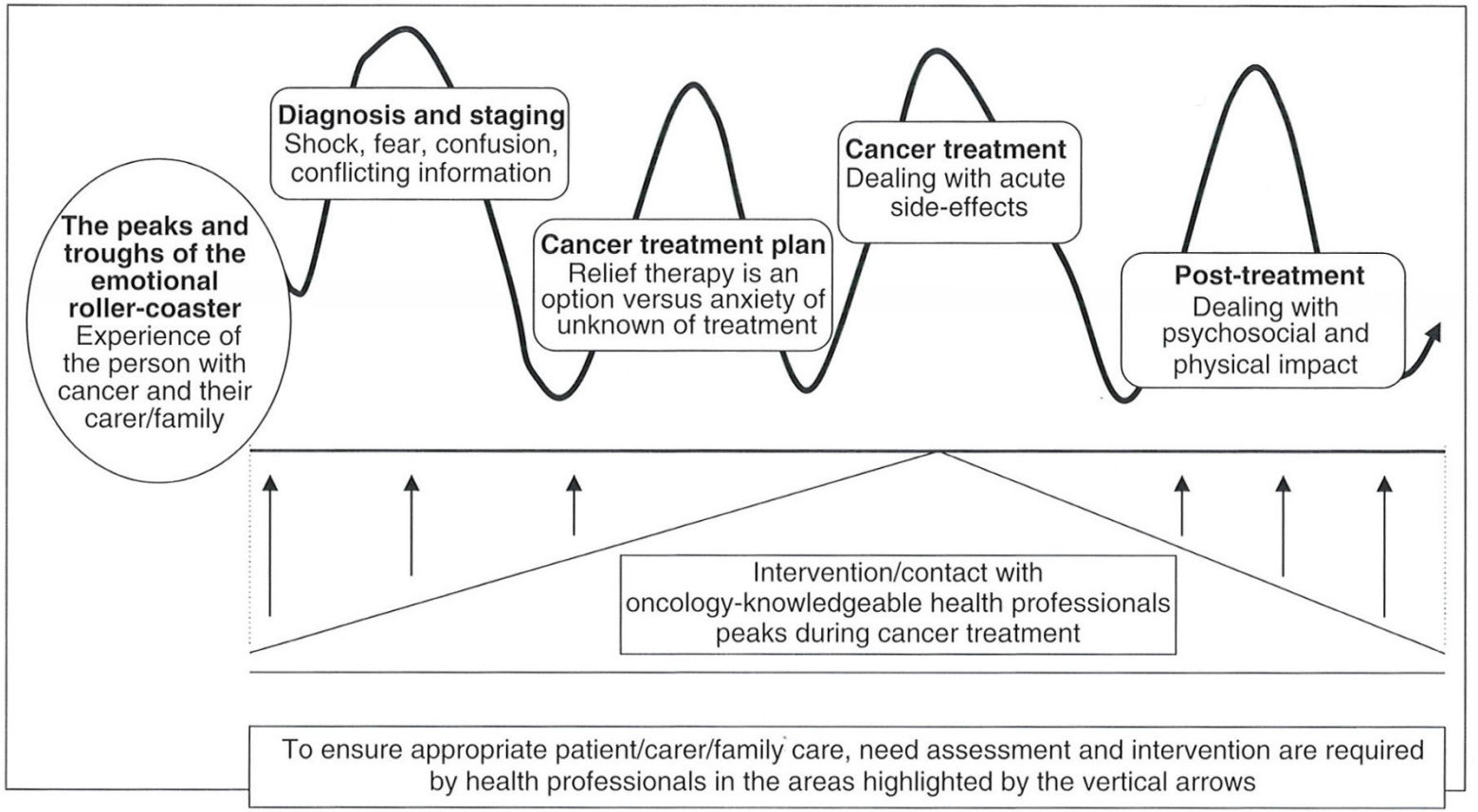


Figure 3-A1. The "roller-coaster" experience of the treatment pathway. *Source:* Corner & Bailey (2008) [84]

Mathematical definition

Formally, the weighted mean of a non-empty set of data

with non-negative weights

is the quantity

which means:

Therefore data elements with a high weight contribute more to the weighted mean than do elements with a low weight. The weights cannot be negative. Some may be zero, but not all of them (since division by zero is not allowed).
The formulas are simplified when the weights are normalized such that they sum up to 1,

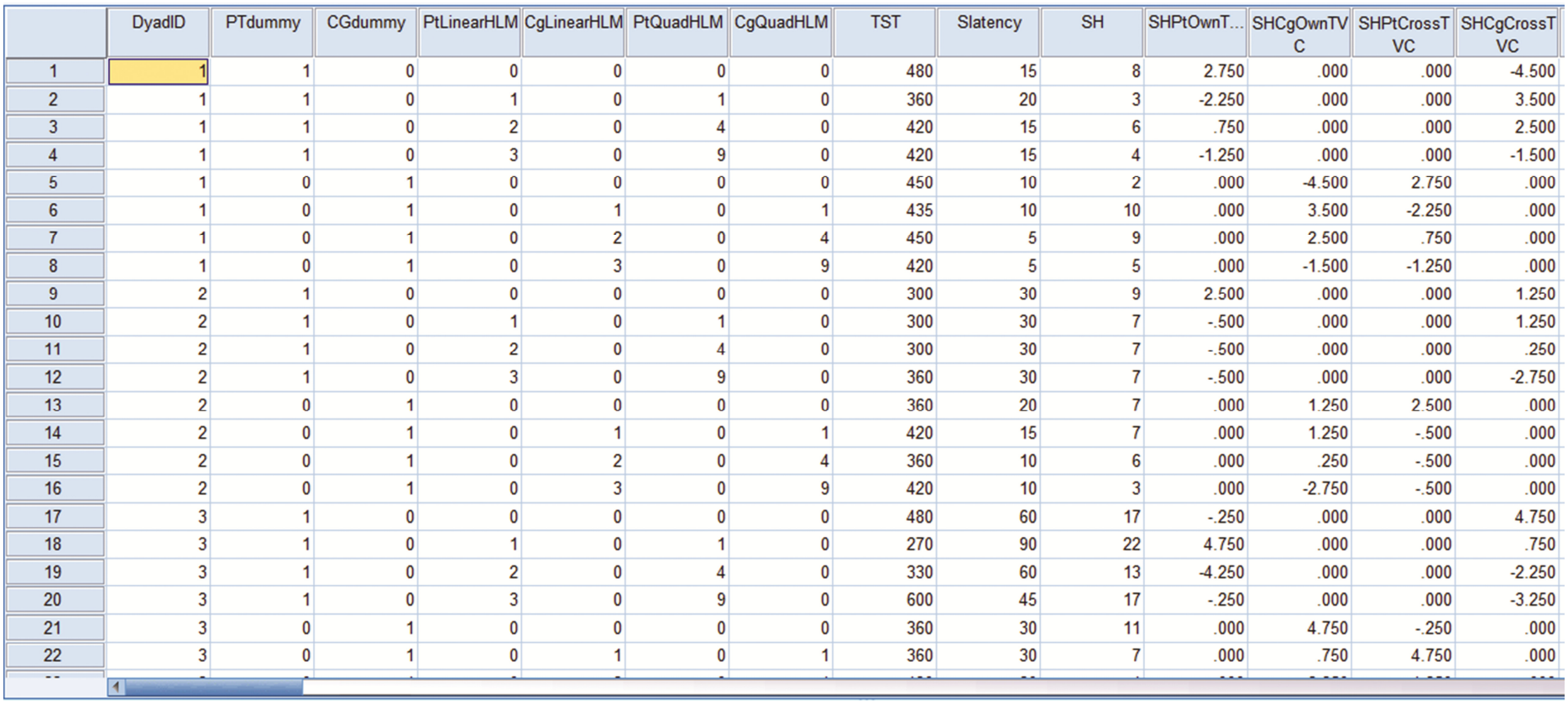
i.e. .

For such normalized weights the weighted mean is simply .

The common mean is a special case of the weighted mean where

all data have equal weights, $w_i = w$.

Figure 4-A1. Mathematical definition of the weighted mean.



	DyadID	PTdummy	CGdummy	PtLinearHLM	CgLinearHLM	PtQuadHLM	CgQuadHLM	TST	Slatency	SH	SHPtOwnT...	SHCgOwnTVC	SHPtCrossTVC	SHCgCrossTVC
1	1	1	0	0	0	0	0	480	15	8	2.750	.000	.000	-4.500
2	1	1	0	1	0	1	0	360	20	3	-2.250	.000	.000	3.500
3	1	1	0	2	0	4	0	420	15	6	.750	.000	.000	2.500
4	1	1	0	3	0	9	0	420	15	4	-1.250	.000	.000	-1.500
5	1	0	1	0	0	0	0	450	10	2	.000	-4.500	2.750	.000
6	1	0	1	0	1	0	1	435	10	10	.000	3.500	-2.250	.000
7	1	0	1	0	2	0	4	450	5	9	.000	2.500	.750	.000
8	1	0	1	0	3	0	9	420	5	5	.000	-1.500	-1.250	.000
9	2	1	0	0	0	0	0	300	30	9	2.500	.000	.000	1.250
10	2	1	0	1	0	1	0	300	30	7	-.500	.000	.000	1.250
11	2	1	0	2	0	4	0	300	30	7	-.500	.000	.000	.250
12	2	1	0	3	0	9	0	360	30	7	-.500	.000	.000	-2.750
13	2	0	1	0	0	0	0	360	20	7	.000	1.250	2.500	.000
14	2	0	1	0	1	0	1	420	15	7	.000	1.250	-.500	.000
15	2	0	1	0	2	0	4	360	10	6	.000	.250	-.500	.000
16	2	0	1	0	3	0	9	420	10	3	.000	-2.750	-.500	.000
17	3	1	0	0	0	0	0	480	60	17	-.250	.000	.000	4.750
18	3	1	0	1	0	1	0	270	90	22	4.750	.000	.000	.750
19	3	1	0	2	0	4	0	330	60	13	-4.250	.000	.000	-2.250
20	3	1	0	3	0	9	0	600	45	17	-.250	.000	.000	-3.250
21	3	0	1	0	0	0	0	360	30	11	.000	4.750	-.250	.000
22	3	0	1	0	1	0	1	360	30	7	.000	.750	4.750	.000

Figure 5-A1. Organisation of data for HLM analysis at Level 1.

Appendix 2. Tables

Table 1-A2. Commonly used sleep-related terms and definitions [4, 11]

Apnoea	Cessation of airflow at the nostrils and mouth lasting at least 10 seconds; the three types of apnoea are obstructive, central, and mixed. Obstructive apnoea is secondary to upper-airway obstruction, central apnoea is associated with a cessation of all respiratory movements, and mixed apnoea has both central and obstructive components.
Arousal	An abrupt change (i.e., over 3-14 seconds) from a deeper stage of non-rapid eye movement sleep to a lighter stage or from rapid eye movement sleep to wakefulness
Deep sleep	A common term for non-rapid eye movement sleep stages 3 and 4 (also called delta or slow wave sleep)
Entrainment	Synchronization of a biologic rhythm by a forcing stimulus such as an environmental time cue (zeitgeber)
Excessive daytime sleepiness	Difficulty in maintaining the alert-awake state usually accompanied by a rapid entrance into sleep when the person is sedentary; results in somnolence and hypersomnia
Insomnia	Difficulty in initiating or maintaining sleep
Periodic limb movement	A rapid partial flexion of the foot at the ankle, extension of the big toe, and partial flexion of the knee and hip that occurs during sleep; the movements occur with a periodicity of 5-90 seconds and last 0.5-5.0 seconds.
Periodic limb movement disorder	A disorder characterised by periodic episodes of repetitive and highly stereotyped limb movements that occur during sleep
Restless legs syndrome	A waking dysaesthesia, most often localised to the calves, which occurs primarily in evening hours; its major manifestation is an irresistible urge to move the legs; it may interfere with sleep onset and maintenance, as well as cause the sufferer great torment while waking.
Sleep apnoea syndrome	A disorder characterised by repetitive episodes of reduced or absent respiratory airflow that occur during sleep and that usually are associated with a reduction in blood oxygen level
Zeitgeber	An environmental time cue, such as sunlight, noise, social interaction, or an alarm, that usually helps an individual entrain to the 24-hour day

Table 2-A2. The nine recommended key sleep parameters [43]

Sleep parameter	Normal characteristics
Total sleep time while in bed: number of minutes of sleep while in bed	Adults normally attempt to sleep 7-9 hours (420-540 minutes) in 24 hours, whereas adolescents 13-18 years old normally sleep 8.5-9.25 hours in a 24-hour period.
Latency: number of minutes between when someone lays down to bed and actually goes to sleep	Adult latency normally is less than 20 minutes.
Awakenings during sleep period: the number of awakenings during a sleep period	Adults normally awaken two to six times during a typical night's sleep of 420 minutes.
Wake after sleep onset (WASO): number of minutes awake or percentage of time awake after sleep onset during the sleep period	Adult WASO time normally is less than 10% of the total sleep minutes, or 42 minutes if the person sleeps 420 minutes (seven hours) during the night.
Napping during the day: total number of minutes of sleep during the daytime; can be intentional or unintentional sleep	Adult napping normally can vary from five minutes to two hours.
Excessive daytime sleepiness: episodes of lapses into sleep of short duration, usually in situations in which the person is inactive for even brief periods; excessive daytime sleepiness can result from acute or chronic sleep deprivation or loss or other pathophysiologic causes.	Adults normally have a minimal chance of dozing while engaged in routine activities.
Quality of perceived sleep: multidimensional perceptions of length and depth of sleep and feelings of being rested upon awakening; subjective assessment of sufficiency of sleep for daytime functioning	Adults normally feel satisfied or very satisfied with their usual sleep patterns and believe that their sleep enhances their daily functioning.
Circadian rhythm: bio-behavioural phenomenon associated with fluctuations in light, hormones, eating, or socializing that repeats approximately every 24 hours (see also **Table 3-A2**)	Circadian rhythm peaks and troughs within a 24-hour period.
Sleep efficiency: the number of minutes of sleep divided by the total number of minutes in bed, multiplied by 100	In adults, 95% sleep efficiency indicates a good night's sleep; less than 80% indicates a bad night's sleep; in a night's sleep of 420 minutes (7 hours), this would be equivalent to 20 minutes to fall asleep and three awakenings of 10 minutes each.

Table 3-A2. Circadian activity rhythm parameters obtained through actigraphic measurements [9, 49, 121, 577, 639]

Circadian parameter	Definition	Meaning	Measurement	Healthy adult values
Mesor	24-h adjusted mean of the activity counts; the mean of the rhythm; half-way between minimum and maximum activity	Higher values represent a more robust activity; mean activity level	Movements/ minute	150.3 (± 17.7) [640, 641] ~138 [642]
Up-mesor	The time of day when an individual switches from low to high activity, i.e., from below the mesor to above the mesor	Higher values suggest a later starting time of activity; the time an individual "gets going" in the morning	Clock time	–
Down-mesor	The time of day when an individual switches from high to low activity, i.e., from above the mesor to below the mesor	Higher values suggest a later time of decline of activity; the time an individual "settles down" for the evening	Clock time	–
Amplitude	Peak-to-nadir difference (peak minus the mesor) the height of the rhythm	Represents the rhythmic change of an individual's activity during a 24-h period; lower values suggest a dampened circadian rhythm	Movements/ minute	109.0 (± 23.4) [640, 641] ~110 [642]
Peak activity	Sum of the mesor and amplitude values	Index of maximum activity for a 24-h period; favourable because it represents more robust circadian rhythms	Movements/ minute	Approximately 250-260 [127]
Acrophase	Actual clock time of the peak amplitude	A later time suggests more phase delay	Clock time	Early afternoon (14:00-15:00) [640, 641]
Circadian quotient	Determined by dividing the amplitude by the mesor	Strength of the circadian rhythm; higher values represent an assessment of degree of activity/sleep consolidation throughout the day	Ratio	Closer to 1.00 [639, 643]
24-h Autocorrelation	The internal correlation of the regularity and consistency of the rhythm from one day to the next	High autocorrelation at or near 24-hours indicates a robust/stable circadian rhythm.	Ratio	Range –1 to +1; optimal = +1.0 [639, 643]
Goodness of fit (R^2 cosinor fit; *F* statistics)	The reduction in squared error from using a model to summarise data compared to using the mean; variance explained by the cosine fit; percentage of variance in the data explained by the fitted cosine curve; the correlation between the fitted curve and the actual data	A measure of how well the data fits into the 24-hour circadian pattern; indicates that the circadian rhythm accounts for a % of the variability in an individual's activity; higher values suggest a more robust rhythm	–	–

Table 4-A2. UICC staging system combined with the TNM classification for breast cancer [67, 71]

UICC Stage	TNM classification	Characteristics	Commonly used terms
0	Tis, N0, M0	Carcinoma *in situ*, no regional lymph node metastasis, no distant metastasis	Carcinoma *in situ*; non-invasive carcinoma
I	T1, N0, M0	Tumour < 2 cm, no regional lymph node metastasis, no distant metastasis	Early stage breast cancer
IIA	T0, N1, M0	No evidence of primary tumour, metastasis to movable ipsilateral axillary node(s), no distant metastasis	
	T1, N1, M0	Tumour ≤ 2 cm, metastasis to movable ipsilateral axillary node(s), no distant metastasis	
	T2, N0, M0	Tumour > 2 cm but ≤ 5 cm, no regional lymph node metastasis, no distant metastasis	
IIB	T2, N1, M0	Tumour > 2 cm but ≤ 5 cm, metastasis to movable ipsilateral axillary node(s), no distant metastasis	
	T3, N0, M0	Tumour > 5 cm, no regional lymph node metastasis, no distant metastasis	
IIIA	T0, N2, M0	No evidence of primary tumour, metastasis to fixed ipsilateral axillary node(s), no distant metastasis	
	T1, N2, M0	Tumour ≤ 2 cm, metastasis to fixed ipsilateral axillary node(s), no distant metastasis	
	T2, N2, M0	Tumour > 2 cm but ≤ 5 cm, metastasis to fixed ipsilateral axillary node(s), no distant metastasis	
	T3, N1, M0	Tumour > 5 cm, metastasis to movable ipsilateral axillary node(s), no distant metastasis	
	T3, N2, M0	Tumour > 5 cm, metastasis to fixed ipsilateral axillary node(s), no distant metastasis	
IIIB	T4, any N, M0	Tumour of any size with direct extension to chest wall or skin, any N, no distant metastasis	Locally advanced carcinoma
IIIC	Any T, N3, M0	Any T, metastasis to ipsilateral internal mammary lymph nodes, no distant metastasis	
IV	Any T, any N, M1	Any T, any N, distant metastasis present	Metastatic breast cancer

Table 5-A2. Evidence categories used by the Department of Health in the National Service Frameworks (DOHNSF) (2001) [116]

Level of Evidence	Evidence Source
A1	Systematic reviews, which include at least one randomised controlled trial (RCT), e.g. systematic reviews from Cochrane or NHS, centre for reviews and dissemination
A2	Other systematic and high-quality reviews, which synthesise references
B1	Individual RCTs
B2	Individual non-randomised, experimental/intervention studies
B3	Individual well-designed non-experimental studies, controlled statistically if appropriate. Includes studies using case control, longitudinal, cohort, matched pairs or cross-sectional random sample methodologies, and well-designed qualitative studies; well-designed analytical studies including secondary analysis
C1	Descriptive and other research or evaluation not in B (e.g. convenience samples)
C2	Case studies and examples of good practice
D	Summary review articles and discussions of relevant literature and conference proceedings not otherwise classified

Table 6-A2. Systematic search results: *sleep/wake patterns in women with non-metastatic breast cancer*

	N	***N***
Medline – EMBASE	3,558	
CINAHL	508	
Total all databases	4,066	
Duplicates	721	
Total papers extracted	3,345	
Papers rejected on title		3,120
Papers rejected on abstract		95
Papers obtained in full		130
Papers extracted through snowballing		6
Papers excluded after review		115
Papers retained and included in review		21

Table 7-A2. STROBE Statement – checklist of items that should be included in reports of observational studies [644]

	Item No.	Recommendation
Title and abstract		
	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any pre-specified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
		Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls
		Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed
		Case-control study—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed
		Case-control study—If applicable, explain how matching of cases and controls was addressed
		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

	Item No.	Recommendation
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—e.g. numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (e.g. demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (e.g., average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorised
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—e.g. analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Table 8-A2. Systematic review results: *sleep-impairing factors in women with breast cancer*

	N	*N*	
Medline – EMBASE[a]	1,567[b]		
CINAHL[a]	794		
Total all databases	2,361		
Papers rejected on title/abstract		2,146	
Papers retained		191	
Papers extracted through snowballing		24	
Papers obtained in full-text		215	
Papers excluded after review		157	Reasons: ▪ No sleep specific measure: 30 ▪ Mixed sample: 20 ▪ Review articles: 5 ▪ No associations tested: 35 ▪ No sleep measurement: 12 ▪ No breast cancer group: 2 ▪ Single item sleep scale only: 4 ▪ Tool development article: 2 ▪ Conference proceedings: 31 ▪ Dissertations: 4 ▪ Other: 12
Papers retained and included in review		58	
Papers related to the chemotherapy period		26	

[a]Limits: 1990-March 2012; English language; abstract available
[b]After duplicates were removed

Table 9-A2. Summaries of the characteristics of the 16 studies (26 articles) included in the systematic review reporting on sleep-impairing factors in women receiving neo-/adjuvant chemotherapy for breast cancer.

Authors/ Study ref	Country	Research design	Timing of assessment	*N*	Patient demographic characteristics	Patient clinical data	Sleep measures	Predictors/correlates/factors examined
Ancoli-Israel et al. [120]; Liu et al. [8]; Liu et al. [145]; Liu et al. [146]; Rissling et al. [125]	USA	Descriptive, exploratory, prospective Repeated measures Correlational	Prior to CThC1, during the 3 weeks of CThC1, before the start of CThC4, and during the 3 weeks of CThC4	97	Mean age 50.7±9.8 years (34-79); 73.2% Caucasian; 68% married; education: 77% college and above Response rate: 80.1%	BC stage: I (30.2%), II (50%), IIIA (19.8%); Neo-adjuvant CT (n=13), adjuvant CT (n=83); Adjuvant CT patients: 40 lumpectomy, 39 mastectomy, 4 double mastectomy CT regimen: AC (31%), AC+taxanes (50.6%); BMI 28.8±6.8 (17.4-51.8) kg/m^2; Menopausal status: Baseline – pre-menop (38%) post-menop (24%); End of study: Peri-menop (15%) post-menop (62%). Sleeping medications: Baseline – Yes (49%); End of study – Yes (45.9%) Analgesics: Baseline – Yes (59.6%); End of study – Yes (25%)	Self-report measures and objective recordings Continuous 72-hour objective measurement starting at the beginning of each assessment point First data collection point: 1 week before the start of treatment Self-report sleep questionnaires and a sleep log Wrist actigraphy PSQI FOSQ	Fatigue Functional status Depression Inflammatory markers (IL-6, IL-1RA, CRP) Climacteric status/symptomatology
Beck et al. [7]	USA	Descriptive Prospective Secondary analysis of two separate RCT data sets (only Study 1 is considered here); analysis was conducted on the baseline data	Prior to treatment and 3 consecutive nights post initial chemotherapy	108	Mean age 50.5±9.3 years (28-75); 91.1% Caucasian; 79.2% married/partnered. Response rate: Unknown	Stage I-IIIA BC: I (21%), II (55%), IIIA (24%); ≥1 month after initial surgery; anthracycline- and/or cyclophosphamide-based CT; intervention and control group included.	Objective (3 consecutive days and nights after initial chemotherapy) and subjective (prior to the treatment initiation) sleep measures PSQI Continuous 72-hour wrist actigraphy	Physical health status and mental health status. Demographic and clinical information (age; ethinc/racial background; marital status; education; disease stage).
Berger [126] Berger & Farr [127]	USA	Descriptive Prospective Repeated measures	CThC1 through CThC3	72	Mean age 49.5±8.6 years (33-69); 65% married; 73% employed; 63% high school, 32% college. Response rate: 94% Attrition rate: 16.7% (60 participants completed the study)	Stage I or II BC: I (44%), II (56%); 53% mastectomy; 46% pre-menopausal, 40% post-menopausal; 64% anthracycline- (AC, CAF) and/or 36% cyclophosphamide-based (CMF) CT.	Objective sleep measures used: continuous 96-hour wrist actigraphy at the time of chemotherapy treatments (CThC1-3); continuous 72-hour wrist actigraphy at CThC1, CThC2, and CThC3 midpoints (days 11-17) Wrist actigraphy; sleep variables: mesor, amplitude, peak activity, nighttime awakenings	Cancer-related fatigue Clinical data (time since surgery; CT regimen; timing of CT administration)
Berger & Higginbotham [104]	USA	Descriptive, pilot study Prospective	CThC3 and CThC4	14	Mean age 52.4 (32-69); 71% married; 64% work-	Stage I or II BC: I (50%), II (50%); 78% lumpectomy; 57% post-menopausal; AC	Objective and self-reported sleep data Sleep data were collected at 48 hours	Cancer-related fatigue

Authors/ Study ref	Country	Research design	Timing of assessment	*N*	Patient demographic characteristics	Patient clinical data	Sleep measures	Predictors/correlates/factors examined
		Repeated measures			ing outside the home (full- or part-time) Response rate: Unknown Attrition rate: 14.3% (12 participants completed the study)	treatment; 71% concurrent use of tamoxifen citrate.	prior to CThC3; continuously during the 21 days of CThC3; 72 hours three weeks after CThC4; 72 hours two months after CThC4 Continuous wrist actigraphy Morin Sleep Diary	
Beck et al. [7]; Berger et al. [121]; Berger et al. [123]; Berger et al. [131]; Berger et al. [143]; Moore et al. [136]	USA	RCT Prospective, longitudinal[104, 126, 127]	Throughout CT treatment and 1-year follow up	219	Mean age 52.0±9.84 years (29-79); 95.3% Caucasian; 72.6% married; 78% employed; 75% post-secondary education Response rate: 82%	BC stage: I (34%), II (53%), IIIA (13%); 55% mastectomy; 54% post-menopausal, 32% pre-menopausal.	Objective and self-reported sleep data Continuous 48-hour wrist actigraphy (2 days before initial chemotherapy); PSQI (day -2 prior to chemotherapy); CThC1-CThC8 continuous 7-day wrist actigraphy and sleep diaries; CThC4 and CThC8 PSQI; 30, 60, 90 days after last chemotherapy continuous 7-day wrist actigraphy and sleep diaries, and PSQI (day 1); 1 year after CThC1 continuous 7-day wrist actigraphy and sleep diaries, and PSQI (day 1) Wrist actigraphy Morin Sleep Diary PSQI	Fatigue Demographic (age, education) and clinical (stage of disease, menopausal status, surgical procedure, body mass index, performance status) variables Anxiety/depression Physical functioning Symptom distress Physical and mental health status Past sleep quality CT prescribed (with or without taxanes)
Bower et al. [166]	USA	Descriptive, exploratory Cross-sectional Correlational Part of a larger study of cognitive functioning after cancer treatment	Within 3 months post-completion of CT	103	Mean age: 51.2 years (32-66); 86% white; 79% married/partnered; 81% post-secondary education Response rate: not reported	Type of treatment: 52% no CT (surgery ± RT); 48% CT (surgery ± RT + CT); time since diagnosis: mean 6.7 months (1.7-12.5); time since last treatment: mean 31.8 days (1-112)	Self-reported sleep data only One measurement PSQI	Fatigue Depressive symptoms Having received chemotherapy or not Three inflammatory markers: IL-1ra, sTNF-RII, CRP
Colagiuri et al. [144]	Denmark	Descriptive, exploratory Cross-sectional Correlational Part of a nationwide cohort of women treated for primary breast cancer	Three to four months post-BC surgery	3002	Mean age: 54.4 years (26-70); 77% married/ partnered; 30% post-tertiary education Response rate: not reported	Type of treatment: 54% mastectomy; 44% receiving CT; 60% post-menopausal; 61% tumours < 20 mm; 12-16 months post-surgery	Self-reported sleep data only One measurement PSQI	Demographics and socioeconomic status (personal income, net wealth, education, marital status, ethnicity, urbanicity, and children) Psychiatric and physical co-morbidity pre-cancer Clinical data (type of surgery, current chemotherapy, hormone therapy, radiation therapy; tumour size, grade, axillary lymph node status, oestrogen receptor

Authors/ Study ref	Country	Research design	Timing of assessment	*N*	Patient demographic characteristics	Patient clinical data	Sleep measures	Predictors/correlates/factors examined
								status) Health-related variables (BMI, menopausal status, smoking status, weekly alcohol intake) Physical functioning Physical activity Psychological morbidity (depression, trait anxiety)
Costantini et al. [137]	USA	Retrospective chart review Cross-sectional	NA	124	Mean age: 51 years (26-80); 50% >50 years; 62% married/partnered Response rate: NA	BC stage: 19% I, 47% II, 32% III; 73% Oestrogen receptor positive; 19% HER2+; 89% adjuvant CT; 43% post-menopausal; 65% AC dose dense; 23% some psychiatric diagnosis; 26% some psychiatric medication; 14% prior sleep aid use; 52% discussed sleep aid use during CT; 32% were prescribed sleep aid during CT; Sleep aids: 31% lorazepam, 29% zolpidem	Retrospective recordings on prescriptions of sleep aid use	Past history of sleep aid use Psychiatric medication use Psychiatric diagnosis Menopausal status
Garrett et al. [153]; Merriman et al. [171]	USA	Descriptive, exploratory Cross-sectional Comparative case-control study Part of a larger longitudinal study evaluating multiple symptoms in patients undergoing primary or adjuvant RT	Approximately one week before the initiation of RT	78	Mean age: 54.7±11.4 years; 68% Caucasian; 39% married/partnered; Mean years of education: 16.2±2.7 years; 43% employed; 26% children at home; 7% parents at home; 40% lives alone. Response rate: not reported	Mean KPS: 88.9±11.3; Time since diagnosis: 5.2±2.7 months; Number of comorbidities: 5.2±2.6; stage of disease: 9% 0, 45% I, 36% II, 10% III; 100% surgery before RT; 56% CT before RT; 44% HT before RT	Objective and self-reported sleep data Continuous sleep recording for 48 hours, two consecutive weekdays One measurement; between-groups comparisons PSQI GSDS Two-day sleep diary Wrist actigraphy	BC or PC status Attentional fatigue (diminished ability to concentrate, difficulty engaging in purposeful activity, and strained interpersonal relationships)
Hanprasitkam et al. [165]	Thailand	Descriptive, exploratory Cross-sectional Correlational	During adjuvant CT (at least one CThC received)	159	Mean age: 49.8±9.4 (27-74) years; 65% married/partnered; 65% employed Response rate: not reported	Time since diagnosis: not reported; BC stage: 12% I, 65% II, 23% III; 87% radical mastectomy; 54% CAF or AC, 46% CMF; 14% one CThC received; 100% premedication with dexamethasone	Self-reported sleep data only One measurement Modified GSDS	Fatigue Haemoglobin Chemotherapy protocol Symptom distress (nausea and vomiting) Family and friend support Religious practices Anxiety Depression
Kuo et al. [129]	Korea	Descriptive, exploratory	CThC3 and CThC4	16	Mean age: 45 (29-59) years; 75% mar-	62.5% regular menstruation; 56% CMF (7 patients, 28-day cycle)	Objective and self-reported sleep data Two measurements: (1) 8^{th}-9^{th} day of	Active versus recovery phase of chemotherapy

Authors/ Study ref	Country	Research design	Timing of assessment	*N*	Patient demographic characteristics	Patient clinical data	Sleep measures	Predictors/correlates/factors examined
		Repeated measures Correlational			ried/partnered; 50% college graduates; 56% employed Response rate: Not reported		CThC3 (active phase), (2) 2 days before CThC4 (recovery phase) Wrist actigraphy (continuous 48 hour recordings) Sleep logs ESS	Physical distress
Payne et al. [128]	USA	Descriptive, exploratory Repeated measures, pilot Comparative Control group matched by age, ethnicity and menopausal status	CThC1 and CThC4	11	Mean age: 47.4±10.4 years; 82% single/ divorced; 64% > high school Response rate: not reported	5 pre-menopausal, 4 peri-menopausal; 27% use of sleep aids	Objective sleep data (+ subjective sleep data through the fatigue questionnaire) Data were collected at four measurement points (i.e., during CThC1 and CThC4 on days 1–3 and at the two-week nadir points) for two consecutive nights each in a sleep laboratory Continuous 48-hour wrist actigraphy Two outcome variables: sleep disturbances, sleep duration	Having breast cancer or not
Roscoe et al. [147]	USA	Descriptive, exploratory Repeated measures Secondary analysis of RCT data examining the efficacy of Paroxetine 20mg in attenuating or preventing the development of fatigue. 49% of final sample on daily paroxetine 20 mg.	CThC2 and CThC4	78	Mean age: 51.7 (34-79) years. Response rate: 63%	CT regimens: 37% CMF, 45% CDoc±F, 14% other; Mean KPS 89 (70-100)	Objective sleep data 6 days after administration of CThC2 and CThC4. Continuous 72-hour wrist actigraphy (days 6, 7 and 8). Three outcome variables: circadian consistency (or autocorrelation)-similarity or dissimilarity of rest and activity patterns across measurement; daytime mean activity-average activity level during the day; daytime per cent sleep-proportion of time spent resting or sleeping during the day.	Fatigue Depressive mood Performance status Overall mood Age Randomisation to paroxetine or placebo
Savard et al. [172]	Canada	Descriptive, exploratory Longitudinal, secondary analysis from a larger CBT intervention study for women receiving treatment for BC	Throughout CT or RT Three assessment points (before treatment initiation, post-treatment, follow-up 3 months)	58	Mean age: 54.6±7.0 (36-70) years; 65.5% married/partnered; 51.7% at least a college degree; 60.3% employed. Response rate: not reported	Time since diagnosis: not reported; BC stage: 67.2% I, 24.1% II, and 8.6% III. Surgery type: 94.8% lumpectomy, 8.6% mastectomy. Treatment: 26 CT+RT; 29 RT; 3 CT only. 76% on HT; 77.6% post-menopausal. 22%-29% psychotropic medication (mainly benzodiazepines) during the study.	Self-report sleep data ISI	Hot flashes (occurrence; prevalence; severity) Hot flashes-related quality of life

Authors/ Study ref	Country	Research design	Timing of assessment	*N*	Patient demographic characteristics	Patient clinical data	Sleep measures	Predictors/correlates/factors examined
Stein et al. [148]	USA	Descriptive, exploratory Cross-sectional Secondary analyses of a larger longitudinal study	4-6 weeks after treatment initiation	70	*CT Patients:* Mean age: 57.1±8.9 (41-78) years; 93% White; 68% Married; 78% attended at least some college; 46% employed.	*CT treatment:* BC stage: 14% I, 68% II, 18% III; 54% mastectomy, 43% lumpectomy; Regimen: 25% A, 39% AC, 32% CAF, 4% mitoxantrone; None HT.	Self-report sleep data PSQI	Hot flashes
Vargas et al. [133]	USA	Descriptive, exploratory Cross-sectional Part of a clinical trial of a cognitive behavioural stress management intervention.	After surgery but before adjuvant treatment for early stage BC	240	Mean age: 50.34±9.03 years; 62.5% Married/partnered; 67.5% Caucasian; 15.58±2.38 years of education; 74.5% employed.	Time since surgery: 40.13±22.70 days; 44.6 pre-menopausal, 42.9% menopausal; BC stage: 16% 0, 37.8% I, 38.2% II, 8.0% III; Type of surgery: 50.8% lumpectomy, 49.2% mastectomy; 29.6% breast reconstruction at surgery; 17.9% prescribed sleep medication; 25% prescribed pain medication; 10.8% prescribed antidepressants; 17.5% prescribed anti-anxiety medication.	Self-report sleep data One assessment point PSQI	Fatigue Functional well-being

Abbreviations: IL-1ra – IL-1 receptor antagonist; sTNF-RII – soluble TNF receptor type II; CRP – C-reactive protein; CThC – chemotherapy cycle; CT – chemotherapy; BMI – body mass index; AC – Adriamycin + Cyclophosphamide; A – Adriamycin; PSQI – Pittsburgh Sleep Quality Index; FOSQ – Functional Outcome of Sleep Questionnaire; RCT – Randomised controlled trial; CAF – Cyclophosphamide + Adriamycin + 5-Fluorouracil; CMF – Cyclophosphamide + Methotrexate + 5-Fluorouracil; F – 5-Fluorouracil; RT – Radiation therapy; HT – Hormonal therapy; NA – Non applicable; HER2 – Human epidermal growth factor receptor 2; KPS – Karnofsky performance status; GSDS – General Sleep Disturbance Scale; ESS – Epworth Sleepiness Scale; CDocF – Cyclophosphamide + Docetaxel + 5-Fluorouracil; ISI – Insomnia Severity Index; CBT – Cognitive behavioural therapy

Table 10-A2. Methodological quality of the 16 studies included in the systematic review.

Study	LE	Study Quality Criteria									
		#1	#2	#3	#4	#5	#6	#7	#8	#9	#10
Ancoli-Israel et al. [120]; Liu et al. [8]; Liu et al. [145]; Liu et al. [146]; Rissling et al. [125]	B3	2	3	2	3	1	2	1	3	2	2
Beck et al. [7]	C1	3	3	2	2	1	1	2	3	1	2
Berger [126]; Berger & Farr [127]	B3	2	2	2	3	1	2	1	2	3	1
Berger & Higginbotham [104]	B3	1	2	2	3	1	1	1	3	3	1
Beck et al. [7]; Berger et al. [121]; Berger et al. [123]; Berger et al. [131]; Berger et al. [143]; Moore et al. [136]	B1	4	3	2	3	1	2	1	3	3	2
Bower et al. [166]	C1	3	2	2	1	1	1	2	1	2	2
Colagiuri et al. [144]	B3	4	2	3	1	1	1	2	1	2	2
Costantini et al. [137]	C1	3	2	1	1	1	1	1	1	1	2
Garrett et al. [153]; Merriman et al. [171]	B3	2	3	1	2	2	1	2	3	1	2
Hanprasitkam et al. [165]	C1	3	2	1	1	1	1	1	1	3	1
Kuo et al. [129]	B3	1	2	1	2	1	1	1	3	2	2
Payne et al. [128]	B3	1	2	2	3	2	2	1	2	1	2
Roscoe et al. [147]	B3	2	2	1	3	1	2	1	2	2	2
Savard et al. [172]	B3	2	3	1	3	1	1	1	1	2	2
Stein et al. [148]	C1	2	3	1	1	1	2	1	1	2	1
Vargas et al [133]	C1	4	2	1	1	1	1	2	1	3	2

Abbreviations: LE – Levels of evidence according to the DOHNSF [116].

Notes: #1 Target group size [<50 participants = 1; 50-99 = 2; 100-200 = 3; >200 = 4]; #2 Sample homogeneity [No = 1; Partial = 2 (unclear inclusion or exclusion criteria OR some criteria were stated but not in full); Yes = 3]; #3 Sample representativeness [None = 1; Random recruitment or recruitment at multiple sites OR ethnic/racial consideration = 2; Random recruitment or recruitment at multiple sites AND ethnic/racial consideration = 3]; #4 Study design [Cross-sectional = 1; Prospective (repeated measures within one specific time point) = 2; Longitudinal (repeated measures over different time-points) = 3]; #5 Comparison group [No = 1; Yes = 2]; #6 Response rates and test for bias [No = 1; Partial = 2 (only one of the two parameters was reported); Yes = 3 (both parameters were reported)]; #7 Time since diagnosis/treatment [No = 1; Yes = 2]; #8 Sleep measurement comprehensiveness [Subjective/self-report measures only = 1; Objective measures only = 2; A combination of the two methods = 3]; #9 Psychometric adequacy of measures of correlates [Not applicable = 1 (Demographic/clinical data were used only); No = 1 (instruments never validated in this population and no psychometric properties were reported); Partial = 2 (only part of the instruments were valid for this population OR validated instruments but no psychometric properties reported in this study OR non-validated instruments, but reliability/validity was tested/reported for the specific study only); Yes = 3 (instruments were validated in this population AND reliability/validity was tested/reported for the specific study; OR biological measures were used)]; #10 Sleep as outcome variable [Secondary = 1; Primary = 2]

Table 11-A2. Effect sizes of associations between objectively recorded sleep/wake parameters and sleep-impairing covariates in women receiving neo-/adjuvant chemotherapy for breast cancer.

	Effect sizes *r* (95% CI)													
	Sleep parameter													
Predictor/ correlate	**TST**	**SL**	**% Sleep (night)**	**WASO (minutes)**	**NOCAW (no.)**	**NOCAW (minutes)**	**TTIB (minutes)**	**% WASO**	**% Sleep (day)**	**% Wake (day)**	**EARLAW**	**SE**	**Mins. wake (day)**	**Mins. sleep (day)**
Age	-.35 (-.51, -.17) [7] -.22 (-.42, -.00) [7, 121, 123, 131, 143] .0 [146]		-.28 (-.45, -.10) [7] -.17 (-.37, -.05) [7, 121, 123, 131, 143]	.18 (-.01, .36) [7] .15 (-.06, .36) [7, 121, 123, 131, 143] .0 [146]	.04 (-.15, .24) [7] .11 (-.11, .32) [7, 121, 123, 131, 143]		-.14 (-.34, .08) [7]	.17 (-.05, .37) [7]	.0 [147]				.0 [146]	.0 [146]
Educational level[a]	.0 [7] .0 [7, 121, 123, 131, 143] .0 [146]		.0 [7] .0 [7, 121, 123, 131, 143]	.0 [7] .0 [7, 121, 123, 131, 143] .0 [146]	.0 [7] .0 [7, 121, 123, 131, 143]		.0 [7]	.0 [7]					.0 [146]	.0 [146]
Race[b]	-.17 (-.36, .03) [146]			-.22 (-.40, -.02) [146]									.0 [146]	.0 [146]
Marital status	.0 [146]			.0 [146]									.0 [146]	.0 [146]
Personal income	.0 [146]			.0 [146]									.0 [146]	.0 [146]
PS									-.17 (-.38, .05)* [147]					
BMI	.26 (.06, .44) [146]			.24 (.04, .42) [146]									.0 [146]	.0 [146]
BC stage	.0 [7] .0 [7, 121, 123, 131, 143] .0 [146]		.0 [7] .0 [7, 121, 123, 131, 143]	.0 [7] .0 [7, 121, 123, 131, 143] .0 [146]	.0 [7] .0 [7, 121, 123, 131, 143]		.0 [7]	.0 [7]					.0 [146]	.0 [146]
Breast cancer status[c]	.22 (.06, .36) [153]	.04 (-.11, .20) [153]			-.11 (-.26, .05) [153]	-.13 (-.28, .03) [153]	.15 (-.01, .29) [153]	-.17 (-.32, -.02) [153]	-.01 (-.16, .15) [153]	.01 (-.15, .16) [153]	.17 (.01, .31) [153]	-.18 (-.32, -.02) [153]	.01 (-.15, .16) [153]	-.01 (-.15, .16) [153]
Breast cancer status[d]	.41 (-.26, .81) [128]													
CT regimen[e]					-.10 (-.38, .19) [126, 127]									
Active CThC period[f]	.0 [129]	.0 [129]		.0 [129]								.0 [129]		

	Effect sizes *r* (95% CI)													
	Sleep parameter													
Predictor/ correlate	**TST**	**SL**	**% Sleep (night)**	**WASO (minutes)**	**NOCAW (no.)**	**NOCAW (minutes)**	**TTIB (minutes)**	**% WASO**	**% Sleep (day)**	**% Wake (day)**	**EARLAW**	**SE**	**Mins. wake (day)**	**Mins. sleep (day)**
Type of breast surgery	.0 [146]			.0 [146]									.0 [146]	.0 [146]
Time from surgery (days)					.0 [126, 127]									
Menopausal status[g]	-.16 (-.29, -.03) [7, 121, 123, 131, 143] -.18 (-.40, .06) [125, 145, 146]		-.12 (-.34, .12) [125]	.15 (.02, .28) [7, 121, 123, 131, 143] .15 (-.09, .37) [125, 145, 146]	.11 (-.03, .24) [7, 121, 123, 131, 143] -.23 (-.44, .01) [125]	.33 (.11, .53) [125]						-.14 (-.27, -.01) [7, 121, 123, 131, 143]	.0 [145, 146]	.0 [145, 146]
Cancer-related fatigue	.0 [120, 146] .0 [7, 121, 123, 131, 143]	.0 [7, 121, 123, 131, 143]	.0 [120]	.03 (-.17, .23) [120, 146] .0 [7, 121, 123, 131, 143]	.0 [120] .03 (-.17, .23) [126, 127] .44 (-.12, .78) [104] .0 [7, 121, 123, 131, 143]		.11 (-.13, .33) [104]		.0 [7, 121, 123, 131, 143] .29 (.07, .48) [147]	.0 [7, 121, 123, 131, 143]		.0 [7, 121, 123, 131, 143]	-.03 (-.22, .17) [120, 146] -.15 (-.31, .02) [7, 121, 123, 131, 143]	.0 [120, 146] .0 [7, 121, 123, 131, 143]
Overall mood									.36 (.15, .54) [147]					
Depression									.36 (.14, .54) [147]					
IL-1	.11 (-.16, .37) [145]			.17 (-.11, .42) [145]										-.13 (-.39, .15) [145]
IL-6	-.06 (-.33, .21) [145]			-.12 (-.38, .16) [145]										.19 (-.09, .44) [145]
CRP	-.04 (-.31, .23) [145]			-.40 (-.61, -.15) [145]										.12 (-.16, .38) [145]

Abbreviations: TST – Total sleep time; SL – Sleep latency; WASO – Wakefulness after sleep onset; TTIB – Total time in bed; NOCAW – Nocturnal awakenings; EARLAW – Early morning awakenings; SE – Sleep efficiency; PS – Performance status; BMI – Body mass index; BC – Breast cancer; CT – Chemotherapy; CThC – Chemotherapy cycle; IL-1 – Interleukin 1; IL-6 – Interleukin 6; CRP – C-Reactive protein; CI – Confidence interval

*Karnofsky Performance Status scale

Notes: [a]With and without education beyond high school; [b]Non-Caucasian v. Caucasian; [c]Versus other type of cancer; [d]Versus no cancer diagnosis/healthy controls; [e]Non-doxorubicin v. doxorubicin; [f]Active CThC period (weeks 1-2) v. recovery CThC period (week 3); [g]Pre-/peri-menopausal v. post-menopausal

Table 12-A2. Effect sizes of associations between self-reported sleep/wake parameters and sleep-impairing covariates in women receiving neo-/adjuvant chemo-therapy for breast cancer.

	Effect sizes *r* (95% CI)									
	Sleep parameter									
Predictor/correlate	**TST**	**SL**	**Perceived SQ**	**SDSTRB**	**NOCAW**	**DDYSF**	**WASO**	**HSE**	**SAU**	**Total scale scores**
Age									-.05 (-.18, .08) [136]	.07 (.04, .11)* [144] .0* [146] .0* [148]
Marital status										.01 (-.02, .05)* [144] .0* [148]
Ethnicity/Race[a]										-.01 (-.05, .02)* [144] -.21 (-.39, -.01)* [146] .0* [148]
Education									.0 [136]	.04 (.01, .08)* [144] .22 (-.02, .43)* [148] .0* [146]
Personal income										.08 (.05, .12)* [144] .0* [146] .0* [148]
Employment status[b]										.0* [148]
Children living at home										.01 (-.03, .04)* [144]
BMI										.06 (.02, .09)* [144] .0* [146]
Number of co-morbidities										.05 (.02, .09)* [144]
Alcohol consumption										.02 (-.02, .05)* [144]
Household net wealth/person										.04 (-.00, .07)* [144]
Urbanicity										.00 (-.03, .04)* [144]
Cigarettes/day										.08 (.05, .12)* [144]
Breast cancer status[d]	.01 (-.15, .16)[†] [153]	.19 (.03, .33)[†] [153]	.05 (-.11, .20)[†] [153]	.26 (.10, .39)[†] [153]	.04 (-.12, .19)[†] [153]	.26 (.11, .40)[†] [153]		.0[†] [153]	.04 (-.11, .20)[†] [153]	.21 (.06, .35)[†] [153]
Tumour size										.01 (-.03, .04)* [144]
Tumour grade										.01 (-.03, .05)* [144]

	Effect sizes *r* (95% CI)									
	Sleep parameter									
Predictor/correlate	**TST**	**SL**	**Perceived SQ**	**SDSTRB**	**NOCAW**	**DDYSF**	**WASO**	**HSE**	**SAU**	**Total scale scores**
Disease stage										.0* [146]
Lymph node status[e]										.01 (-.04, .06)* [144]
Oestrogen receptor status[f]										-.01 (-.05, .03)* [144]
Type of surgery[g]										-.03 (-.06, .01)* [144]
Active CThC period[h]	.0[$] [129]	.0[$] [129]	.45 (-.06, .78)[$,i] [129]		.0[$] [129]	.46 (-.04, .78)[$] [129]		.0[$] [129]		.0* [146]
Past sleep quality									.14 (.01, .27) [136]	
Past sleep aid use									.35 (.18, .50) [137]	
Psychiatric history									.16 (-.01, .33) [137]	.08 (.04, .12)* [144]
Psychiatric medication use									.18 (.01, .35) [137]	
Physical activity										.12 (.08, .15)* [144]
Cancer-related fatigue	.0 [120] .0 [7, 121, 123, 131, 143]	.0 [120] .30 (-.28, .72) [104] .25 (.08, .41)* [7, 121, 123, 131, 143]	.21 (.00, .41)* [120] .31 (.15, .46)* [7, 121, 123, 131, 143] .22 (.10, .34)* [133]	.21 (.00, .41)* [120] .28 (.11, .43)* [7, 121, 123, 131, 143]		.21 (.00, .41)* [120] .42 (.27, .55)* [7, 121, 123, 131, 143]	-.14 (-.62, .42) [104]	.0 [120] -.01 (-.53, .53) [104] .0 [7, 121, 123, 131, 143] .0* [133]	.21 (.00, .41) [120] .25 (.08, .41)* [7, 121, 123, 131, 143]	.50 (.33, .63)* [8, 120, 146] .36 (.20, .50)* [7, 121, 123, 131, 143] .34 (.16, .50)* [166] .47 (.34, .58)[§] [165] -.56 (-.87, -.40)[§] [171] .12 (-.01, .24)* [133] .34 (.20, .47)[§] [165]
Nausea & vomiting										
Overall symptom distress						.79 (.48, .92)[$] [129]				
Hot flashes										.19 (-.07, .43)** [172] .17 (-.06, .39)* [148]
Depression										.52 (.33, .67)* [8, 120] .52 (.36, .65)* [166] .36 (.33, .39)* [144] .38 (.24, .51)[§] [165]
Anxiety (trait)										.28 (.24, .31)* [144] .44 (.31, .56)[§] [165]

	Effect sizes *r* (95% CI)									
	Sleep parameter									
Predictor/correlate	**TST**	**SL**	**Perceived SQ**	**SDSTRB**	**NOCAW**	**DDYSF**	**WASO**	**HSE**	**SAU**	**Total scale scores**
Family support										-.44 (-.56, -.31)[§] [165]
Friend support										-.38 (-.51, -.24)[§] [165]
Religious practices (coping)										-.16 (-.31, -.01)[§] [165]
Menopausal status	.16 (-.08, .39) [125]	-.04 (-.27, .19) [125]	-.19 (-.40, .05) [125]	.13 (-.11, .36) [125]		-.22 (-.44, .02) [125]		-.12 (-.35, .12) [125]	.0* [137] -.11 (-.33, .13) [125]	.0* [7, 121, 123, 131, 143] .08 (.04, .12)* [144] -.21 (-.42, .03) [125, 145, 146]
Treated with CT[i]										.23 (.04, .40)* [166] -.03 (-.06, .01)* [144]
IL-1ra										.03 (-.17, .22)* [166] .32 (.05, .54) [145]
IL-6										.35 (.09, .57) [145]
sTNF-RII										.03 (-.17, .22)* [166]
CRP										.03 (-.17, .22)* [166] .17 (-.11, .42) [145]
Haemoglobin										-.14 (-.29, .02)[§] [165]

Abbreviations: TST – Total sleep time; SL – Sleep latency; SQ – Sleep quality; WASO – Wakefulness after sleep onset; SDSTRB – Nocturnal sleep disturbance; NOCAW – Nocturnal awakenings; DDYSF – Daytime sleepiness/dysfunction; HSE – Habitual sleep efficiency; BMI – Body mass index; BC – Breast cancer; CT – Chemotherapy; CThC – Chemotherapy cycle; IL-1ra – IL-1 receptor antagonist; sTNF-RII – soluble TNF receptor type II; IL-6 – Interleukin 6; CRP – C-Reactive protein; CI – Confidence interval
*PSQI; [†]PSQI, GSDS; [§]GSDS; [$]ESS; [ι]Sleep log; **ISI
Notes: [a]Non-Caucasian v. Caucasian; [b]Employed v. not employed; [c]Versus general medical patients; [d]Versus other type of cancer; [e]1-3 v. >3 lymph nodes involved; [f]Positive v. negative; [g]Mastectomy v. lumpectomy; [h]Active CThC period (weeks 1-2) v. recovery CThC period (week 3); [i]Versus other type of treatment

Table 13-A2. Effect sizes of associations between circadian activity parameters and sleep-impairing covariates in women receiving neo-/adjuvant chemotherapy for breast cancer.

	Effect sizes *r* (95% CI)												
	Sleep parameter												
Predictor/correlate	**Sleep bouts (night, *N*)**	**Sleep bouts (night, mins.)**	**Activity bouts (day)**	**Peak activity**	**Mean activity (daytime)**	**Mesor**	**Acrophase**	**24h Auto-correlation**	**Amplitude**	**Circadian quotient**	**Mesor plus amplitude**	**Up/down mesor**	**Goodness of fit**
Age					.0 [147]			.0 [147]					
Performance status				-.07 (-.20, .06)* [7, 121, 123, 131, 143]	.29 (.07, .48) [147]	-.07 (-.20, .06)* [7, 121, 123, 131, 143]	-.07 (-.20, .06)* [7, 121, 123, 131, 143]	.29 (.07, .48) [147] -.07 (-.20, .06) [7, 121, 123, 131, 143]	-.07 (-.20, .06) [7, 121, 123, 131, 143]	-.07 (-.20, .06) [7, 121, 123, 131, 143]			
Body Mass Index				-.22 (-.34, -.09) [7, 121, 123, 131, 143]		-.22 (-.34, -.09) [7, 121, 123, 131, 143]	-.22 (-.34, -.09) [7, 121, 123, 131, 143]	-.22 (-.34, -.09) [7, 121, 123, 131, 143]	-.22 (-.34, -.09) [7, 121, 123, 131, 143]	-.22 (-.34, -.09) [7, 121, 123, 131, 143]			
Disease stage				-.04 (-.17, .10) [7, 121, 123, 131, 143]		-.04 (-.17, .10) [7, 121, 123, 131, 143]	-.04 (-.17, .10) [7, 121, 123, 131, 143]	-.04 (-.17, .10) [7, 121, 123, 131, 143]	-.04 (-.17, .10) [7, 121, 123, 131, 143]	-.04 (-.17, .10) [7, 121, 123, 131, 143]			
Breast cancer status[a]						-.11 (-.26, .05) [153]	.01 (-.14, .17) [153]	-.02 (-.17, .14) [153]	.0 [153]	.12 (-.04, .27) [153]			
CT regimen[b]						-.44 (-.63, -.14) [126, 127]			-.30 (-.54, -.01) [126, 127]		-.45 (-.64, -.13) [126, 127]		
Timing of CT administration[c]						.12 (-.11, .35) [126, 127]			.15 (-.09, .37) [126, 127]		.27 (.04, .47) [126, 127]		
Time from surgery (days)						.0 [126, 127]			.0 [126, 127]		.0 [126, 127]		
Menopausal status[d]	-.25 (-.46, -.02) [125]	-.06 (-.29, .18) [125]											
Cancer-related fatigue	.0 [120]		.0 [7, 121, 123, 131, 143]	-.19 (-.31, -.05) [7, 121, 123, 131, 143]	-.22 (-.42, .00) [147]	-.35 (-.54, -.13) [126, 127] -.53 (-.83, -.00) [104] -.21 (-.33, -.08) [7, 121, 123, 131, 143]	.0 [120] .09 (-.04, .22) [7, 121, 123, 131, 143]	-.27 (-.46, -.05) [147] -.14 (-.26, -.00) [7, 121, 123, 131, 143]	-.14 (-.27, -.01) [7, 121, 123, 131, 143] -.78 (-.86, -.67) [104] -.40 (-.58, -.18) [126, 127]	.05 (-.08, .18) [7, 121, 123, 131, 143]	-.35 (-.54, .13) [126, 127]	.0 [120]	.0 [120]

	Effect sizes *r* (95% CI)												
	Sleep parameter												
Predictor/correlate	**Sleep bouts (night, *N*)**	**Sleep bouts (night, mins.)**	**Activity bouts (day)**	**Peak activity**	**Mean activity (daytime)**	**Mesor**	**Acrophase**	**24h Auto-correlation**	**Amplitude**	**Circadian quotient**	**Mesor plus amplitude**	**Up/down mesor**	**Goodness of fit**
Overall mood					-.26 (-.46, -.04) [147]			-.37 (-.55, -.16) [147]					
Depression				-.17 (-.30, -.04) [7, 121, 123, 131, 143]	-.28 (-.47, -.06) [147]	-.19 (-.31, -.06) [7, 121, 123, 131, 143]	.0 [120] .10 (-.04, .23) [7, 121, 123, 131, 143]	-.29 (-.48, -.07) [147] -.16 (-.29, -.03) [7, 121, 123, 131, 143]	-.13 (-.26, .00) [7, 121, 123, 131, 143]	.03 (-.10, .16) [7, 121, 123, 131, 143]		.0 [120]	.0 [120]
Anxiety				.03 (-.11, .16) [7, 121, 123, 131, 143]		.06 (-.07, .19) [7, 121, 123, 131, 143]	.08 (-.05, .21) [7, 121, 123, 131, 143]	-.01 (-.14, .13) [7, 121, 123, 131, 143]	.03 (-.10, .16) [7, 121, 123, 131, 143]	.05 (-.09, .18) [7, 121, 123, 131, 143]			

Abbreviations: CT – chemotherapy
*Karnofsky Performance Status scale
Notes: [a]Versus other type of cancer; [b]Non-doxorubicin v. doxorubicin; [c]28-day cycle v. 21-day cycle; [d]Pre-/peri-menopausal v. post-menopausal

Table 14-A2. Systematic search results: *sleep/wake patterns in informal caregivers*

	N	***N***
Medline – EMBASE	3,745	
CINAHL	7,942	
Total all databases	11,687	
Duplicates	1,915	
Total papers extracted	9,772	
Papers rejected based on title		9,697
Papers rejected based on abstract		30
Papers obtained in full		45
Papers excluded after review		6
Papers retained		39
Papers extracted through snowballing		5
Papers pooled for objective 1		44
Papers extracted from pool for objective 2		17

Table 15-A2. Systematic search results: *sleep/wake patterns in couples or patient-caregiver dyads*

	N	***N***
Medline – EMBASE	215	
CINAHL	973	
Total all databases	1,188	
Duplicates	74	
Total papers extracted	1,114	
Papers rejected based on title		1,058
Papers rejected based on abstract		22
Papers obtained in full		34
Papers excluded after review		14
Papers retained		20
Papers extracted through snowballing		7
Papers pooled for objective 1		27
Papers extracted from pool for objective 2		10

Table 16-A2. Methodological characteristics of generic self-report sleep measures identified in the literature

Characteristic	AIS [645]	GSDS [646]	ISI [409]	JSPS [647]	LSEQ [648]	MOS-SS [408]	PSQI [407]	SAQ [649]	VSH [650]	WHIIRS [651, 652]
No. of items	8	21	7	4	10	12	19	17	10	5
Domains/components	1	7	1	1	4	6	7	6	1	1
Global score	×	×	×	×		×	×	×	×	×
Test time, min	–	–	≤ 5	–	2-3	≤ 5	5-10	–	–	–
Recall	30 d	7 d	14 d	30 d	Varies 1-30 d	28 d	30 d	30 d	1 d	28 d
Dimensions measured										
Sleep duration	×	×				×	×		×	
Sleep latency	×	×	×	×	×	×	×		×	×
Bed/wake-times							×	×		
Sleep efficiency							×			
Sleep disturbance					×	×	×	×	×	
Daytime dysfunction	×	×	×				×			
Daytime sleepiness	×	×				×	×	×		
Sleep medications		×					×			
Sleep quality	×	×			×		×			×
Daytime napping						×			×	
Sleep depth									×	
Feelings upon arising/ satisfaction			×	×		×		×	×	
Wakefulness after sleep onset					×	×		×		×
Leg restlessness								×		
Early unplanned awakenings	×		×							×

Characteristic	AIS [645]	GSDS [646]	ISI [409]	JSPS [647]	LSEQ [648]	MOS-SS [408]	PSQI [407]	SAQ [649]	VSH [650]	WHIIRS [651, 652]
Nocturnal awakenings	×	×	×	×	×			×	×	×
Snoring						×				
Respiratory problems						×		×		
Concern due to insomnia			×							
Psychometric characteristics										
Reliability (Cronbach's α)	.79-.90	.79-.89	.74-.78	.63-.79	.46-.79	.75-.86	.83	–	.82	–
Stability (test-retest reliability)	× 1 week			×	×		×	×		
Reproducibility	×	×	×			×	×	×		×
Validity	× Criterion; Convergent; Factor structure analysis; Known-groups	–	× Content; Criterion; Convergent	× Convergent; Known-groups	× Content; Known-groups	× Content; Convergent; Divergent; Known-groups; Factor structure analysis	× Content; Factor structure analysis; Convergent; Divergent; Known-groups; Criterion	× Content; Factor structure analysis; Criterion; Convergent; Known-groups	× Convergent; Known-groups	× Factor structure analysis; Known-groups
Acceptability	Good	Good	Good	Good	Fair	Good	Good	Good	Fair	Good
Use in people affected by (breast) cancer										
Patients		×	×			×	×		×	×
Informal caregivers		×					×			

Abbreviations: ASI – Athens Insomnia Scale; GSDS – General Sleep Disturbance Scale; ISI – Insomnia Severity Index; JSPS – Jenkins Sleep Problem Scale; LSEQ – Leeds Sleep Evaluation Questionnaire; MOS-SS – Medical Outcomes Study Sleep Scale; PSQI – Pittsburgh Sleep Quality Index; SAQ – Sleep Assessment Questionnaire; VSH – Verran and Snyder-Halpern Sleep Scale; WHIIRS – Women's Health Initiative Insomnia Rating Scale

Table 17-A2. Methodological characteristics of the four sleep hygiene measures identified in the literature

Measure	Population	Items/ Domains	Scoring & Ease of use	Reliability	Validity
Sleep Hygiene Awareness and Practice Scale [413]	Insomniacs and healthy individuals USA	32 items 2 domains: awareness (13); practices (19)	*Awareness*: 7-point scale (beneficial to sleep 1-3, no effect 4, disruptive to sleep 5-7) *Practices:* 0-7 (days per week engaging in activity) Two subscale scores Recall time frame: no Ease of use: Poor	Internal: awareness α=.78; practices α=.47 Test-retest: unknown	Content: Poor (no clear rationale for item selection) Construct: Poor (overlapping instrument items)
Sleep Hygiene Index [415]	Healthy individuals USA	13 items 1 domain	5-point scale (Frequency of engagement in behaviours: 1= *never* – 5 = *always*) Global score Recall time frame: no Ease of use: Good	Internal: α=.66 Test-retest (5-week interval): r=.71; p<.01	Content: Acceptable (items were derived from the diagnostic criteria for inadequate sleep hygiene in the International Classification of Sleep Disorders) Construct: Moderate (convergent validity established through positive correlations with established criteria for inadequate sleep hygiene (r=.37-.46; p<.01), and self-reports of sleep quality (r=.48; p<.01) and daytime sleepiness (r=.24; p<.01)
Sleep Hygiene Practice Scale [414]	Insomniacs and healthy individuals Taiwan	30 items 4 domains: arousal-related behaviours; sleep scheduling and timing; eating/drinking behaviours; sleep environment	6-point scale (Frequency of engagement in behaviours: 1 = *never* – 6 = *always*) Four subscale scores Recall time frame: no Ease of use: Moderate	Internal: domain 1 – α=.70, .58; domain 2 – α=.82, .74; domain 3 – α=.72, .70; domain 4 – α=.67, .65 (good sleepers and insomniacs, respectively) Test-retest: unknown	Content: Moderate (items were modified from published instruments and general sleep hygiene guidelines of various sources) Construct: Good (exploratory and confirmatory factor analyses to verify factorial structure)
Sleep Hygiene Self-Test [412]	War veterans with post-traumatic sleep disorder USA	30 items 1 domain	Binary data scale (Engagement in behaviours: yes/no) Global score Recall time frame: 1 month Ease of use: Moderate	Internal: α=.54 Test-retest: unknown	Content: Poor (no clear rationale for item selection) Construct: Poor

Table 18-A2. Methodological characteristics of the thirteen measures of coping identified in the literature

Instrument	Items	Dimensions	Theoretical concept of coping	Reliability	Validity	Notes
Brief Approach/ Avoidance Coping Questionnaire [451]	12	▪ General approach/avoidance ▪ Diversion	Dispositional or trait-like	Internal consistency: Cronbach's α – .65-.68 (12 items), .59 (factor 1), .55 (factor 2); Item-to-total correlations – .19-.45 Stability: Unknown	Principal component analysis and confirmatory factor analysis supported in part questionnaire's structure. Weak-to-moderate correlations between the factors and measures of coping, anxiety, depression, intrusive thoughts and beliefs of locus control.	Overlapping factor structure with factor 1 consisting of both approach and avoidance items. Limited availability of data on cancer populations.
Brief COPE scale [457]	28	▪ Active coping; Planning; Positive reframing; Acceptance; Humour; Religion; Using emotional support; Using instrumental support; Self-distraction; Denial; Venting; Substance use; Behavioural disengagement; Self-blame	Dispositional or trait-like	Internal consistency: Cronbach's α – ranging from .50 to .90 for the 14 subscales Stability: 2-3 weeks after primary surgery for breast cancer, ICC ranged from <.0 to 1.0 for the 14 subscales	Item reduction technique from the original COPE inventory – structure approximates the original scale. Unstable factor structure – requires performing factor analytic procedures in every study. Active coping, planning and acceptance discriminated well between women undergone mastectomy versus lumpectomy for breast cancer.	Feasibility of the scale's use with patients with breast cancer confirmed. Researchers free to use all or a sub-set of the items/dimensions. Situational or state-like version also available.
Cancer Coping Questionnaire [456]	21	▪ Total individual scale (4 subscales: coping, positive focus, diversion, planning) ▪ Interpersonal scale	Situational or state-like	Internal consistency: Cronbach's α – .87 (total individual scale), .82 (interpersonal scale) Stability: r=.90 (total individual scale), .84 (interpersonal scale) for a 4-week interval	Principal component analysis confirmed a four-factor structure for the total individual scale; no data available for the interpersonal scale. Able to discriminate between patients with breast cancer and patients attending a psycho-oncology service. The total individual scale was negatively but weakly correlated with measures of depression, but no correlation with measures of anxiety. Positive moderate-to-strong correlations of both dimensions with measures of coping and adjustment to cancer.	Patient-oriented questionnaire – requires vast adaptation to be administered to informal caregivers. Replication of psychometric properties is needed in future studies of people with cancer.
COPE Inventory [449]	60	▪ Emotion-focused (seeking social support; emotional vending emotions) ▪ Problem-solving (active coping,	Dispositional or trait-like	Internal consistency: Cronbach's α – .45-.92 for the 15 subscales; Item-to-total correlations – -.19 to .45	Confirmatory factor analysis supported the full 15-factor model structure. Adequate subscale correlations with measures of optimism, control, self-esteem, hardiness, and	Researchers free to use all or a sub-set of the items/dimensions. Situational or state-like version also available.

Instrument	Items	Dimensions	Theoretical concept of coping	Reliability	Validity	Notes
		planning, suppression, restraint, seeking social support – instrumental) ▪ Dysfunctional coping (behavioural disengagement, mental disengagement, substance use) ▪ Other strategies (positive reinterpretation/growth, denial, acceptance, turning to religion)		Stability: *r* ranged from .42 to .89	anxiety.	The questionnaire's length may increase participant burden.
Coping Inventory for Stressful Situations [453]	48	▪ Task-oriented ▪ Emotion-oriented ▪ Avoidance-oriented (addressing both distraction and social diversion)	Dispositional or trait-like	Internal consistency: Cronbach's α – >.80 for the 3 dimensions. Stability: Good test-retest reliabilities over a 6-week and 12-week interval.	Factor analysis supported the three-coping dimensions structure. Adequate correlations with measures of coping, depression, anxiety, neuroticism, and extraversion.	Limited availability of data on cancer populations.
Coping Responses Indices [455]	32	▪ Cognitive coping strategies ▪ Behavioural coping strategies ▪ Avoidance coping strategies	Situational or trait-like	Internal consistency: Acceptable internal consistency reliabilities have been reported. Stability: unknown	Factor structure has not been established through rigorous testing.	Two scoring procedures may increase participant burden. Limited availability of data on cancer populations. Requires payment for use.
Coping Strategies Inventory [447]	72	*Primary dimensions* ▪ Problem-solving; Cognitive restructuring; Suppressing emotions; Social support; Problem-avoidance; Wishful thinking; Social withdrawal; Self-criticism *Four secondary and two tertiary dimensions*	Dispositional or trait-like	Internal consistency: Cronbach's α – .72-.94 for the 15 dimensions Stability: rho ranged from .67 to .83.	Factor analytic procedures have supported the inventory's structure.	No available data on cancer populations. The questionnaire's length may increase participant burden.
Coping Strategy Indicator [452]	33	▪ Problem-solving ▪ Seeking support ▪ Avoidance	Dispositional or trait-like	Internal consistency: Cronbach's α – .84-.93 for the 3 dimensions Stability: rho ranged from .77 to .86.	Factor analytic procedures have supported the three-scale solution. Fit indices from a confirmatory factor analysis supported the three-factor structure.	Theoretical flaws in the instruments development. Limited availability of data on populations of adults with cancer.

Instrument	Items	Dimensions	Theoretical concept of coping	Reliability	Validity	Notes
					Adequate convergent validity correlations with measures of coping. One unexpected significant correlation between the problem-solving scale and a measure of seeking social support. Appropriate correlations with measures of locus of control and depression.	
Jalowiec Coping Scale – Revised [450]	60	▪ Confrontive; Evasive; Optimistic; Fatalistic; Emotive; Palliative; Supportive; Self-reliant	Dispositional or trait-like	Internal consistency: Cronbach's α – ranged from .48 to .81 (use) and from .48 to .80 (helpfulness) for the 8 dimensions. Stability: unknown	Rigid content analysis based on literature and a panel of experts. Strong correlations between the two different scoring methods (.85-.95), which suggests that they may measure same aspects of coping. Factor analytic studies failed to replicate the proposed eight-factor structure.	Limited availability of data on populations of adults with cancer. The questionnaire's length may increase participant burden.
Life Situations Inventory [454]	28	▪ Problem-solving ▪ Avoidance ▪ Resignation	Situational or state-like	Internal consistency: Cronbach's α – .75-.82 for the 3 dimensions; inter-scale correlations ranged from .01 to .51. Stability: unknown	No supportive validation data have been provided.	Coping strategies regarding a hypothetical rather than real situation are assessed. No available data on cancer populations.
Measure of Daily Coping [448]	55	▪ Distraction; Situation redefinition; Direct action; Catharsis; Acceptance; Social support; Relaxation; Religion	Situational or state-like	Internal consistency: Cronbach's α – .36-.78; inter-scale correlations ranged from -.28 to .18. Stability: unknown	The Catharsis and Acceptance dimensions correlated with measures of perceived control No other supportive validation data have been provided.	No available data on cancer populations. Coping strategies regarding a real situation are assessed. The questionnaire's length may increase participant burden.
Ways of Coping Checklist [445]	68	▪ Problem-focused coping ▪ Emotion-focused coping	Situational or state-like	Internal consistency: Cronbach's α – .80 (problem-focused), .81 (emotion-focused). Stability: unknown	Most factor-analytic studies failed to support the checklist's hypothesised two-factor structure. Limited validation data are available.	No available data on cancer populations. The questionnaire's length may increase participant burden.
Ways of Coping Questionnaire	66	▪ Confrontation coping; Distancing; Self-controlling; Seeking so-	Situational or state-like	Internal consistency: Cronbach's α – ranged from .56 to .85 for the	Several factor-analytic studies failed to replicate the proposed eight-factor structure.	Limited availability of data on populations of adults with cancer.

Instrument	Items	Dimensions	Theoretical concept of coping	Reliability	Validity	Notes
[446]		cial support; Accepting responsibility; Escape-avoidance; Planful problem-solving; Positive reappraisal		8 dimensions; inter-scale correlations ranged from -.04 to .39. Stability: unknown		The questionnaire's length may increase participant burden.

Abbreviations: ICC – Intraclass correlation coefficient

Table 19-A2. Univariate within-patient and within caregiver associations between outcome and demographic/clinical covariates (*n*=48 dyads)

Covariate	Outcome variables: Patients								Covariate	Outcome variables: Caregivers							
	PSQf	DDISTf	NAPTIME	TST	SL	HSE	WASO	GSQI		PSQf	DDISTf	NAPTIME	TST	SL	HSE	WASO	GSQI
AGEPT[a]	–.29**	–.18†	–.17†					–.28**	AGECG[a]	–.24*		.24*		–.21*			–.22*
RELTYPE[b]		.39**	.40**	–.25†				.29*	RELTYPE[b]		.30**						
RELATDUR[a]	–.24*		–.18†		–.18†	.17†		–.25*	RELATDUR[a]	–.28**	–.22*			–.18†			–.28**
CMRBDPT[b]	.43**	.40**	.	–.46**	.40**	–.52***	.39**	.52***	CMRBDCG[b]		.53***						
PSPT[a]	.23†	.38**		–.25*		–.28*	.25*	.29*	PSCG[a]		.29*						
SLPASTPT[b]	.42**	.38**		–.30*	.32*	–.49***	.42**	.54***	SLPASTCG[b]	.59***	.57***		–.25†	.45**	–.52**	.42**	.65**
SLCAPT[b]	.32**			–.26†				.30*	SLCACG[b]	.26†	.31*			.29*	–.35*	.31*	.37**
SLSROOM[b]		–.32*	–.30*						SLSROOM[b]								
SLSHOUS[b]			–.36*						SLSHOUS[b]					–.25†			
									SEXCG[b]			–.31*					
BMIPT[a]		.22*	.26*														
BCSTAGE[a]	–.24*				–.29*				BCSTAGE[a]								
ALCHLPT[a]				–.25*					ALCHLCG[a]					–.20†	.20†		
EDUCPT[b]									EDUCCG[b]						.26†	–.29*	–.25†

Abbreviations: AGEPT/CG – Age; RELTYPE – Dyad's type of relationship; RELATDUR – Dyad's duration of relationship; CMRBDPT/CG – Presence of comorbidities; PSPT/CG – Performance status; SLPASTPT/CG – Past Sleep History; SLCAPT/CG – Sleep Affected by Cancer Diagnosis; SLSROOM – Dyad sleeps in the same bedroom; SLSHOUS – Dyad sleeps in the same house; SEXCG – Caregiver gender; BMIPT – Patient's Body Mass Index; BCSTAGE – Breast cancer stage; ALCHLPT/CG – Alcohol consumption status; EDUCPT/CG – Educational level; PSQf – Perceived Sleep Quality factor from PSQI; DDISTf – Daily Disturbances factor from PSQI; NAPTIME – Daytime napping duration; TST – Total Sleep Time; SL – self-reported Sleep Latency; HSE – self-reported Habitual Sleep Efficiency; WASO – Wakefulness after sleep onset; GSQI – Global Sleep Quality Index score.

Notes: †$p < .10$; *$p < .05$; **$p < .01$; ***$p < .001$; Repeatedly measured outcome variables and covariates were averaged over 4 points of assessment. Sample size for BMIPT was $N = 45$. Blank cells denote non-significant results. Additional covariates tested (no significant results emerged) included: physical activity; patient's menopausal status; employment status; time since diagnosis; time since initial breast surgery; type of breast surgery; type of chemotherapy regimen received; and smoking status.

Table 20-A2. Explanatory MHLMs predicting patient and caregiver perceived sleep quality (PSQf) with own and cross-partner predictor effects

	Own effects				Cross-partner effects			
	Patient		Caregiver		Patient		Caregiver	
	PE (SE)	r_{ES}	PE (SE)	r_{ES}	PE (SE)	r_{ES}	PE (SE)	r_{ES}
Fixed Effects								
Intercept	1.95 (.71)**		1.57 (.26)***		2.20 (.70)**		1.72 (.29)***	
Linear	2.03 (1.09)†		.22 (.27)^{ns}		1.55 (1.08)^{ns}		.37 (.31)^{ns}	
Quadratic	–.66 (.34)†		–.06 (.08)^{ns}		–.60 (.33)†		–.11 (.09)^{ns}	
PHYSPT_M	.05 (.83)^{ns}	.01			–.13 (.78)^{ns}	–.03	1.57 (.55)**	.45
CRACB_M			.05 (.04)^{ns}	.24	–.03 (.04)^{ns}	–.12	.03 (.03)^{ns}	.14
PSYCHPT_M	–.06 (.38)^{ns}	–.03			.00 (.36)^{ns}	.00	.75 (.30)*	.40
PSYCHCG_M			–.26 (.32)^{ns}	–.13	–.18 (.34)^{ns}	–.10	–.38 (.29)^{ns}	–.22
SHPT_M	–.04 (.06)^{ns}	–.11			–.03 (.05)^{ns}	–.09	.00 (.04)^{ns}	.02
SHCG_M			.00 (.03)^{ns}	.01	–.01 (.03)^{ns}	–.07	.02 (.03)^{ns}	.08
COPNEGPT_M	.12 (.08)^{ns}	.24			.16 (.08)*	.37	.14 (.06)*	.37
COPNEGCG_M			.02 (.05)^{ns}	.05	–.10 (.05)†	–.34	.02 (.04)^{ns}	.08
SDSTRBPT_M	.15 (.07)*	.36			.27 (.07)***	.60	.14 (.05)*	.41
SDSTRBCG_M			.09 (.04)*	.37	.02 (.04)^{ns}	.10	.12 (.04)**	.48
SDSTRBPT_TVC	.18 (.04)***	.46			.21 (.04)***	.50	.02 (.03)^{ns}	.07
SDSTRBCG_TVC			.12 (.05)*	.27	–.08 (.05)†	–.19	.12 (.04)**	.30
SHPT_TVC	.04 (.03)^{ns}	.11			.00 (.04)^{ns}	.02	–.02 (.03)^{ns}	–.07
SHCG_TVC			.04 (.02)^{ns}	.15	.02 (.03)^{ns}	.10	.05 (.02)†	.21
PHYSPT_TVC	.53 (.37)^{ns}	.15			.46 (.37)^{ns}	.14	–.11 (.34)^{ns}	–.04
CRACB_TVC			.08 (.03)**	.30	.09 (.03)**	.33	.06 (.03)*	.23
PSYCHPT_TVC	.45 (.21)*	.23			–.30 (.21)^{ns}	–.17	.42 (.18)*	.26
PSYCHCG_TVC			–.04 (.23)^{ns}	–.02	.07 (.23)^{ns}	.03	–.06 (.22)^{ns}	–.03
COPNEGP_TVC	.07 (.04)^{ns}	.17	.		.13 (.05)**	.29	–.03 (.04)^{ns}	–.07
COPNEGC_TVC			–.13 (.05)**	–.28	.10 (.05)†	.22	–.14 (.05)**	–.32
Random Effects								
Residual	.91				.78			
Intercept	.91***		.61**		.88***		.45**	
Linear	1.96***		.51^{ns}		1.94***		.24^{ns}	
Quadratic	.19**		.07^{ns}		.16***		.04^{ns}	
Estim. parameters	73				93			
Deviance statistic	1138.6				1050.7			
$\chi^2(df)$	89.96 (34)***				87.93 (20)***			

Abbreviations: PE – Parameter estimate (coefficient); SE – Standard error; r_{ES} – Effect size *r*; TVC – time-varying covariate; M – time-invariant covariate (average); *df* – Degrees of freedom; PHYSPT – Physical burden (patient); CRACB – Caregiving burden (caregiver); PSYCHPT/CG – Psychological burden (patient/caregiver); SHPT/CG – Sleep hygiene (patient/caregiver); COPNEGPT/CG – Negative coping (patient/caregiver); SDTSRBPT/CG – Nocturnal sleep disturbances (patient/caregiver); PSQf – PSQI Factor 1 indicating Perceived Sleep Quality.

Notes: The "own effects" model was compared with the deviance statistic from the quadratic model. The "cross-partner effects" model was compared with the deviance statistic from the "own effects" model. All models were controlled for demographic/clinical covariates, including SLPAST, SLCA, AGE, RELATDUR, CMRBDT, PS, and BCSTAGE for patients; and SLPAST, SLCA, AGE, and RELATDUR for caregivers; only significant results (or trends towards significance) are shown. Time-varying (TVC) and time-invariant (mean) components of the predictors tested have been coded so that higher numbers reflect poorer/worse outcomes. $^{ns}p > .10$; $^{\dagger}p < .10$; $^{*}p < .05$; $^{**}p < .01$; $^{***}p < .001$.

Table 21-A2. Explanatory MHLMs predicting patient and caregiver daily disturbance (DDISTf) with own and cross-partner predictor effects

	Own effects				Cross-partner effects			
	Patient		Caregiver		Patient		Caregiver	
	PE (SE)	r_{ES}	PE (SE)	r_{ES}	PE (SE)	r_{ES}	PE (SE)	r_{ES}
Fixed Effects								
Intercept	2.18 (.31)***		1.39 (.28)***		1.96 (.32)***		1.43 (.29)***	
Linear	.09 (.16)^{ns}		.17 (.15)^{ns}		.20 (.17)^{ns}		.17 (.16)^{ns}	
PHYSPT_M	.96 (.28)**	.49			1.01 (.28)**	.53	–.02 (.23)^{ns}	–.02
CRACB_M			.04 (.02)*	.34	.01 (.02)^{ns}	.06	.03 (.02)†	.32
PSYCHPT_M	.18 (.16)^{ns}	.19			.33 (.17)†	.33	.08 (.16)^{ns}	.09
PSYCHCG_M			.37 (.15)*	.39	–.04 (.15)^{ns}	–.05	.39 (.15)*	.42
SHPT_M	.04 (.02)^{ns}	.27			.02 (.02)^{ns}	.13	–.02 (.02)^{ns}	–.18
SHCG_M			.01 (.02)^{ns}	.11	.04 (.02)*	.35	.02 (.02)^{ns}	.18
COPNEGPT_M	–.02 (.04)^{ns}	–.10			–.04 (.04)^{ns}	–.18	.01 (.03)^{ns}	.06
COPNEGCG_M			–.01 (.02)^{ns}	–.08	–.01 (.03)^{ns}	–.08	–.02 (.02)^{ns}	–.14
SHPT_TVC	.05 (.02)*	.39			.04 (.02)*	.16	.03 (.02)^{ns}	.11
SHCG_TVC			.04 (.02)**	.40	–.00 (.01)^{ns}	–.02	.04 (.01)**	.20
PHYSPT_TVC	.74 (.19)***	.54			.70 (.18)***	.28	.03 (.18)^{ns}	.01
CRACB_TVC			.05 (.02)**	.42	.03 (.02)^{ns}	.11	.05 (.02)**	.21
PSYCHPT_TVC	.07 (.12)^{ns}	.11			.08 (.11)^{ns}	.05	.06 (.11)^{ns}	.04
PSYCHCG_TVC			.04 (.14)^{ns}	.04	.26 (.14)†	.14	.03 (.14)^{ns}	.02
COPNEGP_TVC	.06 (.03)*	.33	.		.07 (.03)**	.20	–.02 (.03)^{ns}	–.05
COPNEGC_TVC			.01 (.03)^{ns}	.14	–.02 (.03)^{ns}	–.06	.00 (.03)^{ns}	.01
Random Effects								
Residual	.39				.32			
Intercept	.22***		.12**		.24***		.16***	
Linear	.04**		.05***		.05***		.06***	
Estim. parameters	59				75			
Deviance statistic	748.7				686.6			
$\chi^2(df)$	87.26 (16)***				62.14 (16)***			

Abbreviations: PE – Parameter estimate (coefficient); SE – Standard error; r_{ES} – Effect size *r*; TVC – time-varying covariate; M – time-invariant covariate (average); *df* – Degrees of freedom; PHYSPT – Physical burden (patient); CRACB – Caregiving burden (caregiver); PSYCHPT/CG – Psychological burden (patient/caregiver); SHPT/CG – Sleep hygiene (patient/caregiver); COPNEGPT/CG – Negative coping (patient/caregiver); DDISTf – PSQI Factor 3 indicating Daily Disturbances.

Notes: The "own effects" model was compared with the deviance statistic from the linear model. The "cross-partner effects" model was compared with the deviance statistic from the "own effects" model. All models were controlled for demographic/clinical covariates, including SLPAST, SLCA, AGE, RELATDUR, CMRBDT, PS, and BCSTAGE for patients; and SLPAST, SLCA, AGE, and RELATUR for caregivers; only significant results (or trends towards significance) are shown. Time-varying (TVC) and time-invariant (mean) components of the predictors tested have been coded so that higher numbers reflect poorer/worse outcomes. $^{ns}p > .10$; $^{\dagger}p < .10$; $^{*}p < .05$; $^{**}p < .01$; $^{***}p < .001$.

Table 22-A2. Explanatory MHLMs predicting patient and caregiver daytime napping duration (NAPTIME) with own and cross-partner predictor effects

	Own effects				Cross-partner effects			
	Patient		Caregiver		Patient		Caregiver	
	PE (SE)	r_{ES}	PE (SE)	r_{ES}	PE (SE)	r_{ES}	PE (SE)	r_{ES}
Fixed Effects								
Intercept	23.22 (12.22)†		17.68 (12.61)^{ns}		21.82 (11.98)†		27.64 (12.76)†	
Linear	85.91 (24.79)**		10.49 (4.75)*		103.82 (26.98)†		7.90 (5.46)^{ns}	
Quadratic	–26.53 (7.86)**		–2.43 (1.46)^{ns}		–32.83 (9.04)***		–1.76 (1.56)^{ns}	
PHYSPT_M	31.63 (14.63)*	.35			27.56 (15.04)†	.32	2.95 (11.17)^{ns}	.05
CRACB_M			.07 (.74)^{ns}	.02	.26 (.88)^{ns}	.05	.19 (.70)^{ns}	.05
PSYCHPT_M	2.59 (6.87)^{ns}	.06			3.63 (7.36)^{ns}	.09	–13.63 (5.94)*	–.39
PSYCHCG_M			15.94 (6.08)*	.41	6.75 (7.23)^{ns}	.17	15.88 (5.87)*	.44
SHPT_M	2.75 (1.03)*	.42			2.69 (1.11)*	.41	–.38 (.92)^{ns}	–.08
SHCG_M			.05 (.64)^{ns}	.01	–.55 (.78)^{ns}	–.13	–.77 (.66)^{ns}	–.21
COPNEGPT_M	–1.32 (1.56)^{ns}	–.14			–1.55 (1.69)^{ns}	–.17	3.27 (1.41)*	.39
COPNEGCG_M			–1.26 (1.07)^{ns}	–.20	–.58 (1.26)^{ns}	–.09	–1.12 (1.07)^{ns}	–.19
SDSTRBPT_M	–2.68 (1.33)†	–.33			–2.61 (1.41)†	–.33	1.23 (1.06)^{ns}	.21
SDSTRBCG_M			–.58 (.78)^{ns}	–.12	–1.04 (.86)^{ns}	–.22	–.73 (.77)^{ns}	–.17
SDSTRBPT_TVC	.40 (.76)^{ns}	.06			.82 (.84)^{ns}	.11	–.01 (.51)^{ns}	–.00
SDSTRBCG_TVC			1.47 (.67)*	.23	1.25 (.99)^{ns}	.14	1.25 (.64)†	.22
SHPT_TVC	.40 (.70)^{ns}	.06			1.11 (.71)^{ns}	.18	.67 (.49)^{ns}	.15
SHCG_TVC			.38 (.39)^{ns}	.10	.02 (.55)^{ns}	.00	.36 (.38)^{ns}	.11
PHYSPT_TVC	–3.68 (7.40)^{ns}	–.05			–1.19 (7.38)^{ns}	–.02	4.79 (5.08)^{ns}	.11
CRACB_TVC			–.21 (.41)^{ns}	–.06	1.91 (.60)**	.34	–.27 (.40)^{ns}	–.23
PSYCHPT_TVC	11.74 (4.05)**	.30			10.49 (4.30)*	.27	–4.52 (2.71)†	–.19
PSYCHCG_TVC			3.68 (3.29)^{ns}	.12	–8.73 (4.81)†	–.20	3.92 (3.16)^{ns}	.14
COPNEGP_TVC	1.36 (.93)^{ns}	.16	.		1.40 (.96)^{ns}	.16	.18 (.60)^{ns}	.03
COPNEGC_TVC			–.76 (.69)^{ns}	–.12	.42 (1.02)^{ns}	.08	–.72 (.67)^{ns}	–.12
Random Effects								
Residual	208.83				181.90			
Intercept	380.84***		159.28***		309.95***		130.50***	
Linear	2506.37***		371.03^{ns}		2649.11***		388.34^{ns}	
Quadratic	256.70***		32.83^{ns}		300.65***		32.67^{ns}	
Estim. parameters	79				99			
Deviance statistic	3200.5				3057.1			
$\chi^2(df)$	46.72 (20)***				143.43 (20)***			

Abbreviations: PE – Parameter estimate (coefficient); SE – Standard error; r_{ES} – Effect size *r*; TVC – time-varying covariate; M – time-invariant covariate (average); *df* – Degrees of freedom; PHYSPT – Physical burden (patient); CRACB – Caregiving burden (caregiver); PSYCHPT/CG – Psychological burden (patient/caregiver); SHPT/CG – Sleep hygiene (patient/caregiver); COPNEGPT/CG – Negative coping (patient/caregiver); SDTSRBPT/CG – Nocturnal sleep disturbances (patient/caregiver); NAPTIME – Average daytime napping duration.

Notes: The "own effects" model was compared with the deviance statistic from the quadratic model. The "cross-partner effects" model was compared with the deviance statistic from the "own effects" model. All models were controlled for demographic/clinical covariates, including SLSROOM, SLSHOUS, AGE, RELDYAD, RELATDUR, PS, and BMI for patients; and SLSROOM, SLSHOUS, RELDYAD, RELATUR, and SEXCG for caregivers; only significant results (or trends towards significance) are shown. Time-varying (TVC) and time-invariant (mean) components of the predictors tested have been coded so that higher numbers reflect poorer/worse outcomes. $^{ns}p > .10$; $^{\dagger}p < .10$; $^{*}p < .05$; $^{**}p < .01$; $^{***}p < .001$.

Table 23-A2. Explanatory MHLMs predicting patient and caregiver total sleep time (TST) with own and cross-partner predictor effects

	Own effects				Cross-partner effects			
	Patient		Caregiver		Patient		Caregiver	
	PE (SE)	r_{ES}	PE (SE)	r_{ES}	PE (SE)	r_{ES}	PE (SE)	r_{ES}
Fixed Effects								
Intercept	439.70 (22.12)***		413.35 (20.16)***		433.30 (21.74)***		413.59 (19.48)***	
PHYSPT_M	–45.15 (39.86)^{ns}	–.19			–56.47 (35.97)^{ns}	–.27	35.62 (33.99)^{ns}	.17
CRACB_M			–4.02 (2.53)^{ns}	–.24	–3.80 (2.10)†	–.31	–4.73 (2.61)†	–.29
PSYCHPT_M	8.90 (15.63)^{ns}	.09			11.20 (20.83)^{ns}	.10	30.11 (23.10)^{ns}	.22
PSYCHCG_M			35.87 (23.74)^{ns}	.23	29.03 (20.23)^{ns}	.25	40.27 (22.98)†	.28
SHPT_M	2.16 (2.34)^{ns}	.15			1.00 (2.43)^{ns}	.07	–4.81 (2.90)^{ns}	–.27
SHCG_M			2.39 (1.67)^{ns}	.22	.11 (1.58)^{ns}	.01	2.93 (1.41)*	.33
COPNEGPT_M	2.69 (5.21)^{ns}	.09			2.90 (5.96)^{ns}	.09	3.75 (5.47)^{ns}	.12
COPNEGCG_M			–5.04 (5.37)^{ns}	–.15	2.27 (2.76)^{ns}	.15	–6.29 (5.89)^{ns}	–.18
SDSTRBPT_M	–2.98 (2.72)^{ns}	–.18			–2.55 (3.02)^{ns}	–.15	–.03 (2.90)^{ns}	–.00
SDSTRBCG_M			–5.33 (2.86)†	–.28	–3.67 (2.38)^{ns}	–.27	–6.53 (2.61)*	–.39
Random Effects								
Residual	3089.24				3078.59			
Intercept	2360.40***		3522.29***		1969.57***		2835.80***	
Estim. parameters	24				34			
Deviance statistic	3946.4				3931.45			
$\chi^2(df)$	15.95 (10)^{ns}				30.94 (20)†			

Abbreviations: PE – Parameter estimate (coefficient); SE – Standard error; r_{ES} – Effect size *r*; M – time-invariant covariate (average); *df* – Degrees of freedom; PHYSPT – Physical burden (patient); CRACB – Caregiving burden (caregiver); PSYCHPT/CG – Psychological burden (patient/caregiver); SHPT/CG – Sleep hygiene (patient/caregiver); COPNEGPT/CG – Negative coping (patient/caregiver); SDTSRBPT/CG – Nocturnal sleep disturbances (patient/caregiver); TST – Total Sleep Time.

Notes: The "own effects" model was compared with the deviance statistic from the means-only model. The "cross-partner effects" model was compared with the deviance statistic from the "own effects" model. All models were controlled for demographic/clinical covariates, including SLPAST, SLCA, RELDYAD, CMRBDT, PS, and ALCHL for patients; and SLPAST and RELDYAD for caregivers; only significant results (or trends towards significance) are shown. Time-invariant (mean) components of the predictors tested have been coded so that higher numbers reflect poorer/worse outcomes. $^{ns}p > .10$; $^{\dagger}p < .10$; $^{*}p < .05$; $^{**}p < .01$; $^{***}p < .001$.

Table 24-A2. Explanatory MHLMs predicting patient and caregiver sleep latency (SL) with own and cross-partner predictor effects

	Own effects				Cross-partner effects			
	Patient		Caregiver		Patient		Caregiver	
	PE (SE)	r_{ES}	PE (SE)	r_{ES}	PE (SE)	r_{ES}	PE (SE)	r_{ES}
Fixed Effects								
Intercept	27.68 (3.38)***		17.47 (3.13)***		25.93 (3.22)***		18.94 (3.94)***	
Linear	13.05 (7.88)^{ns}	.24	6.47 (6.07)^{ns}	.15	18.30 (7.84)*	.34	5.21 (6.88)^{ns}	.11
Quadratic	–4.75 (2.64)†	–.26	–1.39 (1.55)^{ns}	–.13	–6.64 (2.63)*	–.36	–1.25 (1.77)^{ns}	–.10
SDSTRBPT_TVC	.45 (.41)^{ns}	.12			.62 (.45)^{ns}	.16	.20 (.38)^{ns}	.06
SDSTRBCG_TVC			.34 (.44)^{ns}	.08	1.09 (.69)^{ns}	.18	.33 (.50)^{ns}	.08
SHPT_TVC	.71 (.40)†	.19			.82 (.41)†	.22	–.63 (.55)^{ns}	–.13
SHCG_TVC			–.18 (.31)^{ns}	–.06	.03 (.41)^{ns}	.00	–.07 (.30)^{ns}	–.03
PHYSPT_TVC	2.54 (5.38)^{ns}	.05			2.30 (4.76)^{ns}	.06	3.35 (3.29)^{ns}	.12
CRACB_TVC			.43 (.24)†	.19	.44 (.24)†	.21	.90 (.53)†	.19
PSYCHPT_TVC	–1.15 (3.10)^{ns}	–.04			–.50 (2.94)^{ns}	–.02	5.74 (4.06)^{ns}	.16
PSYCHCG_TVC			5.76 (6.51)^{ns}	.09	–.45 (3.41)^{ns}	–.02	5.30 (5.36)^{ns}	.11
COPNEGP_TVC	–.59 (.55)^{ns}	–.11	.		–.36 (.56)^{ns}	–.07	–.42 (.54)^{ns}	–.13
COPNEGC_TVC			–1.91(1.37)^{ns}	–.15	.44 (.24)^{ns}	.09	–1.88 (1.32)^{ns}	–.16
Random Effects								
Residual	191.23				172.85			
Intercept	170.57*		32.72^{ns}		186.88**		53.61^{ns}	
Linear	93.91*		371.34^{ns}		127.68**		321.26^{ns}	
Quadratic	10.74*		25.66^{ns}		13.52**		20.96^{ns}	
Estim. parameters	46				56			
Deviance statistic	2990.7				2871.8			
$\chi^2(df)$	46.12 (10)*				118.83 (10)***			

Abbreviations: PE – Parameter estimate (coefficient); SE – Standard error; r_{ES} – Effect size *r*; TVC – time-varying covariate; *df* – Degrees of freedom; PHYSPT – Physical burden (patient); CRACB – Caregiving burden (caregiver); PSYCHPT/CG – Psychological burden (patient/caregiver); SHPT/CG – Sleep hygiene (patient/caregiver); COPNEGPT/CG – Negative coping (patient/caregiver); SDTSRBPT/CG – Nocturnal sleep disturbances (patient/caregiver); SL – Sleep Latency.

Notes: The "own effects" model was compared with the deviance statistic from the quadratic model. The "cross-partner effects" model was compared with the deviance statistic from the "own effects" model. All models were controlled for demographic/clinical covariates, including SLPAST, RELATDUR, CMRBDT, and BCSTAGE for patients; no covariates were entered for caregivers due to lack of significant variability; only significant results (or trends towards significance) are shown. Time-varying (TVC) components of the predictors tested have been coded so that higher numbers reflect poorer/worse outcomes. $^{ns}p > .10$; $^{\dagger}p < .10$; $^{*}p < .05$; $^{**}p < .01$; $^{***}p < .001$.

Table 25-A2. Explanatory MHLMs predicting patient and caregiver habitual sleep efficiency (HSE) with own and cross-partner predictor effects

	Own effects				Cross-partner effects			
	Patient		Caregiver		Patient		Caregiver	
	PE (SE)	r_{ES}	PE (SE)	r_{ES}	PE (SE)	r_{ES}	PE (SE)	r_{ES}
Fixed Effects								
Intercept	85.05 (2.28)***		84.65 (2.18)***		86.49 (2.45)***		84.56 (2.42)***	
Linear	–7.81 (2.91)*		–1.88 (1.74)^{ns}		–8.40 (3.91)*		–.20 (2.30)^{ns}	
Quadratic	2.34 (.98)*		.37 (.55)^{ns}		2.48 (1.24)†		–.05 (.66)^{ns}	
PHYSPT_M	–2.70 (5.16)^{ns}	–.08			–2.04 (4.60)^{ns}	–.08	2.62 (4.18)^{ns}	.11
CRACB_M			–.97 (.30)**	–.54	–.51 (.26)†	–.33	–.94 (.27)**	–.52
PSYCHPT_M	2.57 (1.84)^{ns}	.22			2.28 (2.16)^{ns}	.18	2.69 (2.30)^{ns}	.20
PSYCHCG_M			4.51 (2.44)†	.29	–5.09 (2.08)*	–.39	3.75 (2.43)^{ns}	.26
SHPT_M	–.14 (.31)^{ns}	–.07			–.13 (.33)^{ns}	–.07	.32 (.35)^{ns}	.16
SHCG_M			–.63 (.24)*	–.39	.21 (.21)^{ns}	.17	.51 (.24)*	.36
COPNEGPT_M	1.20 (.53)*	.43			.64 (.50)^{ns}	.22	–.09 (.49)^{ns}	–.03
COPNEGCG_M			–.00 (.40)^{ns}	–.00	–.59 (.34)†	–.29	.02 (.38)^{ns}	.01
SDSTRBPT_M	–.69 (.36)†	–.30			–.91 (.39)*	–.38	.01 (.41)^{ns}	.00
SDSTRBCG_M			–.88 (.31)**	–.42	–.19 (.27)^{ns}	–.12	–.88 (.28)**	–.48
SDSTRBPT_TVC	–.86 (.25)***	–.35			–.81 (.26)**	–.33	–.32 (.23)^{ns}	–.16
SDSTRBCG_TVC			–.28 (.37)^{ns}	–.08	–.56 (.32)†	–.20	–.22 (.29)^{ns}	–.09
SHPT_TVC	–.96 (.23)***	–.41			–.94 (.24)***	–.41	–.09 (.22)^{ns}	–.05
SHCG_TVC			–.27 (.18)^{ns}	–.16	–.39 (.18)*	–.24	–.29 (.17)†	–.20
PHYSPT_TVC	–4.61 (2.31)*	–.21			–4.92 (2.46)*	–.22	–1.86 (2.28)^{ns}	–.09
CRACB_TVC			–.20 (.19)^{ns}	–.12	–.37 (.20)†	–.21	–.24 (.18)^{ns}	–.15
PSYCHPT_TVC	1.23 (1.18)^{ns}	.11			1.70 (1.34)^{ns}	.14	1.47 (1.22)^{ns}	.14
PSYCHCG_TVC			–1.38 (1.55)^{ns}	–.10	–.36 (1.58)^{ns}	–.03	–.62 (1.43)^{ns}	–.05
COPNEGP_TVC	.22 (.32)^{ns}	.08			.16 (.30)^{ns}	.06	–.24 (.27)^{ns}	–.10
COPNEGC_TVC			.69 (.43)^{ns}	.17	–.17 (.33)^{ns}	–.06	.79 (.30)*	.29
Random Effects								
Residual	42.72				36.53			
Intercept	22.98**		33.27***		13.02**		33.46***	
Linear	49.84*		20.41^{ns}		74.23**		47.11†	
Quadratic	6.44**		1.96^{ns}		8.63***		4.19†	
Estim. parameters	65				85			
Deviance statistic	2485.4				2356.5			
$\chi^2(df)$	91.06 (20)***				128.94 (20)***			

Abbreviations: PE – Parameter estimate (coefficient); SE – Standard error; r_{ES} – Effect size *r*; TVC – time-varying covariate; M – time-invariant covariate (average); *df* – Degrees of freedom; PHYSPT – Physical burden (patient); CRACB – Caregiving burden (caregiver); PSYCHPT/CG – Psychological burden (patient/caregiver); SHPT/CG – Sleep hygiene (patient/caregiver); COPNEGPT/CG – Negative coping (patient/caregiver); SDTSRBPT/CG – Nocturnal sleep disturbances (patient/caregiver); HSE – Habitual Sleep Efficiency.

Notes: The "own effects" model was compared with the deviance statistic from the quadratic model. The "cross-partner effects" model was compared with the deviance statistic from the "own effects" model. All models were controlled for demographic/clinical covariates, including SLPAST, RELATDUR, CMRBDT, and PS for patients; and SLPAST, SLCA, RELATUR, EDUCCG, and ALCHLCG for caregivers; only significant results (or trends towards significance) are shown. Time-varying (TVC) and time-invariant (mean) components of the predictors tested have been coded so that higher numbers reflect poorer/worse outcomes. $^{ns}p > .10$; $^{\dagger}p < .10$; $^{*}p < .05$; $^{**}p < .01$; $^{***}p < .001$.

Table 26-A2. Explanatory MHLMs predicting patient and caregiver wakefulness after sleep onset (WASO) with own and cross-partner predictor effects

	Own effects				Cross-partner effects			
	Patient		Caregiver		Patient		Caregiver	
	PE (SE)	r_{ES}	PE (SE)	r_{ES}	PE (SE)	r_{ES}	PE (SE)	r_{ES}
Fixed Effects								
Intercept	65.54 (16.18)***		51.42 (10.33)***		52.02 (18.92)*		55.63 (11.62)***	
Linear	25.66 (26.80)^{ns}		3.75 (8.04)^{ns}		31.09 (29.09)^{ns}		–1.66 (10.53)^{ns}	
Quadratic	–10.66 (8.65)^{ns}		–.41 (2.64)^{ns}		–11.99 (9.50)^{ns}		.97 (3.05)^{ns}	
PHYSPT_M	–22.86 (25.64)^{ns}	–.14			–34.08 (27.47)^{ns}	–.21	3.78 (20.43)^{ns}	.03
CRACB_M			3.12 (1.46)*	.33	.29 (1.61)^{ns}	.03	3.48 (1.28)*	.43
PSYCHPT_M	–17.95 (12.41)^{ns}	–.23			–14.99 (12.76)^{ns}	–.20	–6.51 (11.24)^{ns}	–.10
PSYCHCG_M			–9.61 (13.27)^{ns}	–.12	–30.76 (13.48)*	–.37	–3.68 (11.65)^{ns}	–.05
SHPT_M	3.10 (1.71)†	.28			4.26 (1.88)*	.37	.13 (1.48)^{ns}	.02
SHCG_M			2.94 (1.25)*	.36	–.91 (1.33)^{ns}	–.12	–2.52 (1.11)*	–.37
COPNEGPT_M	6.05 (2.75)*	.34			–3.85 (3.03)^{ns}	–.22	.09 (2.47)^{ns}	.01
COPNEGCG_M			–1.55 (1.36)^{ns}	–.18	1.31 (2.43)^{ns}	.09	–2.33 (1.86)^{ns}	–.21
SDSTRBPT_M	4.63 (2.08)*	.34			5.69 (2.36)*	.39	–2.43 (1.99)^{ns}	–.21
SDSTRBCG_M			2.70 (1.18)*	.35	–.98 (1.75)^{ns}	–.10	3.27 (1.32)*	.40
SDSTRBPT_TVC	6.36 (1.70)***	.38			5.68 (1.46)***	.41	1.21 (1.03)^{ns}	.13
SDSTRBCG_TVC			–.84 (1.45)^{ns}	–.06	4.98 (1.83)**	.30	–.84 (1.34)^{ns}	–.07
SHPT_TVC	3.47 (1.48)*	.24			3.17 (1.30)*	.27	.98 (1.01)^{ns}	.11
SHCG_TVC			1.94 (.63)**	.31	3.39 (1.00)**	.36	1.82 (.78)*	.26
PHYSPT_TVC	4.07 (14.50)^{ns}	.03			9.99 (13.31)^{ns}	.09	5.68 (10.48)^{ns}	.06
CRACB_TVC			.23 (.83)^{ns}	.03	–1.13 (1.07)^{ns}	–.12	.19 (.83)^{ns}	.03
PSYCHPT_TVC	–11.79 (8.23)^{ns}	–.15			–13.27 (7.56)†	–.20	–6.95 (5.60)^{ns}	–.14
PSYCHCG_TVC			6.93 (6.35)^{ns}	.12	3.84 (8.74)^{ns}	.05	3.89 (6.54)^{ns}	.06
COPNEGP_TVC	2.19 (1.86)^{ns}	.13	.		1.81 (1.67)^{ns}	.12	.65 (1.22)^{ns}	.06
COPNEGC_TVC			.32 (1.14)^{ns}	.03	3.05 (1.87)^{ns}	.18	.21 (1.40)^{ns}	.02
Random Effects								
Residual	980.3				795.52			
Intercept	2191.07***		501.33**		1649.41***		502.82***	
Linear	3653.22***		681.43^{ns}		5371.62***		892.91*	
Quadratic	366.21***		70.63†		547.12***		86.91**	
Estim. parameters	64				84			
Deviance statistic	3648.1				3475.7			
$\chi^2(df)$	79.02 (20)***				172.38 (20)***			

Abbreviations: PE – Parameter estimate (coefficient); SE – Standard error; r_{ES} – Effect size *r*; TVC – time-varying covariate; M – time-invariant covariate (average); *df* – Degrees of freedom; PHYSPT – Physical burden (patient); CRACB – Caregiving burden (caregiver); PSYCHPT/CG – Psychological burden (patient/caregiver); SHPT/CG – Sleep hygiene (patient/caregiver); COPNEGPT/CG – Negative coping (patient/caregiver); SDTSRBPT/CG – Nocturnal sleep disturbances (patient/caregiver); WASO – Wakefulness after Sleep Onset.

Notes: The "own effects" model was compared with the deviance statistic from the quadratic model. The "cross-partner effects" model was compared with the deviance statistic from the "own effects" model. All models were controlled for demographic/clinical covariates, including SLPAST, CMRBDT, and PS for patients; and SLPAST, SLCA, and EDUC for caregivers; only significant results (or trends towards significance) are shown. Time-varying (TVC) and time-invariant (mean) components of the predictors tested have been coded so that higher numbers reflect poorer/worse outcomes. $^{ns}p > .10$; $^{\dagger}p < .10$; $^{*}p < .05$; $^{**}p < .01$; $^{***}p < .001$.

Table 27-A2. Explanatory MHLMs predicting patient and caregiver overall sleep/wake impairment (GSQI) with own and cross-partner predictor effects

	Own effects				Cross-partner effects			
	Patient		Caregiver		Patient		Caregiver	
	PE (SE)	r_{ES}	PE (SE)	r_{ES}	PE (SE)	r_{ES}	PE (SE)	r_{ES}
Fixed Effects								
Intercept	3.83 (.76)***		4.22 (.57)***		3.56 (.89)**		4.19 (.63)***	
Linear	2.87 (.99)**	.41	.58 (.47)^{ns}	.18	3.21 (1.31)*	.36	.79 (.60)^{ns}	.19
Quadratic	–.96 (.32)**	–.43	–.15 (.13)^{ns}	–.17	–1.02 (.40)*	–.37	–.22 (.17)^{ns}	–.18
PHYSPT_M	3.17 (1.42)*	.34			3.08 (1.40)*	.36	–1.21 (.97)^{ns}	–.21
CRACB_M			.18 (.08)*	.30	.12 (.09)^{ns}	.24	.21 (.07)**	.44
PSYCHPT_M	–.13 (.58)^{ns}	–.04			–.04 (.73)^{ns}	–.01	–.12 (.66)^{ns}	–.03
PSYCHCG_M			–.14 (.62)^{ns}	–.04	–.75 (.68)^{ns}	–.19	–.47(.64)^{ns}	–.12
SHPT_M	–.01 (.10)^{ns}	–.03			–.03 (.11)^{ns}	–.06	–.02 (.09)^{ns}	–.04
SHCG_M			–.06 (.06)^{ns}	–.15	.02 (.07)^{ns}	.05	–.01 (.07)^{ns}	–.03
COPNEGPT_M	.16 (.19)^{ns}	.14			.20 (.16)^{ns}	.21	.01 (.14)^{ns}	.01
COPNEGCG_M			.10 (.11)^{ns}	.14	–.13 (.11)^{ns}	–.20	.05 (.09)^{ns}	.10
SHPT_TVC	.32 (.08)***	.39			.27 (.07)***	.41	–.01 (.06)^{ns}	–.01
SHCG_TVC			.09 (.03)**	.32	–.02 (.05)^{ns}	–.06	.11 (.04)**	.28
PHYSPT_TVC	2.80 (.68)***	.40			2.57 (.63)***	.42	–.19 (.58)^{ns}	–.04
CRACB_TVC			.12 (.05)*	.23	–.07 (.05)^{ns}	–.15	.14 (.05)**	.30
PSYCHPT_TVC	–.12 (.43)^{ns}	–.03			–.08 (.37)^{ns}	–.02	.54 (.33)^{ns}	.18
PSYCHCG_TVC			.51 (.51)^{ns}	.11	.83 (.43)†	.21	.43 (.39)^{ns}	.12
COPNEGP_TVC	.10 (.11)^{ns}	.10	.		.06 (.09)^{ns}	.08	.04 (.08)^{ns}	.06
COPNEGC_TVC			.13 (.09)^{ns}	.14	.18 (.09)*	.22	.13 (.08)^{ns}	.17
Random Effects								
Residual	2.96				2.82			
Intercept	3.50***		4.02***		3.66***		4.19***	
Linear	7.17***		1.45^{ns}		6.40***		1.55^{ns}	
Quadratic	.71***		.08^{ns}		.57***		.09^{ns}	
Estim. parameters	67				83			
Deviance statistic	1581.6				1497.8			
$\chi^2(df)$	80.36 (16)***				83.80 (16)***			

Abbreviations: PE – Parameter estimate (coefficient); SE – Standard error; r_{ES} – Effect size *r*; TVC – time-varying covariate; M – time-invariant covariate (average); *df* – Degrees of freedom; PHYSPT – Physical burden (patient); CRACB – Caregiving burden (caregiver); PSYCHPT/CG – Psychological burden (patient/caregiver); SHPT/CG – Sleep hygiene (patient/caregiver); COPNEGPT/CG – Negative coping (patient/caregiver); GSQI – Global Sleep Quality Index.

Notes: The "own effects" model was compared with the deviance statistic from the quadratic model. The "cross-partner effects" model was compared with the deviance statistic from the "own effects" model. All models were controlled for demographic/clinical covariates, including SLPAST, SLCA, AGE, RELATDUR, CMRBDT, and PS for patients; and SLPAST, SLCA, AGE, RELATDUR, and EDUC for caregivers; only significant results (or trends towards significance) are shown. Time-varying (TVC) and time-invariant (mean) components of the predictors tested have been coded so that higher numbers reflect poorer/worse outcomes. $^{ns}p > .10$; $^{\dagger}p < .10$; $^{*}p < .05$; $^{**}p < .01$; $^{***}p < .001$.

Appendix 3. Literature Review Methods #1

A3.1. Title of Review

A Critical Review of Women's Sleep-Wake Patterns in the Context of Neo-/Adjuvant Chemotherapy for Early-stage Breast Cancer

A3.2. Search Strategy

A defined search strategy used a wide range of key terms and synonyms including the following (example as conducted in Medline):

1. exp Sleep Disorders, Circadian Rhythm/ or exp Sleep/ or exp Sleep Deprivation/ or exp Sleep Disorders/ or exp "Sleep Initiation and Maintenance Disorders"/ or exp Sleep Disorders, Intrinsic/ or sleep.mp.

2. sleep.mp. or insomnia.mp. or sleep disturbance$.mp. or sleep disorder$.mp. or sleeplessness.mp. or sleepiness.mp. or circadian rhythm$.mp. or circadian activity.mp. or sleep efficiency.mp. or quality of sleep.mp. or sleep quality.mp. or daytime disturbance.mp. or nap$.mp. or awakening.mp. or sleep latency.mp. or sleep regulation.mp. or sleep architecture.mp. or sleep physiology.mp. or drowsiness.mp. or homeostatic.mp. or sleep propensity.mp. or WASO.mp.

3. 1 or 2

4. breast cancer.mp. or exp Breast Neoplasms/

5. 3 and 4

A3.3. Search Results and Study Characteristics

Table 6-A2 outlines the flow of papers through the review. Three thousand three hundred and forty five articles were identified through the searches, twenty-one of which reported on twelve studies examining sleep/wake patterns of women with early-stage breast cancer receiving chemotherapy treatment. **S**ummaries of the methodological characteristics of the studies included can be found in Kotronoulas et al. [119] (**Appendix 7**). In cases of more than one article in the context

of one study, relevant information from all articles was included. In cases of secondary analyses of larger research data, the original study is indicated.

Study design and context: Nine of the 21 papers selected reported on secondary analyses [7, 49, 121, 122, 134, 136] from, or were part [8, 9, 125] of, two of the twelve studies identified. The twelve studies included two cross-sectional [120, 133] and nine longitudinal designs [7, 8, 104, 122, 124, 126-131], while an additional one was a retrospective chart review [137]. Of the longitudinal studies, four aimed at testing an intervention to improve sleep using a control group [7, 122, 124, 130, 131]; the remainder were descriptive, exploratory in nature [8, 104, 126-129], with only one study including a comparison group of age-, ethnicity- and menopausal status-matched healthy women [128]. No cross-sectional study included a comparison group. Sample sizes ranged from as low as 11 to as high as 240 participants.

Three studies included mixed samples of women receiving either adjuvant or neo-adjuvant chemotherapy for early-stage breast cancer [8, 9, 120, 125, 137], whereas the remainder specifically focused on adjuvant chemotherapy only. The two cross-sectional studies described sleep within a month prior to the initiation of chemotherapy [120, 121, 133], whereas five studies reported sleep data only during chemotherapy [104, 126-129, 137]. Finally, five studies explored sleep patterns at variable points before, during and even up to one year after chemotherapy for early-stage breast cancer [7-9, 49, 122, 124, 125, 130, 131, 134, 136].

Sample demographic characteristics: In their vast majority, study samples were derived from the American population, whereas only two studies were conducted in a non-American context (Taiwan [129] and Turkey [130]). No European study was retrieved. Study populations in the American studies were predominantly Caucasian (72%-100%). The age of participants across studies ranged from 26 to 83 years, with a grand weighted mean age slightly overreaching 50 years (50.9±1.2 years; range of means 45.0-54.3 years). The majority of women were married or partnered (62%-76%) and employed (60%-78%) at the time of their participation.

Sample clinical characteristics: In accordance to the selection criteria, women had been diagnosed with stage I (28%-50%), stage II (41%-100%), or stage IIIA (8%-32%) breast cancer. Participants had undergone either lumpectomy (44%-79%) or mastectomy (21%-56%). Where women's menopausal status was reported, 24%-63% were pre-menopausal, 9%-76% were post-menopausal, whereas 7%-36% were peri-menopausal. In the majority of studies, women were scheduled to receive three- or four-weekly cycles of anthracycline-based (mainly doxorubicin, but also epirubicin) and/or cyclophosphamide-based regimens, whereas in two studies [8, 122, 131] a sub-group of women received additional cycles of taxane-based regimens.

Sleep measures: Assessment of sleep through self-reports only was conducted in two studies [130, 133], whereas two studies used only objective sleep measures [126-128]. In seven studies (fourteen papers) a combination of subjective and objective sleep measures were used [7-9, 49, 104, 121, 122, 124, 125, 129, 131, 132, 134, 136]. Although polysomnography is considered the gold standard for

assessing sleep architecture [49], no studies were found that used polysomnography for data collection. Instead, wrist actigraphy was used in nine studies to measure sleep and wake time [7-9, 49, 104, 121, 122, 124-129, 131, 132, 134, 136]. Wrist actigraphs were worn for 48-168 hours across studies, although in most of them women wore the devices for 24-48 hours only. On the other hand, the Pittsburgh Sleep Quality Index (PSQI) [407] was the most frequently used self-report measure in the studies reviewed [7, 8, 49, 120-122, 124, 125, 130, 131, 133, 134], assessing quality of sleep over the previous month. The Morin Sleep Diary [409] was used in two studies [104, 124], whereas generic sleep diaries [7, 49, 122, 131, 134, 136] and sleep logs [129] were used in other studies as well. To assess sleepiness, one study [129] used the Epworth Sleepiness Scale (ESS) [404], whereas the Brief Sleep History [653] was used in one study [124] to determine sleep patterns of women before the diagnosis of cancer.

Level of evidence: Based on the DOHNSF evidence categories, two papers [122, 131] reporting on an individual randomised clinical trial were identified (level of evidence B1), whereas two papers [124, 130] reported on two individual experimental/intervention studies (level of evidence B2). Fourteen papers [7-9, 49, 104, 121, 125-129, 134, 136] reporting on seven studies were classified as level of evidence B3 (**Table 5-A2**). Finally, three papers [120, 133, 137] reporting on three studies were classified as level of evidence C1.

Appendix 4. Literature Review Methods #2

A4.1. Title of Review

A Systematic Review of Factors Affecting Sleep/Wake Patterns of Women Living with a Diagnosis of Breast Cancer

A4.2. Background

The aetiology of sleep/wake impairment in women with breast cancer is multidimensional since multiple factors are likely to alter the normal regulatory processes of sleep [4, 59]. Although several universal sleep-impairing factors exist that apply to the general population and patients with any type of cancer and their caregivers [3, 4, 49], a more focused examination is necessary.

Knowledge of the underlying reasons may guide in-depth assessment and targeted treatment of sleep disorders [60], given that care is specifically rather than vaguely focused on the source of the problem, potentially leading to quicker relief and dramatic improvement in sleep quality and sleep-related outcomes.

A4.3. Objectives

The objectives of the present review will be to synthesise and critically analyse evidence regarding contributing factors, or correlates, affecting sleep patterns of women throughout the trajectory of the experience of living with breast cancer, as well as to identify methodological and research gaps in this body of evidence.

A4.4. Review Questions

- What is the evidence for factors affecting sleep patterns of female patients receiving multi-modal treatment for early stage breast cancer?
- What is the evidence for factors affecting sleep patterns of female patients during survivorship (>3 months after the end of treatment) from breast cancer?

- What is the evidence for factors affecting sleep patterns of female patients with locally advanced or metastatic breast cancer?

A4.5. Search Strategy

Deliberately inclusive search terms will be used so that relevant articles are not missed. The search strategy will include the following terms:

1. exp Sleep Disorders, Circadian Rhythm/ or exp Sleep/ or exp Sleep Deprivation/ or exp Sleep Disorders/ or exp "Sleep Initiation and Maintenance Disorders"/ or exp Sleep Disorders, Intrinsic/ or sleep.mp.
2. sleep.mp. or insomnia.mp. or sleep disturbance$.mp. or sleep disorder$.mp. or sleeplessness.mp. or sleepiness.mp. or circadian rhythm$.mp. or circadian activity.mp. or sleep efficiency.mp. or quality of sleep.mp. or sleep quality.mp. or daytime disturbance.mp. or nap$.mp. or awakening.mp. or sleep latency.mp. or sleep regulation.mp. or sleep architecture.mp. or sleep physiology.mp. or drowsiness.mp. or homeostatic.mp. or sleep propensity.mp. or WASO.mp.
3. 1 or 2
4. breast cancer.mp. or exp Breast Neoplasms/
5. 3 and 4
6. Limit 5 to (period January 1990 – March 2012) and (English language) and (Adults) and (Female)
7. Remove duplicates from 6

A4.6. Electronic Bibliographic Databases

Studies will be identified by systematically searching three research and evidence electronic databases, namely Ovid (Medline 1988 – 2012), EMBASE (1980 – 2012), and CINAHL (Inception – 2012).

A4.7. Hand Search

The reference lists of included studies will be searched by hand for any studies that may have been overlooked.

A4.8. Study Selection Criteria

Inclusion Criteria

To be eligible studies should be published in English; employ any research design (cross-sectional/longitudinal surveys, case-control studies, intervention controlled/non-controlled trials etc.), although less weight will be given to intervention studies because their results may have been influenced by the nature of the intervention and their recruited participants may be unrepresentative of the target population; study adult (≥ 18 years of age) female patients with histologically confirmed diagnosis of breast cancer, irrespective of tumour stage or type of treatment; examine sleep as a primary or secondary variable via use of sleep-specific measures, namely polysomnography or actigraphy (objective) and/or validated sleep scales/instruments (subjective); study patients with no other medical co-morbidities; provide measures of statistical associations between sleep patterns and sleep-impairing factors in the target population; be published in the period between January 1990 and March 2012.

Exclusion Criteria

Studies will be excluded from this review if they utilise generic quality of life measures or symptom scales, or single item sleep scales to elicit information about sleep patterns; report on mixed cancer samples, except if separate analyses and associations are reported for groups of patients with breast cancer; are unpublished studies, conference papers, or dissertation abstracts.

A4.9. Outcome measures

Definition of sleep patterns will be based on the previously proposed key parameters for the assessment of sleep in cancer populations [3]. These parameters are total sleep time, sleep latency, nocturnal awakenings, wake time after sleep onset, napping during the day, daytime sleepiness/dysfunction, quality of perceived sleep, stability of circadian rhythms (e.g. mesor, amplitude, peak activity), and sleep efficiency. Data on predictors of sleep aid use and overall scale scores (as indicators of disturbed sleep) will also be recorded.

A4.10. Search Procedure

The lead reviewer will select studies for inclusion in the review. A second reviewer will independently screen a random third of articles for suitability (using a study suitability for the review form).

A4.11. Study Quality Assessment

Methodological quality of each study will be evaluated through use of an adapted version of the 14-item standardised checklist of pre-defined criteria introduced by Mols and colleagues [138]. Adaptation was based on information from previous similar reviews [139, 140]. Areas of concern include a study's research design, sampling and bias, and data collection and measurement. Studies will be defined as "good quality" if they exceed the third quartile of the obtained scores, and as "moderate quality" if they exceed the second quartile. Clarification of the different methodological components will be aided through use of the STROBE statement checklist for reports of observational studies (**Table 7-A2**) [141].

To promote an evidence-type approach, a validated grading hierarchy will also be used to assess the level of evidence presented according to the type of research using the evidence categories employed by the Department of Health in the National Service Frameworks (DOHNSF, 2001) [116] (**Table 6-A2**).

Studies will be appraised for methodological quality by the lead reviewer. A second reviewer will independently appraise a random third of selected studies. Agreement between reviewers will be assessed by calculating percentage agreement and Cohen's kappa statistic for the two appraisal sets. Any discrepancies will be discussed and resolved by consensus.

A4.12. Data Extraction Strategy

General details

Details (study design, method of data collection, outcome measures, correlate measures, participant summary, sample size, response rate, method of analysis) of the studies eligible for the review will be extracted and compiled into tables by the lead researcher and double-checked.

Tables of Outcomes

The lead reviewer will create skeleton tables containing each predictor variable examined in the included studies according to the sleep parameters these predictors were associated with. Skeleton tables will refer to each of the three review questions. The direction and strength of these associations also will be extracted. All data will be extracted and entered into the table by the lead researcher and double-checked.

Notes on Levels of Evidence for Predictors

Findings will be considered consistent if ≥75% of the studies that investigated a predictor showed the same direction of the association. Four levels of evidence for the identified predictors will be used [138], for which definitions are provided below.

Notes on Data Synthesis

Point 1. If variation between the included studies exists, while sufficient detail for the relevant effect sizes to be calculated is absent, the evidence will be synthesised in a narrative review.

Point 2. Effect sizes will be computed as point-biserial correlation coefficients, or r_s [654, 655]. As a rule of thumb, effect sizes less than 0.10 will be considered small, 0.25 will be considered medium, and effect sizes greater than 0.40 will be considered to be large [507, 654].

Point 3. Separate tables containing the effect sizes for each predictor variable will be drawn up by the lead reviewer. Where three or more studies measure predictors in a similar way (same sleep measure and same/similar sleep-correlate measure), a pooled effect size will be calculated for meta-analysis purposes. When both univariate and adjusted associations between the predictors and outcomes are given in a study, the univariate result will be preferred for consistency. Where only adjusted associations are given, these will be included. Where results can be pooled statistically, an inverse variance random-effects model will be used to allow for heterogeneity between studies [654]. Sensitivity analyses will be performed excluding the adjusted associations from the pooled results. Forest plots of effects sizes and confidence intervals will be created in Microsoft Office® Excel [656].

Point 4. Multiple articles published from the same dataset will be combined into a single study to avoid violating the independence of observations assumption [657]. Multiple articles will be combined into a single study be aggregating all effect sizes for a given predictor into a single effect size estimate. Thus, predictors will have only one effect size for a given sleep parameter rather than multiple ones.

Point 5. In studies where multiple follow-ups are examined, a pooled result will be calculated and reported.

Statistical considerations: Effect size with 95% CI: r_s (…, …), if 0 is included then association is non-significant. If a significant relationship along with the direction of the effect were reported, but p is given as <.05, <.01, or <.001, then assume p value as .05, .01 and .001, respectively. If a significant relationship along with direction of the effect were reported, but no inferential statistics were given, then assume p value as .05. If no direction was reported, then exclude effect size. If a non-significant relationship is reported but no statistical information is provided, then assume effect size as 0. If a study provides data on two or more measures of the same predictor, then a combine effect size is to be computed by transforming r into a Fisher Z_r coefficient, average across the Fisher Z_rs, and convert the resulting Z_r back into an r [657]. Similarly, if a study provides data on multiple measurements of the

same relationship (i.e. longitudinal studies), then a combine effect size is to be computed by transforming *r* into a Fisher Z_r coefficient, average across the Fisher $Z_r s$, and convert the resulting Z_r back into an *r*; cells are to be left blank where the predictor was not examined.

A4.14. Search Results and Study Characteristics

Table 8-A2 outlines the flow of papers through the review. Two thousand five hundred and sixty one articles were identified through initial search. After application of selection criteria, 215 articles were retained and retrieved in full-text. Fifty eight articles were finally included in the current review, 26 of which reported on 16 studies examining sleep-impairing factors/covariates in women with early-stage breast cancer receiving chemotherapy treatment. Summaries of the methodological characteristics of the studies included are provided in **Table 9-A2**. In cases of more than one article in the context of one study, relevant information from all articles was extracted. In cases of secondary analyses of larger research data, the original study is indicated.

Study design and context: Ten of the 26 papers selected reported on secondary analyses from, or were part of, three of the 16 studies identified. Eight studies were parts or secondary analyses of larger projects [7, 133, 144, 147, 148, 153, 166, 171, 172]. Fifteen studies employed a prospective design, nine of which involving repeated sleep measurements [7, 8, 104, 120, 121, 123, 125-129, 131, 143, 145-147, 172] and six relying on cross-sectional data [133, 144, 148, 153, 165, 166, 171]. An additional study was a retrospective chart review [137]. Of the longitudinal studies, four aimed at testing an intervention to improve sleep using a control group [7, 121, 123, 131, 143, 147, 172]; the remainder were descriptive, exploratory in nature, with only one study including a comparison group of age-, ethnicity- and menopausal status-matched healthy women [128]. Similarly, only one cross-sectional, case-control study included a comparison group of men with prostate cancer [153, 171]. Sample sizes ranged from as small as 11 to as large as 3002 participants for a total sample of 4,449 participants (median 88 participants).

Five studies included mixed samples of women about to receive, receiving or having received different types of adjuvant treatment [133, 144, 153, 166, 171, 172], where chemotherapy was administered in 45% (range 44%-56%) of the cases. All other studies exclusively focussed on patients receiving neo-/adjuvant chemotherapy for breast cancer. In terms of the timing of sleep assessments, cross-sectional studies focussed on the period after initial surgery but before adjuvant treatment (*N*=1) [133], during chemotherapy (*N*=3) [144, 148, 165], or within 3 months post-chemotherapy completion [153, 166, 171]. Of the longitudinal studies (*N*=9), sleep assessments spanned different periods, yet only four studies collected pre-chemotherapy sleep data [7, 8, 120, 121, 123, 125, 131, 143, 145, 146, 172]. Sleep assessment frequency varied with studies collecting data on two [7, 104, 128, 129, 147], three [126, 127, 172], four [8, 120, 125, 145, 146], or more than four occasions throughout chemotherapy [7, 121, 123, 131, 136, 143]. Only two studies explicitly stated attrition rates of 14.3% and 16.7% [104, 126, 127].

Sample demographic characteristics: In their vast majority, study samples were derived from the American population; only four studies were conducted in a non-American context, namely Denmark [144], Thailand [165], Korea [129], and Canada [172]. Except for two studies where random sampling techniques were involved [7, 121, 123, 131, 143, 144], the studies relied on convenience samples of women with recruitment taking place at medical centres, community clinics and practices, or through published advertisements. Only four studies explicitly stated response rates, reaching 81% (range 63% to 94%) [7, 8, 120, 121, 123, 125-127, 131, 136, 143, 145-147]. Where reported, study populations in the American studies were predominantly Caucasian (82%; range 67.5%-95.3%). Across studies, participant age ranged from 28 to 80 years, with a grand weighted mean age of 53.4 years (weighted SD 1.9 years; range of means 49.5-57.1 years). The majority of women were married/partnered (74%; range 18%-79.2%) and employed at the time of their participation (68%; range 43%-78%).

Sample clinical characteristics: In accordance to the selection criteria, women had been diagnosed with stage I (31%; range 12%-67.2%), stage II (50%; range 24.1%-68%) or stage IIIA (16%; range 8%-32%). Women had undergone either lumpectomy (46%; range 13%-94.8%) or mastectomy (54%; 8.6%-87%). Where women's menopausal status was reported, 38% (range 32%-57%) were pre-menopausal, whereas 57% (range 22%-60%) were post-menopausal. In the majority of studies, women were scheduled to receive, were receiving or received three- or four-weekly cycles of anthracycline-based (mainly doxorubicin, but also epirubicin) and/or cyclophosphamide-based chemotherapy regimens, in some cases complemented by additional cycles of taxanes [120, 136].

Sleep measures: Assessment of sleep through self-reports only was conducted in six studies [133, 144, 148, 165, 166, 172], whereas three studies utilised only objective sleep measures [126-128, 147]. In six studies, a combination of subjective and objective sleep measures were employed [7, 8, 104, 120, 121, 123, 125, 129, 131, 136, 143, 145, 146, 153, 171]. Although polysomnography is considered the gold standard for assessing sleep architecture [49], no studies were found that used polysomnographic recordings for data collection. Instead, wrist actigraphs were used in nine studies to measure sleep and wake time [7, 8, 104, 120, 121, 123, 125-129, 131, 136, 143, 145-147, 153, 171]. Wrist actigraphs were worn continuously for 48 to 96 hours per time-point across studies, although in most of them (*N*=5) women wore the devices for only 48 hours/assessment point. On the other hand, the Pittsburgh Sleep Quality Index (PSQI) was the most frequently used self-report measure in the studies reviewed (67%, *N*=8). Five studies relied upon self-report data collected through use of sleep diaries/logs with or without concurrent use of objective recordings and/or other self-report measures [7, 8, 104, 120, 121, 123, 125, 129, 131, 136, 143, 145, 146, 153, 171]. Only one study included a specific questionnaire to evaluate sleepiness in women during chemotherapy [129].

Predictors/correlates/covariates examined: Six categories were formulated of sleep-impairing covariates examined in the studies identified. Chemotherapy-related (e.g. symptom distress) (75%; *N*=12) and clinical/medical covariates (62.5%; *N*=10) were the factors most frequently evaluated for their sleep-disrupting effects in the studies reviewed. Considerably less frequent investigation of psy-

chological/emotional (31%; *N*=5), demographic (25%; *N*=4) and biological factors (19%; *N*=3) took place in the included studies.

Methodological quality and Level of evidence: **Table 10-A2** outlines marks awarded according to the quality criteria the studies were evaluated against. In general, the reviewed studies were of fair to good methodological standard (median total score 18; range 14-24; possible range 10-27); however, studies differed widely with respect to individual criteria. Based on the DOHNSF evidence categories, one individual randomised controlled trial was identified (level of evidence B1) [7, 121, 123, 131, 136, 143]. Nine studies were classified as level of evidence B3 (**Table 5-A2**), whereas the remainder were classified as level of evidence C1.

Appendix 5. Literature Review Methods #3

A5.1. Title of Review

Sleep/Wake Patterns and Sleep-Impairing Factors of Persons Providing Informal Care for People with Cancer

A5.2. Search strategy

A defined search strategy used a wide range of key terms and synonyms including the following (example as conducted for Medline):

1. exp Sleep Disorders, Circadian Rhythm/ or exp Sleep/ or exp Sleep Deprivation/ or exp Sleep Disorders/ or exp "Sleep Initiation and Maintenance Disorders"/ or exp Sleep Disorders, Intrinsic/ or sleep.mp.

2. sleep.mp. or insomnia.mp. or sleep disturbance$.mp. or sleep disorder$.mp. or sleeplessness.mp. or sleepiness.mp. or circadian rhythm$.mp. or circadian activity.mp. or sleep efficiency.mp. or quality of sleep.mp. or sleep quality.mp. or daytime disturbance.mp. or nap$.mp. or awakening.mp. or sleep latency.mp. or sleep regulation.mp. or sleep architecture.mp. or sleep physiology.mp. or drowsiness.mp. or homeostatic.mp. or sleep propensity.mp. or WASO.mp.

3. 1 or 2

4. caregiver$.mp. or carer$.mp. or caregiving.mp. or partner$.mp. or family member$.mp. or significant other$.mp. or friend$.mp. or exp Caregivers/

5. 3 and 4

A5.2. Search Results and Study Characteristics

Table 13-A2 outlines the flow of papers through the review. Forty-four papers were pooled to meet the overall purpose of the review, seventeen of which reported on eleven studies that specifically examined sleep/wake patterns of informal caregivers of patients with cancer. Summaries of the methodological characteristics of the included studies can be found in Kotronoulas et al. [182] (**Appendix 8**).

In cases of multiple articles in the context of one study, relevant information from all articles was included. In cases of secondary analyses of larger research data, the original study is indicated.

Study design: The ten studies included seven cross-sectional [23, 25, 27, 30, 232, 234, 237-240, 242, 277, 521, 522] and three longitudinal [28, 29, 244] designs. Of the longitudinal studies, one aimed at testing a brief sleep intervention for caregivers of patients with advanced cancer [29], whereas the other two were descriptive exploratory in nature [28, 244]. Gibbins et al.[244] included a group of patients with advanced cancer to compare sleep patterns with their family members. Only one cross-sectional study included comparison groups of caregivers of elders with Alzheimer's and Parkinson's disease, as well as an additional group of persons in non-caregiving roles [234]. In a sub-report, Willette-Murphy et al.[240] used a case-control design to compare sleep patterns of female caregivers of patients with cancer prior to radiotherapy based on their perceived physical activity. Sample sizes ranged widely from as small as 10 to as large as 103 participants.

Sample characteristics and context: In their majority, study samples were derived from the American and Canadian populations; however, four studies were conducted in a non-American context, i.e. Korea [23], Taiwan [30], Turkey [521], and United Kingdom [244]. Study populations in the American, Canadian and European studies were predominantly Caucasian (79%-100%). The age of caregivers across studies ranged from 15 to 86 years, with a grand weighted mean age of 55.4±9.4 years (range of means 41.2-74.0 years). In the majority of studies caregivers were predominantly female (51.5%-100%), married or partnered (83.6%-100%), and employed (35%-61.5%) at the time of their participation. Four papers reporting on two studies specifically focused on female caregivers [25, 232, 239, 240], whereas in the study of Chang et al.[30] caregivers of women with breast cancer were mainly male (82%). All studies aimed at recruiting family members in caregiving roles, except for one study [232], where however, family members accounted for as much as 92% of the total sample. Most frequently caregivers were patients' spouses (44%-100%) or adult children (5%-34%).

Only two studies focused on sleep patterns of caregivers of patients with a specific diagnosis, namely breast [30] and gastric [23] cancer. Two study sub-reports provided evidence in the context of prostate cancer [25, 239]. In all other studies, care recipients had various diagnoses, mainly breast, lung, or prostate cancer, or leukaemia. Six studies included caregivers of patients with advanced cancer [27-29, 232, 237, 238, 244, 277], two studies included caregivers of patients with non-metastatic disease [25, 30, 239, 240, 242, 522], whereas in three studies stage of disease was not stated [23, 234, 521]. In four studies, participants provided care for a person receiving or scheduled to receive anti-cancer treatment, i.e. chemotherapy [23, 30, 521] or radiotherapy [25, 239, 240, 242, 522].

Data with regard to time since patient diagnosis, duration of caregiving since diagnosis, and hours of daily caregiving were rather inconsistently and only partially reported in the studies. In general, caregivers of patients with non-metastatic cancer were mainly approached within the first year after diagnosis, five to nine months on average [25, 30, 239, 240, 242, 522]. On the other hand, Carter et al.[28] reported that time since diagnosis of advanced cancer ranged from 1 month to 6 years, whereas Teel et al.[234] reported a mean time of 3 years. Where reported, duration of caregiving exceeded even

two years in caregivers with advanced cancer [27, 28, 232, 237, 238, 277], whereas hours of caregiving exceeded 14 per day on average [27, 29, 232, 237, 238]. In caregivers of patients receiving chemotherapy, Aslan et al.[521] reported a mean caregiving duration of 5 months.

Sleep measures: Assessment of sleep through self-reports only was conducted in seven [23, 27, 30, 232, 234, 237, 238, 277, 521] studies , whereas the remainder implemented a combination of subjective and objective sleep measures [25, 28, 29, 239, 240, 242, 244, 522]. Of note, two studies utilised semi-structured interviews to complement subjective sleep data [237, 277].

Although polysomnography is considered the gold standard for assessing sleep architecture [49], no studies were found that used polysomnography for data collection. Instead, wrist actigraphy was used in all four studies to measure sleep and wake time of caregivers, where wrist devices were worn for 48 [25, 239, 240, 242, 522], 72 [28, 29], and 168 [244] hours. On the other hand, the Pittsburgh Sleep Quality Index (PSQI) [407] was the most frequently used self-report measure in the studies reviewed [23, 27-30, 232, 238, 240, 242, 521, 522], assessing quality of sleep over the previous month. The General Sleep Disturbance Scale (GSDS) [646] was used in one study [25, 239, 240, 242, 522], whereas the Verran and Snyder-Halpern Sleep Scale (VSH) [650] was used in another [234]. A generic daily sleep diary [244], sleep logs [29], and sleep-related open-ended questions [237, 521] were used in other studies as well. To assess sleepiness and past history of sleep disturbance, one study [244] used the Epworth Sleepiness Scale (ESS) [404] and author-constructed sleep history questions, respectively.

Level of evidence: Based on the DOHNSF evidence categories, one paper [29] reporting on an individual experimental/intervention study was identified (level of evidence B2). Eight papers [25, 28, 234, 239, 240, 242, 244, 522] reporting on four studies were classified as level of evidence B3 (**Table 5-A2**). Finally, eight papers [23, 27, 30, 232, 237, 238, 277, 521] reporting on six studies were classified as level of evidence C1.

Appendix 6. Literature Review Methods #4

A6.1. Title of Review

Sleep/Wake Patterns and Sleep-Impairing Factors in Care Recipient-Informal Caregiver Dyads in the Context of Major Chronic Illnesses

A6.2. Search Strategy

A defined search strategy used a wide range of key terms and synonyms including the following (example as conducted for OVID):

1. exp Sleep Disorders, Circadian Rhythm/ or exp Sleep/ or exp Sleep Deprivation/ or exp Sleep Disorders/ or exp "Sleep Initiation and Maintenance Disorders"/ or exp Sleep Disorders, Intrinsic/ or sleep.mp.

2. sleep.mp. or insomnia.mp. or sleep disturbance$.mp. or sleep disorder$.mp. or sleeplessness.mp. or sleepiness.mp. or circadian rhythm$.mp. or circadian activity.mp. or sleep efficiency.mp. or quality of sleep.mp. or sleep quality.mp. or daytime disturbance.mp. or nap$.mp. or awakening.mp. or sleep latency.mp. or sleep regulation.mp. or sleep architecture.mp. or sleep physiology.mp. or drowsiness.mp. or homeostatic.mp. or sleep propensity.mp. or WASO.mp.

3. 1 or 2

4. caregiver$.mp. or carer$.mp. or caregiving.mp. or partner$.mp. or family member$.mp. or significant other$.mp. or friend$.mp. or exp Caregivers/

5. dyad$.mp. or dyadic approach.mp. or dyadic context.mp. or couples.mp. or interdepend$.mp. or interpersonal.mp. or patient-caregiver interaction$.mp. or patient-caregiver dyad$.mp.

6. 3 and 4 and 5

A6.3. Search Results and Study Characteristics

Table 13-A2 outlines the flow of papers through the review. Twenty-seven papers were pooled to meet the overall purpose of the review, ten of which reported on ten studies meeting additional eligibility criteria specific to concurrent examination of sleep patterns in patient-caregiver dyads. Summar-

ies of the methodological characteristics of the studies included can be found in Kotronoulas et al. [366] (**Appendix 9**).

Study design: The ten studies included five cross-sectional [233, 242, 247, 251, 285] and five prospective designs [244, 278, 363, 367, 368]. Of the prospective studies, one was a prospective case series to evaluate sleep in patient-caregiver dyads before, during, and after periods of institutional dementia respite care [367]. The remainder were descriptive exploratory in nature. Pollak et al.[278] included a control group of 18 dyads of non-demented elders and their caregivers. Only one cross-sectional study included a comparison group of healthy adults [251]. Sample sizes ranged widely from as low as 6 to as high as 153 dyads.

Sample characteristics and context: Seven studies were conducted with patients with a neurodegenerative disease (i.e., dementia [247, 278, 363, 367] or Parkinson's disease [233, 251, 285]) and their informal caregivers, whereas one study included a group of community elders (>65 years) with mixed related co-morbidities [368]. Only two studies included people diagnosed with cancer and their informal caregivers [242, 244].

In their majority, study samples were derived from the American population; however, five studies were conducted in a non-American context, i.e. United Kingdom [244, 367], Germany [233, 251], and Canada [285]. Where stated, patient and caregiver populations were predominantly Caucasian (81%-100% and 67%-100%, respectively). In the studies reviewed, patients had a grand weighted mean age of 69.2±5.9 years (range of means 64.4-80.7 years), whereas caregivers were slightly younger ($\bar{X}$ = 63.8±1.9 years; range of means 61.7-67.4 years). However, in the studies where patients with dementia were assessed mean age exceeded 78 years, whereas it fluctuated around 65 years for patients with cancer or Parkinson's disease. In the majority of studies, patients were predominantly male (65%-78%) and caregivers were predominantly female (63%-100%).

All studies aimed at recruiting family members in caregiving roles, except for one study [242], where however, family members accounted for as much as 93% of the total sample. Caregivers were either patients' spouses/partners (39%-100%) or children (2%-53%). Most frequently patients and caregivers were living together in the same household (54%-100%). However, only four studies explicitly stated percentages (54%-86%) of patients and caregivers sharing the same bedroom [242, 247, 363, 367]. Finally, data pertinent to time since patient diagnosis and to caregiving responsibilities were reported in only a part of the studies, whereas in the studies conducted in the context of cancer no relevant data were provided [242, 244]. In general, people with dementia [247, 363, 367] and Parkinson's disease [233, 285] had been diagnosed at least 4 and 7 years ago on average, respectively.

Sleep measures: Assessment of sleep through self-reports only was conducted in three studies [233, 251, 285], one study was based only objective recordings [363], whereas the remainder implemented a combination of subjective and objective sleep measures [242, 244, 247, 278, 367, 368]. Although polysomnography is considered the gold standard for assessing sleep architecture [49], only one study was found that used polysomnography for collection of 3-day data on caregivers' sleep [247]. Instead,

wrist actigraphy was used in all seven studies to measure sleep and wake time of patients and caregivers, where wrist devices were worn for 48 [242], 72 [247], 168 [244, 363], 144-192 [368], 214 [278], and 1008 [367] consecutive days. On the other hand, the Pittsburgh Sleep Quality Index (PSQI) [407] was the most frequently used self-report measure in the studies reviewed [242, 247, 285, 367], assessing quality of sleep over the previous month. The General Sleep Disturbance Scale (GSDS) [646] was used in one study [242]. One study used an author-constructed General Sleep Questionnaire [285], whereas two studies used questions derived from non-sleep-specific questionnaires [233, 251]. Daily sleep diaries [242, 244, 247] and sleep logs [278, 368] facilitated data collection in other studies as well. To assess sleepiness, three studies [244, 247, 367] used the Epworth Sleepiness Scale (ESS) [404]. Finally, past history of sleep disturbance was examined in one study [244] via author-constructed sleep history questions.

Methodological Quality and Level of evidence: Overall, studies varied in methodological quality: quality scores ranged from 25 to 33 (highest possible 40), with a mean score of 28.4±2.7. On average, reporting of the studies was of a fair to good standard. Research bias, ethical issues, and introduction and aims were the areas receiving the lowest marks. Based on the DOHNSF evidence categories, one paper [367] reporting on an individual intervention study was identified (level of evidence B2). The remainder nine studies [233, 242, 244, 247, 251, 278, 285, 363, 368] were classified as level of evidence B3 (**Table 5-A2**).

Appendix 7. Published Articles

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Review

A critical review of women's sleep–wake patterns in the context of neo-/adjuvant chemotherapy for early-stage breast cancer

Grigorios Kotronoulas [a,*], Yvonne Wengström [a,b], Nora Kearney [a]

[a] School of Nursing & Midwifery, University of Dundee, 11 Airlie Place, Dundee, DD1 4HJ, UK
[b] Division of Nursing, Karolinska Institutet, Huddinge, Sweden

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ABSTRACT

Complaints of poor nocturnal sleep and daytime dysfunction may be frequent among women receiving chemotherapy for breast cancer. A critical review of the literature was conducted, which aimed at summarising and critically analysing findings regarding sleep in women with early-stage breast cancer across neo-/adjuvant chemotherapy treatment. A systematic search of three electronic databases (Medline, CINAHL, EMBASE) was conducted from January 1980 to July 2011. Twenty-one articles reporting on 12 studies were included for analysis based on pre-specified selection criteria. Varying deficits in sleep parameters may be evident in a significant part of this population. Yet, research data are not equally distributed among the different sleep components, or across all major time points throughout chemotherapy. More systematic investigation of the experience of disrupted sleep in this population with longitudinal mixed-methods studies is warranted to ensure that person-tailored and clinically meaningful care is delivered.

Introduction

Empirical data suggest that sleep constitutes an area of functioning that is frequently impaired in women who go through the lived experience of breast cancer.[1–4] The magnitude of the problem has led to an impressive number of studies undertaken to explore in varying methodological ways alterations in sleep patterns of women with breast cancer as a result of both the disease itself and the treatment.[1,3,5–13] Given the improved screening techniques and earlier diagnosis,[14] a significant part of sleep research has been conducted in the context of early-stage breast cancer. Given also the increased frequency of women for whom chemotherapy is recommended to reduce the risk of breast cancer recurrence,[15] much of this research has been focused especially on the impact of adjuvant/neo-adjuvant chemotherapy on sleep.

It can be argued that research in this area has been legitimised as highly significant due to the increased vulnerability of this specific population[4]: the cumulative effect of toxic agents on bodily functions, the physical impact of concurrent, frequent, severe and/or distressing symptoms, the emotional burden of daily disruptions in life, as well as a host of anxieties and depressed mood, may contribute to a spectrum of experienced sleep disruptions even before, but mainly during and following chemotherapy. Moreover, such body and life changes may become especially important for women already susceptible to sleep alterations given the unseen or evidenced impact of breast cancer diagnosis and of primary breast surgery.

Disordered sleep can strongly influence clinical and care-related outcomes,[16] including fatigue,[17–19] performance status,[20] mood,[21] immune function,[22] quality of life,[7,23] and survival.[24–26] In addition, the subjective importance women with breast cancer attribute to sleep problems may have potential consequences for behaviours associated with self-care, help-seeking strategies and reporting of disturbances to the health care team, as well as acceptance and compliance with recommended therapeutic interventions.[27,28] Collectively seen, this reported significance warrants clinical awareness and ongoing assessment, while dictates the need for continuing intervention by the health care team. The aim of this review was to summarise and critically analyse current evidence regarding the sleep patterns of women before, during and after neo-/adjuvant chemotherapy for breast cancer, as well as to discuss in detail methodologic and research gaps in this body of evidence.

Methods

A systematic search was carried out to identify original research studies conducted in the context of early-stage breast cancer, specifically focussing on examination of women's sleep patterns in the context of chemotherapy treatment.

* Corresponding author. Tel.: +44 0 1382 384963; fax: +44 0 1382 388533.
E-mail address: g.kotronoulas@dundee.ac.uk (G. Kotronoulas).

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An electronic search of three research and evidence databases (Medline, CINAHL, EMBASE) was conducted. A defined search strategy was devised using a wide range of key terms and synonyms including the following: *insomnia*, *sleep disturbance*, *sleeplessness*, *sleepiness*, *circadian rhythms*, *sleep efficiency*, *sleep quality*, *daytime disturbance*, *awakenings*, *sleep latency*, *drowsiness*, *wakefulness* and *breast cancer*. The reference lists of retrieved papers were also examined for any studies that may have been overlooked. Reference lists of key topical literature reviews[4,16,29–38] also were examined. Additional literature was sought through use of the search engine Google Scholar.

Studies were eligible in this review if they were written in the English language; were conducted with adult (> 18 years of age) women diagnosed with early-stage (I–IIIA) breast cancer[39]; examined sleep prior to, during and after adjuvant/neo-adjuvant chemotherapy treatment in chemotherapy naïve patients; did not report on patients pre-selected for insomnia or impaired sleep; implemented an exploratory design, although intervention studies were also included if they provided baseline and/or control arm sleep data; examined sleep as a primary or secondary variable via use of sleep-specific measures; and were published as original articles in peer-reviewed journals from January 1980 to July 2011 representing the period in which sleep-specific instruments were developed, and studies of sleep within different clinical populations emerged. Studies using generic quality of life measures or single item tools to elicit information about sleep patterns, unpublished studies, dissertation studies, and conference presentations were excluded.

Study characteristics were extracted using a systematic scheme. Due to heterogeneity of the studies retrieved, findings were only integrated in a narrative synthesis. In order to summarise findings with regard to specific sleep parameters, weighted grand means ($\overline{X}$) and weighted standard deviations were calculated adjusting for different study sample sizes. Moreover, the evidence categories employed by the Department of Health in the National Service Frameworks (DOHNSF, 2001) (cited in Anderson et al., 2004[40]) were used for levelling evidence, and aiding appraisal of quality of the papers reviewed. However, no studies were excluded on the grounds of quality.

Search results and study characteristics

Three thousand three hundred forty-five articles were identified through the searches (Fig. 1), of which twenty-one reported on twelve studies conducted in the context of chemotherapy for early-stage breast cancer (Table 1). In cases of multiple articles in the context of one study, relevant information from all articles was included. Nine of the 21 papers reported on secondary analyses[41–46] from, or were part[47–49] of, two of the twelve studies identified.

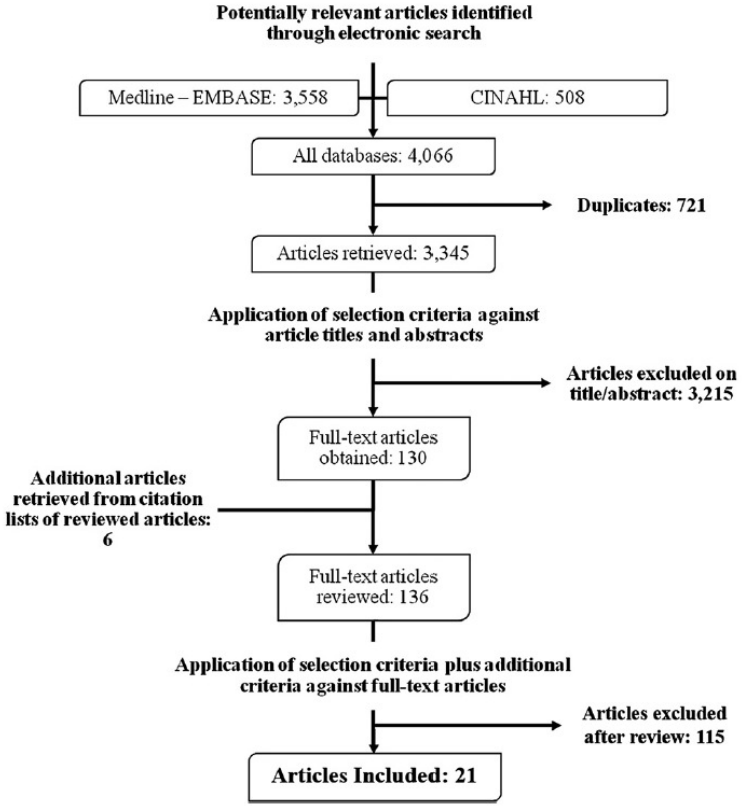

Fig. 1. Flow diagram of the article selection process.

Table 1
Summary of methodological characteristics of the included studies regarding sleep patterns in women with early-stage breast cancer across chemotherapy treatment.

Authors, date & country	Research design	Objective(s)	Sample characteristics	Sleep measures	Limitations	LE
Ancoli-Israel et al., 2006, USA[50]	Descriptive, exploratory Cross-sectional Correlational	To examine sleep, fatigue, and circadian rhythms before the start of adjuvant/neo-adjuvant chemotherapy.	$n = 85$; mean age 51.2 ± 10.0 years (34–79); 74% Caucasian; 67% married; Stage I–IIIA breast cancer: I (33%), II (41%), IIIA (26%); anthracycline-based chemotherapy; 13 neo-adjuvant, 72 adjuvant treatment (36 lumpectomy, 32 mastectomy) Non-probability, convenience, consecutive sampling Response rate: 66.4%	PSQI; FOSQ; continuous 72-h wrist actigraphy [7.3 ± 5.9 days (1–28) before the start of treatment]	No comparison group; mixed treatment sample; lack of information with regard to time since diagnosis or surgery, menopausal status; inadequate sample size for statistical analyses – Type I or Type II errors; no generalisability to diverse racial or ethnic groups; actigraphs were worn for 3 days instead of 5, which is the appropriate time.	C1
Beck et al., 2010, USA[41]	Descriptive Prospective Secondary analysis of two separate RCT datasets	To characterise sleep quality and quantity prior to and in the first three nights after initial adjuvant chemotherapy.	*Study 1*: $n = 108$; mean age 50.5 ± 9.3 years (28–75); 91.1% Caucasian; 79.2% married/partnered; Stage I–IIIA breast cancer: I (21%), II (55%), IIIA (24%); ≥1 month after initial surgery; anthracycline- and/or cyclophosphamide-based treatment; intervention and control group included. *Study 2*: $n = 85$; mean age 51 ± 9.5 years (35–74); 93.9% Caucasian; 72% married/partnered; stage I–IIIA breast cancer: I (37%), II (50%), IIIA (14%); anthracycline-based treatment; control group only included. Non-probability, convenience, consecutive sampling Response rate: Unknown	PSQI: prior to the treatment initiation; Continuous 72-h wrist actigraphy after initial chemotherapy	Not all variables in the two studies could be matched – reduced number of covariates included; limited generalisability to diverse racial or ethnic groups; no analyses of influences of pre-medications, menopausal status, chemotherapy regimens or doses; actigraphs were worn for 3 days instead of 5, which is the appropriate time; actigraphy data from both Study 1 intervention and control groups were considered for analyses.	B3
Berger 1998[52]; Berger & Farr 1999,[53] USA	Descriptive Prospective Repeated measures	To describe the patterns of fatigue and activity and rest, and their relationship during adjuvant chemotherapy To identify indicators involving circadian activity/rest cycles associated with higher levels of fatigue.	$n = 72$; mean age 49.5 ± 8.6 years (33–69); 65% married; 73% employed; Stage I or II breast cancer: I (44%), II (56%); 53% mastectomy; 46% pre-menopausal, 40% post-menopausal; anthracycline- (AC, CAF) and/or cyclophosphamide-based (CMF) treatment Non-probability, convenience, consecutive sampling Response rate: 94% Attrition rate: 16.7% (60 participants completed the study)	Continuous 96-h wrist actigraphy at the time of chemotherapy treatments (Tx1-3); continuous 72-h wrist actigraphy at Tx1, Tx2, and Tx3 mid-points (days 11–17)	Lack of baseline data to compare over-time changes in sleep during chemotherapy; full actigraphy datasets available only for a small subset (17/72 women); no analyses of influences of pre-medications or menopausal status; actigraphs were worn for 3 or 4 days instead of 5, which is the appropriate time.	B3
Berger & Higginbotham 2000,[5] USA	Descriptive Prospective Repeated measures	To examine patterns of and relationships between activity, sleep, symptom distress, health status, and fatigue during and following adjuvant chemotherapy.	$n = 14$; mean age 52.4 (32–69); 71% married; 64% employed; stage I or II breast cancer: I (50%), II (50%); 78% lumpectomy; 57% post-menopausal; AC treatment; 71% concurrent use of tamoxifen citrate Non-probability, convenience, consecutive sampling Response rate: Unknown Attrition rate: 14.3% (12 participants completed the study)	Continuous wrist actigraphy, MSD: 48 h prior to Tx3, continuously during the 21 days of Tx3, 72 h three weeks after Tx4, 72 h two months after Tx4	Lack of baseline data to compare over-time changes in sleep during chemotherapy; incomplete actigraphy datasets; small study sample to allow statistical associations with covariates; effects of menopausal status or tamoxifen use not evaluated.	B3
Berger et al., 2002,[55] USA	Feasibility, quasi-experimental, no control group Prospective Repeated measures	To evaluate the feasibility of an intervention designed to promote sleep and modify fatigue during adjuvant chemotherapy.	$n = 25$; mean age 54.3 ± 6.8 years (40–65); 100% Caucasian; 84% married; 60% employed; stage I or II breast cancer: I (44%), II (56%); 56% mastectomy; 76% post-menopausal; doxorubicin-based treatment Non-probability, convenience, consecutive sampling Response rate: 89% Attrition rate: 12% (22 participants completed the study)	Continuous 216-h wrist actigraphy; adapted MSD: 2 days prior to and during the first 7 days of each of the 4 Tx of treatment PSQI; Brief Sleep History; SHAPS: 2 days prior to initial chemotherapy (baseline)	Missing data from objective and subjective sleep measures; inconsistencies between objective and subjective sleep data; delay in the delivery of the intervention due to recruitment challenges (10 participants); timing of behavioural intervention might have led to lower adherence.	B2

Berger et al., 2007,[42] USA[a]	Descriptive, exploratory Cross-sectional Correlational	To describe values of sleep/wake, activity/rest, circadian activity rhythms, and fatigue, and examine their inter-relations prior to initial adjuvant chemotherapy.	$n = 130$; mean age 51.4 ± 9.7 years (34–83); 91.5% Caucasian; 70% married; 78% employed; stage I–IIIA breast cancer: I (36%), II (48%), IIIA (16%); 54% mastectomy; 53% post-menopausal, 36% pre-menopausal Stratified random sampling Response rate: Unknown	Continuous 48-h wrist actigraphy (2 days before initial chemotherapy); PSQI (day-2 prior to chemotherapy)	No comparison group; lack of information with regard to time since diagnosis or surgery; very low correspondence between subjective and objective sleep measures; full datasets available for 91.4% (night) and 71.5% (day) participants; actigraphs were worn for 2 days instead of 5, which is the appropriate time.	B3
Berger et al., 2009,[54,63] USA[a]	Randomised-controlled intervention trial	To determine the effects of behavioural therapy including stimulus control, sleep restriction, relaxation therapy, and sleep hygiene on sleep quality and fatigue during adjuvant chemotherapy.[54,63]	$n = 219$; mean age 52 years (29–79); 95% Caucasian; 73% married/partnered; 75% employed; stage I–IIIA breast cancer: I (33%), II (53%), IIIA (14%); 56% mastectomy; 56% post-menopausal, 33% pre-menopausal; 20% use of sleep aids; doxorubicin/cyclophoshamide-based treatment ± taxanes. Stratified random sampling Response rate: 69.5% Attrition rate: 8.2% (201 participants until 30 days post-chemotherapy); 21% (173 participants until one year post-chemotherapy)	Continuous wrist actigraphy, daily sleep diary: 48 h prior to initial treatment, 168 h following each treatment (4–8 Tx), and 168 h 30, 60, 90 days, and 1 year after the last treatment; PSQI (day-2 prior to initial treatment)	Baseline values of overall good sleep quality might have created a post-chemotherapy floor effect; lack of true baseline values; lack of participant racial/ethnic diversity; sleep diary recording may have influenced sleep behaviours; delivery of intervention by non-sleep specialists may have contributed to lower dose-response to behavioural therapy.	B1
Berger et al., 2009,[43] USA[a]	Descriptive Prospective Secondary analysis	To examine patterns and differences among sleep and hot flashes based on menopausal status (pre/peri/post) throughout adjuvant chemotherapy.	Total sample characteristics as in Berger et al., 2009.[54,63] Data from $n = 212$ participants were analysed: mean age 52.0 ± 9.8 years (29–79); 95.3% Caucasian; 72.6% married/partnered; breast cancer stage: I (34%), II (53%), IIIA (13%); 55.5% mastectomy; doxorubicin/cyclophoshamide-based treatment (42%) ± taxanes (58%). *Pre-menopausal*: $n = 69$ *Peri-menopausal*: $n = 24$ *Post-menopausal*: $n = 119$	Continuous wrist actigraphy, daily sleep diary: within 48 h prior to initial treatment, 168 h after the Tx4, and 168 h 30 days after the last treatment; PSQI: day −2 prior to initial treatment, day 7 after Tx4, day 1 thirty days after the last treatment	Single-item subjective measures of menopausal status and hot flashes; inability of the actigraphy to obtain a valid measure of sleep latency; lack of information with regard to time since diagnosis or surgery; absence of data on covariates such as anxiety, depression, and stressful life events; small sample size of the peri-menopausal women group; no generalisability to diverse racial or ethnic groups.	B3
Berger et al., 2009,[44] USA[a]	Descriptive Prospective Secondary analysis	To examine patterns of circadian activity rhythms and relationships with fatigue anxiety/depression, demographic/medical variables during adjuvant chemotherapy.	Total sample characteristics as in Berger et al., 2009.[54,63] Data from $n = 190$ participants were analysed; no other data were reported.	Continuous wrist actigraphy, daily sleep diary: within 48 h prior to initial treatment, 168 h after Tx3, and 168 h 30 days after the last treatment; PSQI: day −2 prior to initial treatment, day 7 after Tx3, day 1 thirty days after the last treatment	Lack of comparison data of circadian activity rhythms in healthy midlife women; lack of true baseline values; lack of information with regard to time since diagnosis or surgery; lack of data regarding use of sleep aids; no generalisability to diverse racial or ethnic groups.	B3
Costantini et al., 2011,[59] USA	Retrospective chart review Cross-sectional	To describe the sleep aid prescribing practices of oncologists treating women receiving adjuvant/neo-adjuvant chemotherapy at a single institution.	$n = 124$; mean age 51 years (26–80); 62% married; Stage I–IIIA breast cancer: I (19%), II (47%), III (32%); AC dose dense (65%), AC q21 days (35%); 11% neo-adjuvant, 89% adjuvant treatment; 23% psychiatric diagnoses; 26% psychiatric medications; 14% prior sleep aid use.	–	No generalisability to diverse racial or ethnic groups, or to other clinical centres; possibility of missing data due to sleep problems never recorded, or use of sleep aids never reported by the women; mixed treatment sample.	C1
Demiralp et al., 2010,[56] Turkey	Quasi-experimental with control group Prospective Repeated measures	To investigate the effect of progressive muscle relaxation training on sleep quality and fatigue during adjuvant chemotherapy.	$n = 27$; age range 25–65; no other data were reported, but no differences were found between the intervention ($n = 14$) and control ($n = 13$) group. Non-probability, convenience, consecutive sampling Response rate: Unknown Attrition rate: Unknown	PSQI (recall time frame: 1 month): before initial treatment, day 7 after Tx1, day 1 after Tx3, day 6 after Tx4	Small sample size; no generalisability to diverse racial or ethnic groups; possible bias as women were assigned to intervention or control groups; use of subjective sleep measures only – responses might have been influenced by participation in the intervention group rather than actual effects of the intervention.	B2

(*continued on next page*)

Table 1 (*continued*)

Authors, date & country	Research design	Objective(s)	Sample characteristics	Sleep measures	Limitations	LE
Kuo et al., 2006,[57] Taiwan	Descriptive Prospective Repeated measures	To explore the quality of sleep and related factors during adjuvant chemotherapy.	$n = 16$; mean age 45 years (29–59); 75% married; 56% employed; 62.5% pre-menopausal; breast cancer stage I or II; cyclophosphamide-based treatment: CEF (44%), CMF (56%%) Non-probability, convenience, consecutive sampling Response rate: Unknown	Continuous 48-h wrist actigraphy; IFMHN Sleep Log (Chinese version); ESS: days 8 and 9 after Tx3, days 20 and 21 after Tx3	Inadequate sample size for statistical analyses – Type I or Type II errors; no generalisability to diverse racial or ethnic groups; lack of information with regard to time since diagnosis or surgery; lack of data regarding use of sleep aids; lack of pre-treatment sleep data; actigraphs were worn for 2 days instead of 5, which is the appropriate time.	B3
Liu et al., 2009,[47] USA[b]	Descriptive Prospective Repeated measures	To combine pre-treatment sleep disturbances, fatigue and depression into one cluster, and explore associations between pre-treatment cluster categories and longitudinal profiles of these symptoms during adjuvant/neo-adjuvant treatment.	$n = 76$; mean age 51.1 ± 9.1 (34–79) years; 72.4% Caucasian; 68.4% married; stage I–III breast cancer: I (33%), II (49%), III (18%); 45% post-menopausal, 40% pre-menopausal; doxorubicin-based treatment: AC + fluorouracil/taxanes (95%), CEF (5%) Non-probability, convenience, consecutive sampling Response rate: 83.3% (enrolled 95: dropped after enrolment 6, baseline data unavailable 13) Attrition rate: Unknown	PSQI (recall time frame: 1 month): before initial treatment (within 1 week), during each week of the 3 weeks of Tx1, during each week of the 3 weeks of Tx4	Small sample size of the SCI 0 and SCI 3 groups; no generalisability to diverse racial or ethnic groups; lack of information with regard to time since diagnosis or surgery.	B3
Moore et al., 2011,[45] USA[a]	Descriptive Prospective Secondary analysis	To determine the frequency of sleep aid use, and the characteristics of participants taking sleep aids during adjuvant chemotherapy.	Total sample characteristics as in Berger et al., 2009.[54,63] Data from $n = 219$ participants were analysed	Adapted MSD: 2 days before and 7 days after each Tx, 7 days 30, 60, and 90 days after the last Tx, and one year after Tx1.	Possible missing or inaccurate data: data collection was based on participants' entries on the sleep diary; possibly biased results due to patient participation in a clinical trial to improve sleep, which might have created floor effects.	B3
Payne et al., 2006,[58] USA	Descriptive, correlational Prospective Repeated measures Pilot study	To evaluate over-time changes in fatigue, sleep disturbances, and depressive symptoms, and serum cortisol, melatonin, serotonin, and bilirubin during adjuvant compared to a healthy comparison group ($n = 11$) that was matched by age, ethnicity, and menopausal status, and to determine whether any correlations exist between the subjective parameters and biomarkers in the subjects studied.	$n = 11$; mean age 47.4 ± 10.4 years; 18% married; 45% pre-menopausal, 36% peri-menopausal; 100% stage II breast cancer; 55% mastectomy; doxorubicin-based treatment: AC q3weeks; 27% use of sleeping pills Non-probability, convenience, consecutive sampling Response rate: 91.7% Attrition rate: Unknown	Continuous 72-h wrist actigraphy: days −1 to +2 during Tx1 and Tx4; Self-reports on sleep disturbances obtained from the demographic form, and the PFS.	Inadequate sample size for correlation analyses – Type I or Type II errors; lack of information with regard to time since diagnosis or surgery; actigraphs were worn for 3 days instead of 5, which is the appropriate time; no generalisability to diverse racial or ethnic groups.	B3

Rissling et al., 2010,[48] USA[b]	Descriptive Prospective	To examine sleep quality and mood according to menopausal status (pre-pre; pre/peri–peri; post–post) prior to treatment and at the end of four Tx of adjuvant/neo-adjuvant chemotherapy.	$n = 69$ *Pre-pre group*: $n = 12$; mean age 41.6 ± 1.3 (34–49) years; 58% Caucasian; 58% married; stage I–III breast cancer: I (25%), II (50%), III (17%); anthracycline-based chemotherapy. *Pre/peri-peri group*: $n = 21$; mean age 45.6 ± 1.5 (34–61) years; 76% Caucasian; 86% married; stage I–III breast cancer: I (24%), II (57%), III (19%); anthracycline-based chemotherapy. *Post–post group*: $n = 36$; mean age 57.9 ± 1.3 (43–79) years; 78% Caucasian; 56% married; stage I–III breast cancer: I (31%), II (36%), III (25%); anthracycline-based chemotherapy. Non-probability, convenience, consecutive sampling Response rate: 83.3% (enrolled 95: dropped after enrolment 6, dropped from analysis 20) Attrition rate: Unknown	Continuous 72-h wrist actigraphy: before initial treatment, during each week of the 3 weeks of Tx1, during each week of the 3 weeks of Tx4 PSQI (recall time frame: 1 month): before initial treatment (within 1 week), during each week of the 3 weeks of Tx1, during each week of the 3 weeks of Tx4	Lack of non-cancer comparison group; small pre-menopausal group; uneven group sizes; no follow-up after Tx4; no measure of important covariates such as pain; lack of objective measurement of menopausal status; lack of information with regard to time since diagnosis or surgery; actigraphs were worn for 3 days instead of 5, which is the appropriate time; no generalisability to diverse racial or ethnic groups.	B3
Savard et al., 2009,[49] USA[b]	Descriptive Prospective Repeated measures	To assess the longitudinal course of sleep–wake activity rhythms before and during adjuvant/neo-adjuvant chemotherapy	$n = 95$; mean age 50.7 ± 9.7 (34–79) years; 69.2% married; 94% employed; stage I–III breast cancer: I (29%), II (49%), III (21%); 49% post-menopausal, 43% pre-menopausal; 48% mastectomy; 89% adjuvant chemotherapy; doxorubicin-based treatment: AC ± fluorouracil/taxanes (91%); 27% prior use of hormone replacement therapy Non-probability, convenience, consecutive sampling Response rate: 83.3% Attrition rate: Unknown	Continuous 72-h wrist actigraphy: before initial treatment, during each week of the 3 weeks of Tx1, during each week of the 3 weeks of Tx4	Absence of sleep measurements at Tx2 and Tx3 renders development of chronic sleep impairments unclear; heterogeneity of chemotherapy regimens received; mixed treatment sample; lack of information with regard to time since diagnosis or surgery; actigraphs were worn for 3 days instead of 5, which is the appropriate time; no generalisability to diverse racial or ethnic groups.	B3
Vargas et al., 2009,[51] USA	Descriptive, exploratory, correlational Cross-sectional Part of a larger clinical trial	To determine the frequency of sleep disturbances prior to adjuvant treatment, and whether greater sleep dysfunction uniquely predicts poorer functional outcomes.	$n = 240$; mean age 50.3 ± 9.0 years; 68% Caucasian; 63% married; 75% employed; stage –III breast cancer: 0 (16%), I (38%), II (38%), III (8%); 43% post-menopausal, 45% pre-menopausal; 51% lumpectomy; 18% prescribed sleep medication, 25% pain medication, 18% anti-anxiety medication; mean time from surgery 40.1 ± 22.7 days Non-probability, convenience, consecutive sampling Response rate: Unknown Attrition rate: Unknown	PSQI (recall time frame: 1 month): before initial treatment.	Only subjective sleep measures were used: self-report and recall biases; no information on sleep habits prior to enrolment; unclear whether sufficient variance was achieved to allow possible associations to emerge; direction of causality was not established; no generalisability to diverse racial or ethnic groups.	C1
Wielgus et al., 2009,[46] USA[a]	Descriptive, exploratory Secondary analysis	To identify the predictors of fatigue 30 days after completing adjuvant chemotherapy.	Total sample characteristics as in Berger et al., 2009.[54,63] Data from $n = 96$ participants were analysed: mean age 50.7 ± 10.3 years (29-83); 95% Caucasian; 72% married/partnered; 73% employed; stage I–IIIA breast cancer: I (8%), II (69%), IIIA (23%); 60% mastectomy; doxorubicin/cyclophoshamide-based treatment followed by taxane.	Continuous wrist actigraphy: within 48 h before, and during the peak (days 2–4) and rebound (days 5–7) after initial treatment, and 168 h 30 days after the last treatment; Daily sleep diary: 2 days before, and during the peak (2 days) and rebound (2 days) after initial treatment, and for 7 days 30 days after the last treatment; PSQI: day −2 prior to initial treatment, day 1 thirty days after the last treatment	Inadequate sample size for regression analyses, problems with multicolinearity; lack of information with regard to time since diagnosis or surgery; other covariates such as pain were not examined; no generalisability to diverse racial or ethnic groups.	B3

Abbreviations: LE: Level of Evidence based on the DOHNSF framework; PSQI: Pittsburgh Sleep Quality Index; SHAPS: Sleep Hygiene Awareness and Practice Scale; FOSQ: Functional Outcomes of Sleepiness Questionnaire; MSD: Morin Sleep Diary; IFMHN: International Foundation for Mental Health and Neurosciences; Tx; chemotherapy cycle; AC: doxorubicin plus cyclophosphamide; CEF: cyclophosphamide, epirubicin, 5-fluorouracil; CMF: cyclophosphamide, methotrexate, 5-fluorouracil; ESS: Epworth Sleepiness Scale; PFS: Piper Fatigue Scale.

[a] All reports are based on the same project.

Study design and context

The twelve studies included two cross-sectional[50,51], nine longitudinal designs,[5,41,47,52–58] and one retrospective chart review.[59] Of the longitudinal studies, four aimed at testing an intervention to improve sleep using a control group[41,54–56]; the remainder were descriptive, exploratory in nature,[5,47,52,53,57,58] with only one study including a comparison group of age-, ethnicity- and menopausal status-matched healthy women.[58] No cross-sectional study included a comparison group. Sample sizes ranged from as low as 11 to as high as 240 participants.

Three studies included mixed samples of women receiving adjuvant or neo-adjuvant chemotherapy,[47–50,59] whereas the remainder specifically focused on adjuvant chemotherapy only. The two cross-sectional studies described sleep quality within a month prior to the initiation of chemotherapy,[42,50,51] whereas five studies explored sleep patterns only during treatment.[5,52,53,57–59] Finally, five studies examined sleep at variable points before, during and even up to one year after chemotherapy.[41,43–49,54–56]

Sample demographic and clinical characteristics

With the exception of two studies,[56,57] samples were derived from the American population. No European study was retrieved. Study populations in the American studies were predominantly Caucasian (72–100%). The age of participants across studies ranged from 26 to 83 years, with a grand weighted mean age of 51 years (50.9 ± 1.2 years; range of means 45.0–54.3 years). The majority of women were married or partnered (62–76%) and employed (60–78%) at the time of their participation.

Study participants had been diagnosed with stage I (28–50%), stage II (41–100%), or stage IIIA (8–32%) breast cancer, and had undergone either lumpectomy (44–79%) or mastectomy (21–56%). Where women's menopausal status was reported, 24–63% were pre-menopausal, 9–76% were post-menopausal, whereas 7–36% were peri-menopausal. In the majority of studies, women were scheduled to receive three- or four-weekly chemotherapy cycles (Tx) of anthracycline-based (mainly doxorubicin, but also epirubicin) and/or cyclophosphamide-based regimens, whereas in two studies[47,54] a sub-group of women received additional Tx of taxane-based regimens.

Sleep measures

In most studies a combination of subjective and objective sleep measures were used.[5,41,42,44–50,54,55,57] Yet, assessment of sleep through self-reports only was conducted in two studies,[51,56] whereas two studies used only objective sleep measures.[52,53,58] Although polysomnography is considered the gold standard for assessing sleep architecture,[30] no studies were found that used polysomnography for data collection. Instead, wrist actigraphy was used in nine studies to objectively measure sleep and wakefulness.[5,41,42,44–50,52–55,57,58] Wrist actigraphs were worn for 48–168 h across studies, although in most of them women wore the devices for 24–48 h only. On the other hand, the Pittsburgh Sleep Quality Index (PSQI)[60] was the most frequently used self-report measure in the studies reviewed,[41,42,44,46–48,50,51,54–56] assessing quality of sleep over the previous month (see Table 2 for further information on the scale).

Analysis of evidence with regard to sleep

The selected studies were summarised and analysed to provide evidence with regard to the overall incidence of sleep-related problems, as well as to the nine proposed key sleep parameters for patients with cancer[30,31] (Table 2). Data pertinent to perceived sleep disturbances and use of sleep aids also were summarised into respective categories.

Overall incidence of sleep-related problems

At varying time points prior to chemotherapy – mainly 48–72 h,[42,43,49,54,55] but also within 1 week–1 month,[47,48,50] pre-treatment incidence rates of sleep problems ranged from 57% to 71%[41,42,47,51] when using an established cut-off score of 5.0 on the PSQI, and from 26%[42] to >50%[51,55] when using the suggested adjusted cut-off score of 8.0 for patients with cancer[61].

During adjuvant chemotherapy,[62] Tx1[5,41,43,44,47,49,52,53,58] (initial reaction to treatment), Tx3[44,55,57] and Tx4[43,47,49,54,56] (peak of cumulative discomfort[58]) were selected as key mid-points in the studies reviewed. However, incidence rates of sleep problems were never reported. The period after initial chemotherapy, i.e., first 2 days–2 weeks, was characterised by sleep fragmentation that disrupted maintenance of habitual sleep patterns.[41,52,53,58] As well, during Tx3 and Tx4, severity of sleep disruptions increased compared with pretreatment.[47]

Purposeful assessment of women's sleep patterns soon after (mainly within the following 30–60 days) the last Tx was infrequently included as a clinical endpoint in the studies reviewed.[5,43,44,54,63] The *end* of chemotherapy might denote normalisation of sleep and rest patterns for some women; yet, for others non-restorative nocturnal sleep and daytime sleepiness may persist. The ongoing sleep disruptions evidenced suggest that sleep alterations can become chronic,[29] especially if additional adjuvant treatment modalities are recommended.

Sleep quality

Throughout the course of chemotherapy, subjective sleep was reported as generally and consistently poor in the studies reviewed.[41–43,47,48,50,51,54–57] At varying time points after initial breast surgery, but within 30 days prior to the initiation of chemotherapy treatment, global PSQI sleep quality scores ranged between 6.58 and 8.80 ($\overline{X} = 7.46$).[41,42,48,50,51,54–56] Within the first week after initial treatment, sleep was similarly poor, and further deteriorated following Tx3.[56,57] By Tx4, a further, yet slight, deterioration in global sleep quality scores was evident.[43,48,54,56] Interestingly, a trend of poorer sleep during the first two weeks with slight improvements over the third week following Tx3 and Tx4 was reported.[47,57] However, whether this was a clinically significant finding it was not explored. Thirty days to one year after the end of four Tx of anthracycline-based chemotherapy regimens with or without four additional taxane Tx, overall sleep quality scores showed only minimal over-time improvements in women receiving control healthy eating information.[43,54] Of note, perceived sleep quality was found to fluctuate between fairly good to fairly poor throughout treatment. However, only partial or no significant over-time relationships between distinct time points exist,[54,56,63] which could suggest that fluctuations in perceived sleep quality are subtle rather than marked, and ratings of greater sleep disruption may be associated with temporal adverse events during a period of consistently poor quality of sleep.

Sleep efficiency

Despite several other disruptions, sleep efficiency might remain within normal range for the majority of women and across almost all phases of chemotherapy. Predominantly within the first week prior to chemotherapy initiation sleep efficiency was found to be at or above the normal cut-off value of 85%, with a weighted grand

Table 2
Sleep parameters of women receiving chemotherapy for early-stage breast cancer.

Sleep parameter	Definition[31,34,42,44,49,60,70–73]	Sleep measure	Pre-treatment	Tx1	Tx2	Tx3	Tx4	Post-treatment[a]
Sleep Quality	Multidimensional perceptions of length and depth of sleep and feelings of being rested upon awakening.	PSQI[b] global score (0–21)	7.46 ± 0.76*,[1]	6.81 ± 2.66†,[2]	–	7.03 ± 2.55†,[3]	7.54 ± 0.14*,[4]	6.88 ± 3.22†,[5] 7.16 ± 3.37†,[6] 6.39 ± 3.60†,[7]
		PSQI perceived sleep quality (0–3)	1.19 ± 0.24*,[8]	1.30 ± 0.63†,[2]	–	1.38 ± 0.76†,[3]	1.24 ± 0.18*,[9]	–
Sleep Efficiency	Number of minutes of sleep divided by the total number of minutes in bed, multiplied by 100. In adults, 95% sleep efficiency indicates a good night's sleep; less than 80% indicates a bad night's sleep.	Actigraphy-based (%)	85.2 ± 5.7*,[10]	87.3 ± 2.4*,[11]	88.3 ± 1.2*,[12]	86.4 ± 2.6*,[13]	81.8 ± 8.9*,[14]	87.8 ± 9.7†,[5] 84.6 ± 1.4*,[15] 88.0 ± 10.5†,[6] 88.0 ± 11.0†,[7]
		PSQI sleep efficiency (0–3)	0.76 ± 0.18*,[16]	0.81 ± 0.17†,[2]	–	0.87 ± 0.14†,[3]	1.09 ± 0.15*,[17]	–
		Sleep diary-based (%)	89.0 ± 0.1†,[18]	85.0 ± 0.1†,[19]	87.0 ± 0.1†,[19]	89.8 ± 2.6*,[20]	88.0 ± 0.1†,[19]	92.0 ± 0.1†,[5] 92.0 ± 0.1†,[15] 91.0 ± 0.1†,[6] 91.0 ± 0.1†,[7]
Total Nocturnal Sleep Time	Number of minutes of sleep while in bed. Adults normally attempt to sleep 420–540 min in 24 h.	Actigraphy-based (minutes)	392.4 ± 18.1*,[21]	422.1 ± 32.9*,[22]	449.7 ± 74.3†,[19]	435.2 ± 28.4*,[23]	420.9 ± 42.1*,[24]	418.9 ± 64.1†,[5] 406.1 ± 85.4†,[25] 418.4 ± 70.0†,[6] 415.0 ± 70.4†,[7]
		PSQI total sleep time (0–3)	0.89 ± 0.12*,[26]	0.53 ± 0.77†,[2]	–	0.53 ± 0.77†,[3]	0.80 ± 0.03*,[17]	–
		Sleep diary-based (minutes)	428.8†,[18]	425.6 ± 80.2†,[19]	444.1 ± 79.7†,[19]	445.9 ± 0.3*,[20]	452.8 ± 83.3†,[19]	461.5 ± 14.3†,[27] 459.8 ± 71.5†,[25] 441.7 ± 70.2†,[6] 436.5 ± 47.1†,[7]
Sleep-Onset Latency	Number of minutes between when someone lays down to bed and actually goes to sleep. Normally, less than 20 min in adults.	Actigraphy-based (minutes)	11.4 ± 17.9†,[28]	–	15.6 ± 9.0†,[29]	20.5 ± 4.2*,[30]	25.8 ± 24.8†,[31]	26.2 ± 20.4†,[32]
		PSQI sleep latency (0–3)	1.15 ± 0.19*,[8]	1.53 ± 0.66†,[2]	–	2.00 ± 1.00†,[3]	1.07 ± 0.52*,[17]	–
		Sleep diary-based (minutes)	–	–	–	35.1 ± 30.5†,[33] 23.1 ± 18.3†,[34]	–	–
Nocturnal Awakenings	Number of awakenings during a sleep period. Adults normally awaken 2–6 times during a typical night's sleep of 420 min.	Actigraphy-based (number)	19.8 ± 21.0*,[35]	21.8 ± 18.1*,[36] 27.2 ± 16.0†,[37]	20.5 ± 15.7*,[36] 19.9 ± 18.1*,[38]	19.8 ± 14.6*,[39] 22.7 ± 7.8*,[38]	15.8 ± 8.3*,[40]	10.6 ± 4.2†,[5] 10.8 ± 1.0*,[41] 10.8 ± 5.2†,[6] 10.7 ± 5.3†,[7]
		Sleep diarybased (number)	2.3†,[18]	2.5 ± 1.3†,[19]	2.2 ± 1.1†,[19]	2.1 ± 0.1*,[42]	2.2 ± 1.2†,[19]	1.9 ± 1.1†,[5] 1.8 ± 1.1†,[25] 1.9 ± 1.1†,[6] 1.9 ± 1.0†,[7]
Wake After Sleep Onset (WASO)	Number of minutes awake or percentage of time awake after sleep onset during the sleep period. Adult WASO time normally is less than 10% of the total sleep duration if the person sleeps 420 min during the night.	Actigraphy-based (minutes)	77.4 ± 33.0*,[43]	74.2 ± 63.1†,[19] 76.5 ± 56.3†,[44] 63.5 ± 50.9†,[44] 67.2 ± 66.3†,[44]	61.0 ± 8.6†,[19] 33.9 ± 22.0†,[29]	62.9 ± 2.2*,[45] 48.4 ± 0.9*,[46] 46.3 ± 15.2*,[47]	90.6 ± 45.5*,[40]	59.0 ± 42.1†,[48] 75.3 ± 1.4*,[15] 56.3 ± 47.1†,[6] 56.8 ± 54.3†,[7]
		Actigraphy-based (%)	17.5 ± 6.9*,[49]	14.9 ± 10.7†,[44] 12.0 ± 10.7†,[44] 12.3 ± 13.1†,[44]	–	–	–	–
		Sleep diary-based (minutes)	32.6†,[18]	49.9 ± 43.4†,[19]	39.5 ± 38.2†,[19]	34.3 ± 30.4†,[19]	39.2 ± 39.2†,[19]	26.1 ± 23.4†,[48] 24.8 ± 22.9†,[25] 24.1 ± 20.6†,[6] 31.5 ± 48.3†,[7]

(continued on next page)

Table 2 (*continued*)

Sleep parameter	Definition[31,34,42,44,49,60,70–73]	Sleep measure	Pre-treatment	Tx1	Tx2	Tx3	Tx4	Post-treatment[a]
Daytime Napping	Total number of minutes of sleep during the daytime; can be intentional or unintentional sleep. Adult napping normally can vary from 5 min to 2 h.	Actigraphy-based (minutes)	64.8 ± 12*,[49]	–	66.9 ± 53.2†,[50]	135.8 ± 74.0†,[51] 107.9 ± 91.5†,[52]	–	–
		Actigraphy-based (%)	8.0 ± 1.0*,[49]	10.6 ± 7.1†,[53]	–	–	–	–
		Sleep diary-based (minutes)	–	–	17.1 ± 28.5†,[54]	34.5 ± 26.7†,[51] 17.6 ± 20.6†,[52]	–	–
Daytime Sleepiness/ Dysfunction	Episodes of lapses into sleep of short duration, usually in situations in which the person is inactive for even brief periods; excessive daytime sleepiness can result from acute or chronic sleep deprivation or loss or other pathophysiologic causes. Adults normally have a minimal chance of dozing while engaged in routine activities.	PSQI daytime dysfunction (0–3)	0.82 ± 0.18*,[55]	1,07 ± 0.86†,[2]	–	0.84 ± 0.80†,[3]	0.98 ± 0.28*,[56]	–
		ESS[c] (>6 slight sleepiness)	–	–	–	6.0 ± 3.5†,[33] 4.3 ± 3.6†,[34]	–	–
Circadian rhythms	Mesor: 24-h adjusted mean of the activity counts; half-way between minimum and maximum activity; higher values represent a more robust activity; mean activity level.	Actigraphy-based	132.3 ± 24.6†,[57]	105.8 ± 22*,[58] 119.2 ± 21.5†,[59] sig. ↓ from baseline†,[60]	103.6 ± 17.7†,[61] 111.5 ± 4.7*,[62]	102.9 ± 3.2*,[63] 110.1 ± 1.5*,[64]	117.6 ± 26.1†,[65] sig. ↓↓↓ from baseline & Tx1†,[66]	129.9 ± 23.3†,[67] 114.0 ± 22.8†,[32]
	Amplitude: peak-to-nadir difference (peak minus the mesor) the height of the rhythm; represents the rhythmic change of an individual's activity during a 24-h period; lower values suggest a dampened circadian rhythm.	Actigraphy-based	97.2 ± 22.8†,[57]	79.9 ± 2.0*,[58] 93.3 ± 13.9†,[59] sig. ↓ from baseline†,[60]	82.6 ± 18.1†,[61] 92.9 ± 1.8*,[62]	79.1 ± 1.8*,[63] 86.6 ± 3.2*,[64]	91.4 ± 26.4†,[65] sig. ↓↓↓ from baseline & Tx1†,[68]	99.0 ± 22.2†,[67] 88.5 ± 26.2†,[32]
	Acrophase: actual clock time of the peak amplitude; a later time suggests more phase delay.	Actigraphy-based (time)	14:40†,[69] 12:59†,[57] ~14:45†,[70]	14:33†,[71] ns ↓ from baseline†,[72]	–	14:35†,[71]	ns ↓ from baseline†,[68]	14:38†,[67]
	Up-mesor: time of day when an individual switches from low to high activity, i.e., from below the mesor to above the mesor; higher values suggest a later starting time of activity; the time an individual "gets going" in the morning.	Actigraphy-based (time)	07:13†,[69] ~07:00†,[70]	sig. ↑ from baseline†,[73]	–	–	sig. ↑ from baseline & Tx1†,[68]	–
	Down-mesor: time of day when an individual switches from high to low activity, i.e., from above the mesor to below the mesor; higher values suggest a later time of decline of activity; the time an individual "settles down" for the evening.	Actigraphy-based (time)	22:20†,[69] ~22:20†,[70]	sig. ↓ from baseline†,[60]	–	–	sig. ↓ from baseline & Tx1†,[74]	–
	Peak activity: sum of the mesor and amplitude values; index of maximum activity for a 24-h period; favourable because it represents more robust circadian rhythms.	Actigraphy-based	188.4 ± 35.9†,[57]	185.1 ± 6.2*,[75] 231.2 ± 48.2†,[59]	192.8 ± 57.2†,[61] 211.6 ± 33.6†,[59]	181.6 ± 2.3*,[58] 205.6 ± 42.3†,[59]	–	228.9 ± 42.6†,[67]
	24-h autocorrelation: internal correlation of the regularity and consistency of the rhythm from one day to the next; high autocorrelation at or near 24-h indicates a robust/stable circadian rhythm.	Actigraphy-based	–	0.37 ± 0.04*,[76]	–	0.35 ± 0.13†,[71]	–	0.48 ± 0.15†,[67]
	Circadian quotient: determined by dividing the amplitude by the mesor; Strength of the circadian rhythm; higher values represent an assessment of degree of activity/sleep consolidation throughout the day.	Actigraphy-based	–	0.73 ± 0.13†,[71]	–	0.74 ± 0.13†,[71]	–	0.76 ± 0.11†,[67]
	Goodness of fit: measure of how well the data fits into the 24-h circadian pattern; indicates that the circadian rhythm accounts for a % of the variability in an individual's activity; higher values suggest a more robust rhythm.	Actigraphy-based	0.61 ± 0.11†,[57] 688†,[69] ~0.45†,[70]	sig. ↓ from baseline†,[60]	–	–	sig. ↓ from baseline & Tx1†,[68]	–
Perceived Sleep Disturbances	Perceived factors interfering with nocturnal sleep, including nighttime awakenings, early morning wake, need to use the bathroom, uncomfortable breathing, coughing or snoring, feelings of extreme cold or hot, bad dreams, pain, and others.	PSQI sleep disturbances (0–3)	1.49 ± 0.07*,[8]	1.46 ± 0.77†,[2]	–	1.30 ± 0.48†,[3]	1.51 ± 0.15*,[17]	–
Use of Sleep Aids	Systematic or spontaneous use of prescribed medications or over-the-counter sleep aids.	PSQI sleep medications (0–3)	0.83 ± 0.24*,[8]	0.07 ± 0.27†,[2]	–	0.07 ± 0.27†,[3]	0.75–1.14†,[77]	–

Notes: *Weighted grand mean ± weighted standard deviation; †Single report mean ± standard deviation; ns: statistically non-significant; sig.: statistically significant; Tx: chemotherapy cycle; PSQI: Pittsburgh Sleep Quality Index; ESS: Epworth Sleepiness Scale.

[1] 7–30 days prior to adjuvant or neo-adjuvant treatment[41,42,48,50,51,54–56]; [2] Day 7; control group[56]; [3] Day 1; control group[56]; [4] Days 1–21 after adjuvant or neo-adjuvant treatment[43,48,54,56]; [5] 30 days after adjuvant treatment, 4–8 Tx received, control group[54]; [6] 90 days after adjuvant treatment, 4–8 Tx received, control group[54]; [7] 1 year after adjuvant treatment, 4–8 Tx received, control group[54]; [8] 7–28 days prior to adjuvant or neo-adjuvant treatment[41,42,48,50,56]; [9] Days 6–21, adjuvant or neo-adjuvant treatment[48,56]; [10] 2–7 days (range 1–28 days) prior to adjuvant or neo-adjuvant treatment[42,43,48,50,54]; [11] Days 1–3, 7[41,54]; [12] Days 1–7, 19[5,54]; [13] Various days between 1 and 21[5,54,57]; [14] Days 1–7, 21[5,43,48,54]; [15] 60 days after adjuvant treatment, 4–8 Tx received[5,54]; [16] Within 28 days prior to adjuvant or neo-adjuvant treatment[41–43,48,50,54,56]; [17] Days 1–21[48,56]; [18] 2 days prior to adjuvant treatment, total sample[54]; [19] Days 1–7, control group[54]; [20] Days 1–7, 8,9, 20[54,57]; [21] 1–3 days (range 1–28 days) prior to adjuvant or neo-adjuvant treatment[42,48,50,54,58]; [22] Days 1–7[54,58]; [23] Various days between 1 and 21[54,57,58]; [24] Days 1–7[48,54,58]; [25] 60 days after adjuvant treatment; 4–8 Tx received, control group[54]; [26] Within 28 days prior to adjuvant or neo-adjuvant treatment[41,48,50,56]; [27] 30–37 days after adjuvant treatment; 4–8 Tx completed, control group[54]; [28] 1–3 days prior to adjuvant treatment[42]; [29] Day 19[5]; [30] Days 1–21[5,57]; [31] Day 21[5]; [32] Eight weeks after adjuvant treatment[5]; [33] Days 8–9[57]; [34] Day 20[57]; [35] 1–3 days (range 1–28 days) prior to adjuvant or neo-adjuvant treatment[42,43,48,50,54]; [36] Days 1–7[52,54]; [37] Days 10–18[52]; [38] Days 10–21[5,52]; [39] Days 1–10[5,52,54]; [40] Days 1–21[5,48,54]; [41] 56–60 days after adjuvant treatment, 4–8 Tx received, control group[5,54]; [42] Days 1–21[54,57]; [43] 1–3 days (range 1–28 days) prior to adjuvant or neo-adjuvant treatment[42,48,50,54]; [44] Days 1–3, study 2[41]; [45] Days 1–7[5,54]; [46] Days 5–10[5,57]; [47] Days 11–21[5,57]; [48] 30 days after adjuvant treatment, 4–8 Tx completed[43,54]; [49] Within a week (1–28 days) prior to adjuvant or neo-adjuvant treatment[42,50]; [50] Day 19; intervention group[55]; [51] Days 1–3; intervention group[55]; [52] Days 5–7; intervention group[55]; [53] Days 5–7[46]; [54] Day 19; intervention group[55]; [55] Within a month prior to adjuvant or neo-adjuvant treatment[41,42,46,48,50,56]; [56] Days 6, 1–21[48,56]; [57] 2 consecutive days prior to adjuvant treatment[42]; [58] Days 1–7[44,52]; [59] Days 15–20[52]; [60] 3 consecutive days during the first week after C1[49]; [61] Days 1–3[52]; [62] Days 15–21[5,52]; [63] Days 1–10[5,44,52]; [64] Days 11–21[5,52]; [65] 3 consecutive days 3 weeks after C4[5]; [66] 3 consecutive days during each of the first 2 weeks after C4[49]; [67] 30 days after adjuvant treatment[44]; [68] 3 consecutive days during each of the 3 weeks after C4[49]; [69] 3 consecutive days an average of 7.3 days prior to neo-adjuvant treatment[50]; [70] 3 consecutive days an average of 7.7 days prior to adjuvant or neo-adjuvant treatment[49]; [71] Days 1–7[44]; [72] 3 consecutive days during each of the 3 weeks after C1[49]; [73] 3 consecutive days during weeks 1 and 3 after C1[49]; [74] 3 consecutive days during the first week after C4[49]; [75] Days 1–7[44,46,52]; [76] Days 1–7[44,46]; [77] Days 1–21 after adjuvant or neo-adjuvant treatment, depending on menopausal status.[48]

[a] 4–8 Tx received.

[b] The PSQI contains 19 items, which are used to generate scores (0–3; 0 = *no difficulty* to 3 = *severe difficulty*) on the following seven components of sleep: sleep quality, habitual sleep efficiency, daytime dysfunction, sleep latency, sleep disturbances, sleep duration, and use of sleep medications. These components can be added together to yield a global score ranging from 0–21.[60] A higher score indicates poorer sleep quality, with scores ≥ 5 indicating possible sleep pathology. However, in patients with breast cancer a cut-off score of 8 has been suggested as a more valid criterion for identifying bad sleepers.[61]

[c] The ESS is an 8-item self-report measure of recent daytime sleepiness. A total score can be yielded ranging from 0 to 21.Scores >6 and >10 are indicative of slight and moderate levels of daytime sleepiness, respectively.[73]

mean of 85.2% (range of means 75.9–89.1%) based on actigraphic recordings,[42,43,48,50,54] a finding further supported by relevant self-report data (Table 2). Even so, considerable variability in this parameter also was evident, and although not explored in the studies reviewed, it might have been related to the time elapsed since diagnosis or primary surgery. The week following Tx1, and throughout the period following Tx2 and Tx3, no major changes were recorded or reported compared to baseline. However, during the first week after Tx4 objective sleep efficiency was found to average at 81.8%,[43,48,54] with PSQI data also supporting this trend.[48,56] Four weeks to one year following four to eight Tx of adjuvant treatment objective sleep efficiency may be restored close to or above the normal limit.[5,43,54] Yet, for some women sleep efficiency might remain low in the first two months following treatment,[5] although it remains unclear whether this might be due to increased anticipatory anxiety because of other treatment modalities beginning around this period of time.

Total sleep time

One to three days prior to chemotherapy total sleep time was reported as ranging from 360 to 406.4 min with a weighted grand mean of 392.4 min (6.54 h) based on actigraphic data.[42,43,46,48,50,54,58] Although subjective ratings may have been somewhat more favourable,[41,48,50,54,56] an overall sleep duration of 7 h or less was indicated for the month prior to treatment. Conversely, a trend of somewhat longer sleep at night seemed to be maintained during chemotherapy treatment, with actigraphic measures yielding weighted grand means of slightly more than 7 h of sleep the first three days post-treatment initiation,[41,54,58] and 7–10 days after Tx3,[54,57] whereas a drop to approximately 7 h per night on average was evident following Tx4.[43,48,54,58] Again, the days immediately before and after administration of chemotherapy might be the ones where nocturnal sleep time shows the greatest deficits.[58] Control group data from a randomised clinical trial suggested that at different time points following adjuvant treatment women's nocturnal sleep time was slightly below 7 h per night[43,54]; yet, explanatory mechanisms for these trends were not provided.

Sleep-onset latency

The month prior to chemotherapy initiation, a weighted grand mean of 1.15 (range 0.92–1.49) on the PSQI sleep latency component was yielded, implying that sleep latency may fluctuate between 16 and 30 min per night.[41,42,48,50,56] Based on a three-day actigraphic measurement, Berger et al.[42] reported a mean latency of 11.4 ± 17.9 min, however ranging from 0 to 187 min each night. Furthermore, complaints of prolonged time to sleep onset may be evident at least in 25% of women prior to chemotherapy initiation.[41] Despite data deriving from rather small studies, thus precluding generalisability, after initial administration[56] and over treatment continuation,[58] a trend of consistent increases in subjective sleep latency is evidenced, with perceived time to fall asleep possibly averaging to 35 min the week after Tx3,[57] and objective latency for all three weeks exceeding 20 min.[5,57] Three weeks after Tx4 perceived sleep latency might approximate baseline levels,[48] although actigraphic data might suggest that difficulty falling asleep still is prominent exceeding 25 min on average.[5]

Nocturnal awakenings

Nighttime awakenings may be prominent among women across all phases of chemotherapy, with their duration possibly exceeding 5 min per episode regardless of chemotherapy phase.[48] At pretreatment, at least 60% of the women might report waking up in

the middle of the night or early morning,[41] with actigraphically recorded episodes of awakening during the week prior to chemotherapy initiation averaging close to 20/night ($\bar{X}$ = 19.8/night; range of means 9.1–60.0).[42,43,48,50,54] During the first few nights (days 1–7) after initial chemotherapy awakenings may further increase in frequency[41,52,54] with the first night's sleep being described as the most fragmented[41]; however, as time elapses a decline until the next treatment may be seen.[52] Over treatment continuation, awakenings seem to become stabilised at this high level, again being increasingly more frequent in the immediate period (next four days) after each Tx than in the intermittent one. Despite a decline in their frequency, awakenings may still be prominent approximately 4, 8, and 12 weeks after the end of chemotherapy,[5,43,54] although it is unclear to what extent this might be the result of other concurrent treatment modalities. Interestingly, self-reports may not corroborate objective findings, with perceived awakening episodes not exceeding an average of 3/night irrespective of chemotherapy phase.[54,57]

Wake time after sleep onset (WASO)

The nights before chemotherapy initiation women may spend approximately 20% of their total rest time in wakefulness ($\bar{X}$ actigraphic % wake time = 17.6%).[42,50] Pretreatment time awake after sleep onset may be as high as 77.4 min per night (range of means 55.5–129 min/night),[42,48,50,54] very similar to the week after initial treatment,[41,54] especially the first three nights.[41] Manifestation of multiple nocturnal awakenings during the course of chemotherapy may result in increased nighttime restlessness and prolonged time in sleeplessness post sleep onset, possibly exceeding 1 h per night.[5,43,48,54,57] As with awakenings, WASO may be increased the week after administration of chemotherapy, but then show a decline of approximately 15 min on average until the next treatment is received.[5,54,57] One to three months following treatment, WASO still may be elevated for reasons possibly similar to those suggested earlier for nocturnal awakenings. Using a 7-day sleep diary, Berger et al.[54] were able to demonstrate changes in self-reported WASO during the course of treatment with greater increases occurring the week after Tx1 and Tx4, and a somewhat significant decline 30 days or more after the end of treatment. Nevertheless, self-reported time in wakefulness was considerably lower (approximately 23–33 min lower) than the objectively recorded, and warrants future investigation.

Daytime napping

Pretreatment daytime nap time may be increased, exceeding 1 h per day ($\bar{X}$ actigraphic nap time = 64.8 min),[42,50] possibly corresponding to approximately 8% of a 24-hour cycle.[42,50] During treatment, the overall pattern of rest may become increased,[52] and women who may be less active during the day, may take more naps.[53,57] Specifically, 5–7 days after initial treatment with adjuvant anthracycline- and taxane-based chemotherapy, daytime napping of the women in the control group reached a mean of 10.6 ± 7.1% of the total wake time.[46] Disappointingly, evidence with regard to daytime napping throughout chemotherapy is near to zero. Although an average duration of 7.5 min of each napping episode may be recorded,[50] possible fluctuations over treatment are virtually unknown. Berger and Higginbotham[5] recorded increases in the total rest patterns of women before and after Tx3 and Tx4, which they theoretically explained as a need for more time in bed every night and more time napping during the day. In a small intervention feasibility study, a trend of increased napping time the first three days after Tx3 was recorded as compared to pretreatment and days 5–7 post-treatment, which might have been related to concurrently increased levels of fatigue.[55] Again, subjective and objective data were widely discordant, thus introducing the possibility of actigraphy actually overestimating nap time. Self-reports suggested an increase from ~17 min prior to treatment to 35 min immediately after and a drop to 17 min at the end of the first week.[55]

Daytime sleepiness/dysfunction

Daytime sleepiness per se has not been systematically examined in women receiving chemotherapy for early-stage breast cancer. Instead, the broader term of daytime dysfunction as measured by the PSQI has received greater attention, but mainly during the pretreatment period. Converging evidence suggests that daytime dysfunction may be prevalent less than one week on average the month prior to chemotherapy initiation ($\bar{X}$ PSQI daytime dysfunction = 0.82; range of means 0.58–0.98).[41,42,46,48,50,56] Self-reported daytime dysfunction might be elevated during the first week post initial treatment, and remain relatively increased over treatment continuation[48,56,57] (Table 2). At this period, daytime sleepiness might be more prominent the first week after chemotherapy rather that during the recovery phase, that is the following two weeks in a three-weekly administered regimen.[57] Following treatment levels of daytime dysfunction associated with sleepiness remain unknown.

Circadian rhythms

Pre-treatment circadian rhythms in women with early-stage breast cancer may be robust and synchronised,[42,49,50] as evidenced by near to normal acrophases, mesors and amplitudes. Nevertheless, progressively disrupted circadian activity and rest cycles such as low activity, less consolidation of higher daytime, and lower nighttime activity during chemotherapy may be evident.[5,44,46,49,52,53] Circadian rhythms may be significantly more impaired during the first week following the first treatment with more activity during the night and less constant bedtime and wake time, with a transient return to baseline levels during the second and third weeks.[49] Similarly dampened circadian rhythms may be prevalent especially after Tx3 and Tx4, where with the exception of acrophase, mesor, amplitude, up-mesor, down-mesor and rhythmicity may remain impaired.[5,44,46,49,52] Although low daytime inactivity may or may not depend on the prior night's sleep,[42] women who are more phase-delayed may report more daily dysfunction.[50] Following chemotherapy, sleep architecture might continue to be disrupted with increased light sleep, less deep sleep, and less REM sleep compared to normative data.[64] Yet, circadian rhythms of women might be significantly closer to normal compared to Tx1 and Tx3.[44]

Perceived sleep disturbances

Based on PSQI component scores, sleep disturbances, including pain, hot flash, cold, coughing and/or snoring, and difficulty breathing have been described as highly prevalent across chemotherapy for early-stage breast cancer. However, the greatest part of available data focuses on the pretreatment period, where sleep disturbances may occur at least once or twice a week ($\bar{X}$ PSQI sleep disturbance = 1.49; range of means 1.40–1.58).[41,42,48,50,56] Consistently high levels of sleep disturbances after initial treatment, and over chemotherapy continuation also were reported in the studies selected,[48,56] without however evidence of significant over-time variations. Moreover, Payne et al.[58] concluded with no significant within-Tx time effects on sleep disturbances, suggesting that the

latter were equally prevalent both the night before and the night after Tx1 and Tx4.

Use of sleep aids

Actual use of sleep aids over the course of chemotherapy for early-stage breast cancer was inconsistently reported in the majority of the studies. Overall, an average need for a sleep aid of less than once a week the month prior to chemotherapy was evident.[41,42,48,50,56] An equally prevalent need was described by Rissling et al.[48] following Tx4. In the only studies which endeavoured to describe patterns of sleep aid use in this population, Moore et al.[45] found that 17–20% women were using a sleep aid two days prior to chemotherapy initiation, which slightly increased to 23% the first night post-treatment with a decline to 14% seven days later. This pattern was similar during Tx2-4, whereas an overtime decrease in sleep aid use was noted up to one year later. In their retrospective chart review, Costantini et al.[59] found that nearly 14% of the women were making use of a sleep aid prior to treatment, whereas ~32% were prescribed a sleep aid during chemotherapy. Prescription sedatives/hypnotics – mainly benzodiazepines and non-benzodiazepines – might be the most frequently used sleep aids, followed by over-the-counter analgesics, whereas use of alcohol or herbs may be rather infrequent.[45,59]

Discussion and future implications

The present critical review highlights the diversity of research findings, reveals current gaps, and stresses the need for a more systematic investigation of the experience of disrupted sleep in women receiving chemotherapy for early-stage breast cancer. Admittedly, varying deficits in sleep parameters may be evident in a significant part of this population. Yet, research data are not equally distributed among the different sleep components, or across all major time points throughout chemotherapy. Especially with regard to women's circadian rhythms, daytime rest patterns, and use of sleep aids more focused investigation is warranted. Other variables such as nighttime dreaming and feelings upon arising have been only superficially reported, with strange dreams being infrequent at least before treatment initiation,[5] and only moderate levels of energy after a night's sleep possibly throughout treatment.[44,46] However, the potential links between circadian rhythm parameters and feelings upon arising[44] worth further examination in future studies to identify patients at risk for non-restorative nocturnal sleep.

Current evidence is not without limitations. A large part of longitudinal evidence is derived from multiple secondary analyses of clinical trial datasets[43,44,54] rather than individual exploratory studies. This dearth of actual data, along with the possibility of a Hawthorne effect[65] among participants in the control groups, limit the generalisability of findings, and urge for more longitudinal exploratory research. In other studies assessment of sleep parameters was conducted in an incomplete fashion, over only specific chemotherapy cycles (Tx3[57] only) without baseline (Tx1-3[52]), or without post-treatment data available (baseline to Tx4[49]), thus compromising conclusions. While of course some studies have included a post-treatment assessment with relative consistency,[43,44,54] they have included patients with varying adjuvant chemotherapy protocols, differing in terms of chemotherapy agents administered but, most importantly, in duration. It is reasonable to assume that sleep patterns might be differently affected in women with fewer Tx (four compared to six or eight), or with more aggressive chemotherapy (anthracycline-based versus anthracycline-based followed by taxanes); however, this hypothesis cannot be verified as yet. Apart from deliberately selecting post-treatment assessment points being the same for the entire sample, future studies need to examine the sleep-impairing effect of the accumulated distress in neo-/adjuvant chemotherapy protocols of varying duration.

In all but two studies,[51,66] time after surgery was not reported making it unclear whether evidenced sleep deficits could be attributed to distress associated with surgical procedures,[67] given that patients might have been assessed too close to the time-within 2–3 weeks – after surgery. What is more, while individuals with primary sleep disorders were excluded in all studies, no study evaluated women's past history of poor sleep, or present sleep habits; hence, data derived from women prone to poor sleep might have led to an overestimation of the actual magnitude of sleep disorders in this population. The inclusion of women with different menopausal status may also have blurred findings pertinent to changes in sleep parameters across chemotherapy. Even in the studies where separate analyses were performed, small sample sizes might have undermined results, thus highlighting the need for future studies with large comparison groups to be undertaken. Similarly, where data from mixed samples of women scheduled to receive neo-adjuvant or adjuvant chemotherapy were analysed,[47,49,50] results also might reflect an overestimation of sleep problems. While unclear, women to receive neo-adjuvant treatment might have been assessed close to the time after diagnosis, when sleep might be profoundly affected by the emotional impact of a diagnosis of a life-threatening disease. In any case, future comparison studies can significantly contribute to the establishment of potential differences in the sleep patterns of the two treatment groups.

Issues regarding the collection of sleep data need also be examined. Recall bias may have affected data on the self-reported sleep quality of women across chemotherapy as in some studies[41,51,54,56] individuals were asked to report on their sleep patterns over the previous month. If retrospective self-report measures elicited information that reflected shorter (previous week) rather than longer (previous month) periods of time, reliability of subjective sleep data would improve. In that way, comparability with objective sleep data that derive from brief assessment periods (ranging from two to seven days) could also be achieved, and sleep data contemplation could be enhanced. In any case, more longitudinal research implementing ambulatory polysomnography,[68] longer periods of wrist actigraphy,[49] and daily sleep diaries is warranted in this population.

Collectively seen, whereas several sleep parameters may become affected over the course of treatment, disruptions need to be viewed from a clinical perspective, thus allowing for health professionals to reach meaningful conclusions. For instance, whereas greater pre-treatment sleep disturbance might anticipate for maintenance of poor sleep quality during treatment,[47] among women reporting lower pre-treatment sleep disruptions, adverse effects on their sleep patterns might be more prominent during treatment[47]; yet, more research is needed to implicitly confirm this hypothesis and allow for patients at risk for disrupted sleep to be identified. Along these lines, it is equally important to identify and monitor what the individual contribution of each sleep parameter to a woman's overall sleep problem might be. For some individuals prolonged sleep-onset latency can be a major complaint in the absence of other sleep disruptions, whereas for others nocturnal awakenings may represent the primary cause of distress and non-restorative sleep. Sleep history or sleep hygiene also might be of value in predicting alterations in sleep parameters when distressing events occur, but further research is warranted. Past poor sleep quality may be associated with use of sleep aids during chemotherapy.[59] However, do disrupted sleep patterns over treatment prompt women with no past history of poor sleep to seek help? The

importance women attribute to specific disrupted sleep parameters also needs to be examined as it can enhance provision of tailored care. In research terms, future implementation of longitudinal mixed-methods studies[69] could also give us a better understanding of the experience of poor sleep, and how this experience evolves across treatment, thereby permitting provision of care targeted to the specific needs of specific individuals.[4]

Authorship

All authors have equally contributed to the preparation of this manuscript.

Conflicts of interest

None declared.

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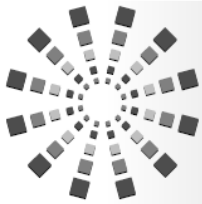

Grigorios Kotronoulas, MSc, BSN
Yvonne Wengström, PhD, OCN
Nora Kearney, MSc, RGN

Sleep Patterns and Sleep-Impairing Factors of Persons Providing Informal Care for People With Cancer

A Critical Review of the Literature

KEY WORDS
Cancer
Caregivers
Critical review
Informal care
Sleep-impairing factors
Sleep patterns
Sleep-wake disturbances

Background: Sleep is increasingly recognized as an area of functioning that may be greatly affected in persons who are practically and emotionally involved in the care of patients with cancer. Clinician awareness is required to ensure that effective care for informal caregivers with sleep problems is provided. **Objective:** A 2-fold critical review of the published literature was conducted, which aimed at summarizing and critically analyzing evidence regarding sleep patterns of informal caregivers of adults with cancer and contributing factors to sleep-wake disturbances. **Methods:** Using a wide range of key terms and synonyms, 3 electronic databases (MEDLINE, CINAHL, EMBASE) were systematically searched for the period between January 1990 and July 2011. **Results:** Based on prespecified selection criteria, 44 articles were pooled to provide evidence on sleep-impairing factors in the context of informal caregiving, 17 of which specifically addressed sleep patterns of caregivers of people with cancer. **Conclusions:** At least 4 of 10 caregivers may report at least 1 sleep problem. Short sleep duration, nocturnal awakenings, wakefulness after sleep onset, and daytime dysfunction seem to be the areas most affected irrespective of stage or type of disease, yet circadian activity remains understudied. In addition, despite a wide spectrum of potential sleep-impairing factors, underlying causal pathways are yet to be explored.

Author Affiliations: School of Nursing & Midwifery, University of Dundee, Scotland (Mr Kotronoulas, Prof Wengström, and Prof Kearney); and Department of Neurobiology, Division of Nursing, Care Science and Society, Karolinska Institutet, Huddinge, Sweden (Prof Wengström).

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Correspondence: Grigorios Kotronoulas, MSc, BSN, School of Nursing & Midwifery, University of Dundee, 11 Airlie Pl, DD1 4HJ, Scotland (g.kotronoulas@dundee.ac.uk).

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Implications for Practice: More longitudinal, mixed-methods, and comparison studies are warranted to explore caregiver sleep disorders in relation to the gravity of the caregiving situation in the context of diverse types of cancer and disease severity.

When cancer becomes a reality, spouses, partners, other family members, and friends may actively participate in shaping the patient's illness experience.[1] Regardless of its nature, support provided by persons "considered as family" by the patient[2]—often recognized by health professionals as "informal caregivers"—has been found to be equally or more beneficial than support derived from other sources.[1,3] From the health system's perspective, the expectation of caregiving in significant others also is high. The shift in the balance of care from hospitals to the community,[4] coupled with the shortage of healthcare providers,[5] has greatly impacted on the roles and responsibilities of informal caregivers, who are expected to provide primary, ongoing care and daily support at home.[6–8]

Caregiving for a chronically ill person has been seen as "an increase in care that surpasses the bounds of normal or usual care."[9] The practical and emotional involvement in patients' journeys often affects caregivers' own lives[10]: they may be forced to make changes, take on new roles and responsibilities, or give up past activities.[11] Such stressful life changes can create strain and burden[7] entailing both objective and subjective dimensions.[9] Objective burden consists of the elements of time and effort required for individuals to attend to the needs of others.[12,13] On the other hand, subjective burden usually refers to perceived beliefs, feelings, and assumptions regarding the caregiver role.[9,14–16] As burden and strain build on, caregivers' physical well-being might be at stake. Possible reasons include little time to rest, engagement in fewer self-care behaviors, or failure to seek medical care for themselves when sick.[5,17] Of note, alterations in habitual sleep patterns may place an additional, considerable threat to caregivers' quality of life.[18,19]

Sleep research in the context of cancer caregiving has gained some interest in the last 15 years, yet disturbed sleep remains one of the least assessed symptoms in this population.[20] Nonetheless, difficulty falling and staying asleep, experience of restless and nonrestorative sleep, and development of insomnia and chronic sleep loss may be common complaints raised by caregivers of patients with cancer.[21,22] Albeit poorly explained, these might be of greater severity compared with caregivers of patients with other illnesses such as AIDS or age-related dementias.[23] In any case, frequency and severity of sleep problems may vary widely, mainly but not solely depending on the overall caregiving situation.

Admittedly, not all caregivers develop sleep problems, and when these do occur, they may not be easily explained or categorized. For instance, although some caregivers may complain about their sleep, objectively assessed sleep patterns may not replicate their complaints or not be significantly worse than noncaregivers. Several underlying factors may play either a detrimental or protecting role to the development of sleep problems and may have different significance for different persons. In agreement with the Three Factor Insomnia Model of Spielman et al,[24,25] such factors can predispose caregivers to sleep problems, precipitate sleep disruptions, or perpetuate these, acting both interchangeably and in tandem.

Given that caregivers are now legitimized as persons affected by cancer in profound ways,[26] clinician awareness of caregiver sources of distress can be seen as the only way to ensure that timely and appropriate care is provided. However, our understanding of such distress in caregivers is still limited. To evaluate the sleep-related distress in caregivers of adults with cancer, a 2-part critical review of the empiric literature was conducted. This review aimed at summarizing and critically analyzing evidence regarding changes in the sleep patterns of informal caregivers of adults with cancer (part A) and at examining the roles of sleep-impairing factors in sleep problems in this population (part B). A thorough discussion of methodological and research gaps in this body of evidence also was provided.

■ Review Methodology

The present review was conducted in a 2-fold manner to address its 2 objectives. Initially, given the limited sleep research conducted in the context of cancer caregiving, all relevant publications were retrieved irrespective of disease context to form a large pool of evidence, especially with regard to sleep-impairing factors in informal caregivers. From this pool of studies, original articles were extracted that specifically examined sleep patterns of informal caregivers of adults with cancer.

Studies were identified by systematically searching 3 electronic databases (MEDLINE, CINAHL, EMBASE). A comprehensive search strategy was devised, using a wide range of key terms, and synonyms were used including the following: *sleep disorders, insomnia, sleep disturbance, sleeplessness, sleepiness, circadian rhythm, sleep efficiency, sleep quality, sleep latency, drowsiness, wakefulness, caregiver, partner, family member,* and *significant other.* The reference lists of 3 topical research reviews[20,27,28] as well as those of retrieved articles were examined for any studies that might have been overlooked. Additional literature was sought through use of the search engine Google Scholar.

Selection Criteria

Studies published as original articles in peer-reviewed journals from January 1990 to July 2011 were considered, representing the period in which sleep-specific instruments were developed, and studies of sleep in informal caregivers emerged.

In the first stage, studies were eligible if they (*a*) were written in English, (*b*) were conducted with adult (>18 years of age) individuals as providing informal care irrespective of their relation to the ill person, and (*c*) examined sleep via use of sleep-specific subjective and objective measures. Subsequently, sleep studies conducted in the context of cancer were considered. Intervention studies also were eligible if they provided baseline and/or control arm sleep data. Studies were excluded from the present review if undertaken in the context of a terminal illness or conducted with bereaved caregivers. Unpublished studies, dissertation abstracts, or conference presentations also were omitted.

A short list of articles was initially compiled, where titles and abstracts were screened to assess relevance to the review. Potentially eligible articles were retrieved in full and checked for adherence. Study characteristics were extracted using a systematic scheme. Because of heterogeneity of the studies retrieved, findings were integrated in a narrative synthesis.

■ Search Findings

Seventeen articles reporting on 11 studies were retrieved that specifically examined sleep patterns of informal caregivers of patients with cancer (Figure 1). Methodological characteristics of these studies are summarized in the Table. In cases of multiple articles in the context of one study, relevant information from all articles was included. In part A, the selected studies were summarized and critically analyzed to provide evidence with regard to overall incidence of sleep-related problems, as well as to specific key sleep parameters.[21,45] Sleep data were further analyzed on the grounds of patient disease stage. A separate analysis was conducted for studies focusing on caregivers of persons with a specific type of cancer. Finally, sleep findings potentially unique in this population of caregivers were also considered (see Figure 2 for an organizational schematic).

Twenty-seven additional articles were identified that examined caregivers' sleep in the context of a chronic illness: cancer,[44,46–48] dementia,[49–67] Parkinson's disease,[68–70] and stroke.[71] In total, 44 articles formed a pool of evidence addressing potential factors interfering with nocturnal sleep and/or triggering daytime dysfunction (part B). Factors were categorized into 2 broad themes: those directly relating to the person and his/her lifestyle habits or behaviors and those relating to the caregiving experience also including patient-related parameters (Figure 2). This categorization aimed at highlighting that such factors can be independent of the caregiving situation, as well as directly or indirectly related to it.[28]

Part A: Evidence With Regard to Sleep Patterns

SAMPLE CHARACTERISTICS AND CONTEXT

Caregiver age across studies ranged from 15 to 86 years, with a grand weighted mean age of 55.4 ± 9.4 years (range of means, 41.2–74.0 years). The typical caregiver was white (79%–100%), female (51.5%–100%), married or partnered (83.6%–100%), and employed (35%–61.5%) at the time of participation. All but one study[23] aimed at recruiting family members in caregiving roles. Most frequently, caregivers were the patients' spouses (44%–100%) or adult children (5%–34%).

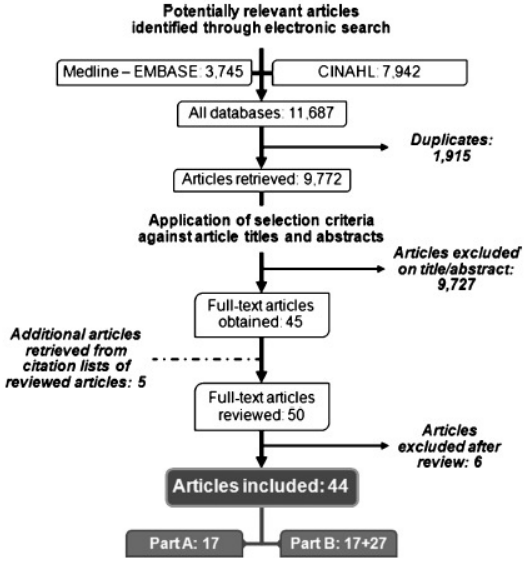

Figure 1 ■ Flow diagram of the article selection process.

Table • Summary of Methodological Characteristics of the Articles Included Regarding Sleep Patterns in Caregivers of People With Cancer

Authors, Date; Country	Research Design	Objective(s)	Sample Characteristics	Sleep Measures
Aslan et al,[29] 2009; Turkey	Descriptive, exploratory Cross-sectional	To determine the quality of sleep, reasons for sleep disturbances, and nonpharmacological strategies vs sleep disturbances of family caregivers of patients with cancer receiving outpatient chemotherapy	n = 90 Mean age 41.2 ± 11.3 (15–70) y; 53.3% female; 86.7% married; 44.4% spouse, 34.4% child, 11.1% relative; 40% concurrent illness; duration of caregiving: median 5 mo (3 d to 1 y); patient type of cancer: breast (34.4%), lung (11.1%), colorectal (10%)	*Subjective*. PSQI (recall time frame: 1 mo); open-ended questions on reasons and nonpharmacological strategies for sleep disturbances—timing of data collection was not stated
Carney et al,[30] 2011; United States[a]	Descriptive, correlational Cross-sectional Part of a larger longitudinal study	To evaluate for differences in the severity of self-reported sleep disturbance and objective measures of nocturnal sleep/rest and daytime wake/activity in oncology patients and their family caregivers at the initiation of primary or adjuvant radiation therapy	n = 102 dyads *Caregivers*. Mean age 61.7 ± 10.4 y; 71.6% female; 95.1% married/partnered; 78.2% white; 46.5% employed; 91.2% spouse/partner; 80.8% partner in same bed; patient type of cancer: breast, prostate, lung, brain	*Objective*. Continuous 48h wrist actigraphy—2 d before treatment initiation *Subjective*. PSQI (recall time frame: 1 mo), GSDS (recall time frame: 1 wk)—approximately 1 wk before treatment initiation
Carter and Chang,[31] 2000; United States[b]	Descriptive, correlational Cross-sectional	To describe the sleep problems and depression levels of primary caregivers of patients with advanced cancer, and to explore the relations between these 2 variables in a natural setting	n = 51 Mean age 53.7 ± 14.3 (26–75) y; 80.4% female; 84.3% white; 60.8% spouse, 29.4% child; 82.4% at least 1 additional role; mean duration of caregiving: 24.3 ± 29.0 (3–142) mo; caregiving per day: 15.8 ± 8.9 h; caregivers coresiding with the patient; patient type of cancer: lung, colorectal, other; patients had received at least 1 type of conventional treatment	*Subjective*. PSQI (recall time frame: 1 mo)—timing of data collection was not stated
Carter,[32] 2002; United States[b]	Descriptive, exploratory Cross-sectional	To explore descriptions of caregivers of patients with advanced cancer of sleep and depression, and descriptions of connections between these 2 variables over time; to compare qualitative descriptions with quantitative scores	n = 47 Mean age 53.7 (26–75) y; 87.2% female; 82% white; 41% wife, 28% daughter, 20% husband; >50% employed; 55% at least 1 additional role; mean duration of caregiving 24.3 (3–142) mo; caregiving per day: 15.8 h; caregivers coresiding with the patient; patient type of cancer: lung, colorectal, other; patients had received at least 1 type of conventional treatment	*Subjective*. PSQI (recall time frame: 1 mo); open-ended one-time interviews—timing of data collection was not stated

continues

Table • Summary of Methodological Characteristics of the Articles Included Regarding Sleep Patterns in Caregivers of People With Cancer, Continued

Authors, Date; Country	Research Design	Objective(s)	Sample Characteristics	Sleep Measures
Carter,[33] 2003; United States	Descriptive, correlational Prospective	To describe over time changes in sleep quality and depressive symptoms of family caregivers of patients with advanced cancer receiving treatment (chemotherapy or radiotherapy) on an outpatient basis; to explore feasibility of data collection methods and instruments	n = 10 Mean age 61 (39–81) y; 80% female; 80% white; 90% spouse, 10% sibling; mean duration of caregiving: 5.7 mo; caregiving per day: 19.7 (10–24) h; caregivers coresiding with the patient; 90% sleep in the same bed with the patient; 10% change in sleeping arrangements; patient type of cancer: lung (60%), leukemia (20%), breast, prostate	*Objective*: Continuous 72-h wrist actigraphy—weeks 1, 5, and 10 *Subjective*: PSQI (recall time frame: 1 mo), author-constructed daily sleep logs (3 d each week)—weeks 1, 5, and 10
Carter,[34] 2006; United States	Feasibility, experimental, intervention-control Prospective	To test the feasibility and effectiveness of a brief behavioral intervention (sleep hygiene, stimulus control, relaxation techniques) to address the needs and sleep goals of family caregivers of patients with advanced cancer	n = 30 (15 intervention, 15 control) Mean age 53 ± 17 (21–85) y; 63% female; 80% white; 57% spouse, 30% adult child; caregiving per day: 17 ± 7 (2–24) h; caregivers coresiding with the patient	*Objective*: Continuous 72-h wrist actigraphy—preintervention, week 3, week 5, and months 2, 3, and 4 postbaseline *Subjective*: PSQI (recall time frame: 1 wk), author-constructed daily sleep logs (3 d each time-point)—preintervention, week 3, week 5, and months 2, 3, and 4 postbaseline
Carter and Acton,[35] 2006; United States[b]	Descriptive, correlational Cross-sectional	To examine the relationships of personality and coping with caregiver depression and sleep disturbances in family caregivers of patients with advanced cancer	n = 51 Mean age 54 (26–75) y; 80% female; 85% white; 61% spouse, 29% child; mean duration of caregiving: 24 mo; caregiving per day: 16 h; caregivers coresiding with the patient; patient type of cancer: lung, colorectal, other; patients had received at least 1 type of conventional treatment	*Subjective*: PSQI (recall time frame: 1 mo)—timing of data collection was not stated
Chang et al,[36] 2007; Taiwan	Descriptive, correlational Cross-sectional	To examine the association between sleep quality and quality of life (QoL) of primary caregivers of newly diagnosed (1–18 mo) women with nonmetastatic breast cancer	n = 61 Mean age 45.1 ± 10.8 (24–67) y; 82% male; 83% married; 69% spouse, 31% other (son, daughter, daughter-in-law); time since patient diagnosis: 5.3 ± 4.3 (1–18) mo	*Subjective*: PSQI (recall time frame: 1 mo)—timing of data collection was not stated
Cho et al,[37] 2006; Korea	Descriptive, correlational Cross-sectional Part of a larger study	To describe the sleep quality of family caregivers of patients with gastric cancer receiving chemotherapy treatment; to explore gender differences in sleep quality, and its relationship to fatigue and depressive symptoms	n = 103 Mean age 48.3 ± 11.4 (21–73) y; 78% male; 94% married; 84% spouse, 11% other (daughter, daughter-in-law); 56% homemaker, 35% employed; 11% change in employment status	*Subjective*: PSQI (recall time frame: 1 mo)—questionnaire administer to caregivers, whose patient had already received their first chemotherapy cycle

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Table • Summary of Methodological Characteristics of the Articles Included Regarding Sleep Patterns in Caregivers of People With Cancer, Continued

Authors, Date; Country	Research Design	Objective(s)	Sample Characteristics	Sleep Measures
Dhruva et al,[38] 2011; United States[a]	Descriptive, correlational Cross-sectional Part of a larger longitudinal study	To describe values for nocturnal sleep/rest, daytime/wake activity, and circadian activity rhythm parameters, and to evaluate the relationships between subjective and objective sleep measures and fatigue severity in family caregivers of oncology patients at the initiation of primary or adjuvant radiation therapy	n = 103 Mean age 61.7 ± 10.4 (34–86) y; 71.6% female; 92.2% married/partnered; 78.4% white; 47.5% employed; 91.2% spouse/partner; 99% coresiding with the patient; caregiver mean no. of comorbidities 4.2 ± 2.9; patient type of cancer: prostate (59%), breast (26%), lung (8%), brain (7%)	*Objective*: Continuous 48-h wrist actigraphy—2 d before treatment initiation *Subjective*: PSQI (recall time frame: 1 mo); GSDS (recall time frame: 1 wk)—approximately 1 wk before treatment initiation; daily sleep diary (2 d of objective data collection)
Flaskerud et al,[23] 2000; United States	Descriptive, comparative Cross-sectional	To describe and compare the depressive mood, anxiety, anger and sleep problems of informal female caregivers of people with AIDS, age-related dementias, and advanced cancer	n = 117 (total sample): n = 41 (care receiver with cancer) *Caregivers of people with cancer*: mean age 51.5 ± 14.2 (26–74) y; 80% white; 80% married; 92% family member; mean duration of caregiving: 2.0 ± 2.4 (<1–12) y; caregiving per day: 14.9 ± 8.5 (1–24) h	*Subjective*: PSQI (recall time frame: 1 mo)—timing of data collection was not stated
Gibbins et al,[39] 2009; United Kingdom	Descriptive, observational Prospective	To determine the prevalence of sleep-wake disturbances, to determine the amount of daytime spent in activity and rest, and to examine the relationship between sleep disturbances, physical and psychological symptoms, and QoL in patients with advanced cancer and their family caregivers	n = 60 dyads *Caregivers*: Mean age 66 (27–80) y; 55% male; 100% spouse; patient type of cancer: lung, breast, prostate, colorectal; no active treatment received within 2 wk prior to participation	*Objective*: Continuous 7-d wrist-actigraphy *Subjective*: Author-constructed sleep history inventory—baseline; daily sleep diaries—7-d data collection; ESS—day 7
Hearson et al,[19] 2011; Canada	Descriptive, exploratory Cross-sectional	To examine and describe the concept of sleep disturbance as experienced by family caregivers of community-dwelling patients with advanced cancer	n = 13 Mean age 58.5 ± 9.7 y; 76.9% female; 100% white; 61.5% employed; 54% spouse, 31% child, 15% sibling; 69.2% coresiding with the patient; duration of caregiving: 69.3% 0–12 mo; patient type of cancer: lung (31%), lymphoma (23%), bladder (15%); mainly bed-ridden patients who required assistance with care	*Objective*: Continuous 72-h wrist-actigraphy (n = 12) *Subjective*: Semistructured interviews regarding sleep patterns; affecting factors, consequences, and strategies used; PSQI (recall time frame: 1 wk); ESS; Carter's daily sleep logs (3 d during objective data collection)—timing of data collection was not stated

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Table • Summary of Methodological Characteristics of the Articles Included Regarding Sleep Patterns in Caregivers of People With Cancer, Continued

Authors, Date; Country	Research Design	Objective(s)	Sample Characteristics	Sleep Measures
Fletcher et al,[40] 2008; United States[a]	Descriptive, correlational Cross-sectional Part of a larger longitudinal study	To determine the prevalence and severity of depression, anxiety, pain, sleep disturbance, and fatigue; determine the relationships among these symptoms and between these symptoms and functional status and QoL; evaluate for differences in functional status and QoL between individuals with low and high levels of these symptoms; and determine which factors predicted individuals' functional status and QoL in female family caregivers of patients with prostate cancer at the initiation of primary or adjuvant radiotherapy	n = 60 Mean age 64.2 ± 8.8 y; 80% white; 93.3% married/partnered; 36.7% employed; coresiding with the patient; mean no. of comorbidities: 4.8 ± 3.0; patient time since diagnosis: 9.7 ± 15.5 mo	*Subjective*: GSDS (recall time frame: 1 wk)—approximately 1 wk before treatment initiation
Fletcher et al,[41] 2009; United States[a]	Descriptive, correlational Prospective Part of a larger longitudinal study	To evaluate predictors of and trajectories for evening and morning fatigue in family caregivers of patients with prostate cancer receiving primary or adjuvant radiation therapy	n = 60 Mean age 64.2 ± 8.8 y; 80% white; 93.3% married/partnered; 36.7% employed; coresiding with the patient; mean no. of comorbidities: 4.8 ± 3.0; time since patient diagnosis: 9.7 ± 15.5 mo	*Subjective*: GSDS (recall time frame: 1 wk)—approximately 1 wk before treatment initiation
Teel and Press,[42] 1999; United States	Descriptive, comparative Cross-sectional	To examine indicators of fatigue among elder spouse caregivers of patients with Alzheimer's disease, Parkinson's disease, and cancer and to explore similarities and differences in fatigue reported by caregiving and non-caregiving individuals	n = 92 (total sample of caregivers); n = 33 (care receiver with cancer); n = 33 (noncaregivers) *Caregivers of people with cancer*: Mean age 70 y; 51.5% female; 94% white; coresiding with the patient; mean duration of caregiving: 1.2 y; caregiving per day: 6.2 h; mean time since patient diagnosis: 3.0 y	*Subjective*: VSH Sleep Scale (recall time frame: previous night)—timing of data collection was not stated
Willette-Murphy et al,[43] 2009; United States[a]	Descriptive, correlational, comparative Cross-sectional	To evaluate for differences in subjective and objective measures of sleep between physically active and inactive female family caregivers of patients with cancer at the initiation of primary or adjuvant radiation therapy and to evaluate for differences in demographic, clinical, and symptom characteristics between women in the 2 groups	n = 68 (total sample); n = 38 (active group); n = 30 (inactive group) *Active group*: Mean age 65.5 ± 8.3 y; 100% spouses; coresiding with the patient; mean no. of comorbidities 5.3 ± 2.7; 34.2% work outside the home; KPS 92.3 ± 12.3 *Inactive group*: Mean age 62.8 ± 9.3 y; 100% spouses; coresiding with the patient; mean no. of comorbidities 3.8 ± 3.2; 40% work outside the home; KPS 96.3 ± 7.1	*Objective*: Continuous 48-h wrist actigraphy—2 d before treatment initiation *Subjective*: PSQI (recall time frame: 1 mo); GSDS (recall time frame: 1 wk)—approximately 1 wk before treatment initiation; daily sleep diary (2 d of objective data collection)

Abbreviations: ESS, Epworth Sleepiness Scale; GSDS, General Sleep Disturbance Scale; KPS, Karnofsky Performance Status; PSQI, Pittsburgh Sleep Quality Index; VSH Sleep Scale, Verran and Snyder-Halpern Sleep Scale.
[a]All articles are based on the same larger longitudinal study.[44]
[b]All articles are based on the same project.

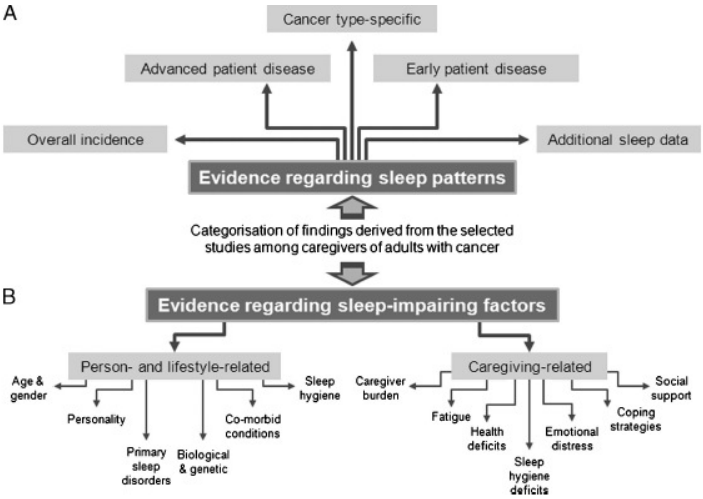

Figure 2 ■ Organizational schematic of the analysis of data regarding sleep patterns (part A; upper panel) and sleep-impairing factors (part B; lower panel) in caregivers of adults with cancer.

Only 2 studies were cancer type–specific, thus focusing on the sleep patterns of caregivers in the context of breast[36] and gastric[37] cancer. Two study subreports provided evidence in the context of prostate cancer.[40,41] Six studies included caregivers of patients with advanced cancer,[19,23,31–34,39] whereas 2 included caregivers of patients with nonmetastatic disease.[30,36,38,40,41,43] In 4 studies, participants provided care for a person receiving or scheduled to receive chemotherapy[29,36,37] or radiotherapy[30,38,40,41,43] treatment.

Data relating to time since patient diagnosis, duration of caregiving since diagnosis, and hours of daily caregiving were inconsistently reported in the studies. Caregivers of patients with nonmetastatic cancer were mainly approached within the first year (5–9 months on average) after diagnosis.[30,36,38,40,41,43] On the other hand, Carter et al[33] reported that time since diagnosis of advanced cancer ranged from 1 month to 6 years, whereas Teel and Press[42] reported a mean time of 3 years. Where reported, duration of caregiving exceeded even 2 years in caregivers with advanced cancer,[19,23,31–34] whereas hours of caregiving exceeded 14 per day on average.[23,31,32,34] In caregivers of patients receiving chemotherapy, Aslan et al[29] reported a mean caregiving duration of 5 months.

SLEEP MEASURES

In 6 studies, only self-report sleep measures were used,[23,29,31,32,34,36,37,42] whereas in the remainder a combination of subjective and objective sleep measures was implemented.[19,30,33,34,38–41,43] Wrist actigraphy was used in 5 studies, where wrist devices were continuously worn for 48,[30,38,40,41,43] 72,[19,33,34] and 168[39] hours. On the other hand, the Pittsburgh Sleep Quality Index (PSQI)[72] was the most frequently used self-report measure in the studies reviewed,[19,23,29–31,33,34,36–38,43] assessing quality of sleep over the previous month.

OVERALL INCIDENCE OF SLEEP-RELATED PROBLEMS

Based on different sleep measures and cutoff scores, between 36% and 95% of caregivers reported disrupted nocturnal sleep associated with poor sleep quality.[23,29,31–35,37,40,41,43] According to disease stage, prevalence rates ranged from 36% to 80% during the early phases of cancer[29,30,36–38,43] and from 42% to 95% when care for patients with advanced disease was provided.[23,31–35,40] Across active patient treatment, 37% to 59% of caregivers reported sleep problems prior to treatment initiation,[30,38,40] whereas sleep problems were reported by more than 70% of the respondents during the patient's treatment.[29,33,36,37]

SLEEP PATTERNS IN THE CONTEXT OF PATIENT ADVANCED DISEASE

In long-term family caregivers of patients with advanced-stage cancer, particularly poor sleep was reported: perceived sleep duration of 5.3 to 7.8 hours per night; habitual sleep efficiency ranging from 74% to 80%; trouble falling and staying asleep; and restless, nonrestorative sleep coupled with daytime dysfunction.[19,23,31–34,39] Along these lines, actigraphic data revealed similar trends: actual sleep time of even less than 5 hours per night (range, 4.8–6.6 hours), sleep latency (ie, the time to fall asleep) ranging from 11 to 45 minutes, and sleep efficiency (ie, the number of minutes of sleep divided by the total number of minutes in bed, multiplied by 100) ranging from 73% to more than 90%.[19,33,34,39] Time awake during the night fluctuated between 38 and 54 minutes on average over 16 weeks of observation.[34] In a sample of older caregivers, wakefulness after sleep onset (WASO) accounted for an average of 9%, thus suggesting wakefulness of at least 60 minutes per night.[39]

Three studies implemented a prospective design, without, however, this being related to any major events or transitions.

In the studies of Carter,[33,34] where observation spanned over 10[33] and 16[34] weeks, all sleep variables varied widely both within and between time points. Although fluctuations pointed to no specific direction, over time sleep disturbance was evident. Gibbins et al[39] recorded sleep for a small interval of 7 consecutive days. Despite within time-point variations, caregiver sleep parameters remained relatively stable and somewhat disturbed across time. Of note, generally low daytime activity levels were recorded, with large periods of the day (28%–31% of the day) spent immobile. At this time, caregivers took approximately 9 naps a day, each lasting 9 minutes on average.[39]

SLEEP PATTERNS IN THE CONTEXT OF PATIENT EARLY-STAGE DISEASE

Sleep data relating to this specific population are generally scant. Nevertheless, 2 recent, largely heterogeneous, cross-sectional studies provided some descriptive, yet inconclusive, evidence. In the first study,[29] 90 family caregivers providing care for an average of 5 months to patients receiving chemotherapy treatment were studied. Increased sleep latency and daytime dysfunction, short sleep duration (6–7 hours per night), and multiple nocturnal disturbances were self-reported. Conversely, habitual sleep efficiency remained at a satisfactory level.[29]

Dhruva et al[38] reported subjective and objective sleep data of 103 family caregivers of patients with prostate, breast, lung, or brain cancer. Data were collected before initiation of primary or adjuvant radiotherapy. In this sample of relatively older caregivers, objective sleep measurements indicated no major disturbances: sleep onset latency (~13 minutes on average), total sleep time (~7 hours on average), sleep efficiency (~84%), and daytime sleep (~6% of wake time) were fairly adequate. However, the number of nightly awakenings exceeded 17 per night, possibly explaining the increased time in WASO (13% of total sleep time).[38] All but one circadian rhythm parameter (acrophase) was outside normal values. This is indicative of low daytime and higher nighttime activity; however, this trend was not found to correspond with deficits in other subjective and objective sleep variables.

SLEEP PATTERNS IN THE CONTEXT OF SPECIFIC DISEASE TYPE

Few studies targeted caregivers of patients with a specific type of cancer, and their limited exploratory scope precludes generalizability. Results from 2 reports indicated only moderate levels of nocturnal disruption and wakefulness among female family caregivers of patients with prostate cancer at the initiation of radiation therapy.[40,43] Patient and caregiver good functional status and low treatment-related burden might have played a role in the relative absence of sleep problems, yet such relationships were not explored.

Conversely, Cho et al[37] highlighted the presence of poor sleep quality, difficulty with falling asleep, and daytime dysfunction after the first cycle of chemotherapy for gastric cancer. Caregivers were predominantly female middle-aged family members. However, neither caregiving characteristics nor detailed data with regard to key sleep parameters were provided. Specifically, whether caregivers were recruited at different time points in the course of chemotherapy remains unknown. Among 61 family caregivers of women with newly diagnosed, early-stage breast cancer, 8 of 10 caregivers reported poor sleep quality.[36] Sleep latency and duration, as well as daytime dysfunction, were the areas predominantly affected in this group, yet specific details were not provided.

ADDITIONAL SLEEP DATA RELEVANT TO PERSONS IN CAREGIVING ROLES

Overestimation of self-reported sleep problems compared with objective assessment has been suggested.[39,43] Nevertheless, Carter[33] reported that caregivers typically underrated their sleep disturbance when compared with actigraphic measures. Perhaps, caregivers perceived their own sleep disturbance as less important when compared with the patient's advanced illness.[19,29]

Interestingly, less than 20% of caregivers might actually use some prescribed or over-the-counter sleep medication.[29,31,36–39] This behavior is possibly driven from fears of not being alert to provide care to the patient during the night,[31,32,34,37] or from cultural beliefs surrounding the use of sleep medication.[37] Such beliefs can well explain why most caregivers never discuss their sleep problems with health professionals.[19] Nevertheless, nonpharmacological strategies (eg, lifestyle and behavioral practices, biological treatments) have been identified as a potential resort for caregivers of persons with cancer to get through the sleep-deprived days.[19,29]

Part B: Evidence With Regard to Sleep-Impairing Factors

PERSON- AND LIFESTYLE-RELATED FACTORS

Age and Gender. Aging and female gender are 2 of the most widely documented risk factors for changes in habitual sleep patterns in the general population.[73–78] Yet, lack of consistency exists with regard to sleep-impairing effects of aging on informal caregivers.[29,31,42,79] Possibly, this reflects methodological inadequacies and/or significant variability in the caregiver samples' characteristics. Lower habitual sleep efficiency was reported among older caregivers of patients with breast cancer during chemotherapy[36]; however, whether this was a true association or mediated by coexisting factors remained unexplained. Whereas disrupted nocturnal sleep[51,58] and longer time in bed[49] have also been reported in older caregivers of persons with dementia, greater daytime dysfunction might be more prevalent in younger individuals.[66] This is perhaps an indication that daytime dysfunction may be of greater importance to younger, more active, and possibly still employed caregivers, whereas the older ones can compensate their sleep loss through increased daytime napping.

Disrupted sleep in female caregivers of elderly people[80] or patients with Parkinson's disease[70] and in male caregivers of spouses with moderate to severe dementia[59] has been reported. Nevertheless, clinical or statistical differences in sleep by gender are absent among caregivers of patients with cancer.[29,31,32,36,37] Is this related to the fact that male and female participants in

these studies were equally distressed? Although Cho et al[37] reported an absence of significant differences in perceived sleep quality, female caregivers did report greater frequency of depressive symptoms and fatigue severity than did the males. The same was true for a sample of caregivers of patients with advanced cancer.[31] Importantly, overrepresentation of female[31,37] or male[36] caregivers in such caregiver samples (>77% of participants) might have not allowed for this association to reach statistical significance.

Personality. Personality features have been suggested as possible mediators of disrupted sleep in caregivers of patients with cancer.[35] Despite some weak to moderate correlations, Carter and Acton[35] failed to include these personality parameters in a predictive model of sleep patterns. Moreover, whether the association between personality and sleep is gender-specific is shrouded with ambiguity. Similarly, it remains unclear whether the actual association of type of personality with sleep is an indirect one, with depression and/or coping being the link between the 2 variables. In several studies, personality traits emerged as a strong predictor of caregiver depression and coping.[81–84] Thus, a more substantial hypothesis would be that personality deficits lead to increased levels of depressive mood and poor coping; these in turn interfere with caregiver sleep architecture.

Primary Sleep Disorders. Primary sleep disorders such as sleep-disordered breathing or periodic leg movements can perpetuate a disturbed sleep-wake cycle. This may be true even when the caregiving demands are less urgent or the majority of other triggers have ceased. Similarly, a history of unstable habitual sleep patterns also can increase susceptibility for disrupted sleep. Impressively, examination of those covariates in informal caregivers remains near zero. Only recently, Gibbins et al[39] examined the presence of a notable history of disordered sleep in caregivers of patients with advanced cancer, where 12% of poor sleepers reported past sleep problems. However, sleep history was not specifically examined as a potential contributor to caregiver sleep disturbances.

Biological and Genetic Factors. Until recently, research relevant to the roles of proinflammatory cytokines in sleep disturbances of caregivers of patients with cancer was scant.[85–88] Findings from a longitudinal, repeated-measures study suggested that certain functional genetic variations in the tumor necrosis factor α[44] and interleukin 6[47] genes might act as copredictors of baseline level and trajectories of sleep disturbances. Despite some significant between-groups differences, participants had fairly low levels of clinical sleep disturbance, implying the need for more research with larger samples and with greater variability in levels of sleep disturbances.

Comorbid Conditions. Declining health might also precipitate alterations in habitual sleep patterns of caregivers of patients with cancer, similarly to other caregiver populations.[28] Nonetheless, underlying complexity, lack of directionality, and lack of sufficiency in self-rated measures of physical health may have been responsible for discrepancies in relevant evidence[29]: whereas some studies favor a link between health status and caregiver sleep,[49,71] others have failed to show a statistical association.[52,66] In any case, mediators including age, health habits, gender, and level of psychological distress should be taken into account when the relationship between caregiving, health problems, and sleep is examined.[28]

Sleep Hygiene. Habitual sleep routines might play a role in the regulation of sleep patterns in caregivers of patients with cancer.[89–92] Sleep hygiene recommendations have been almost uniformly included as part of various cognitive-behavioral techniques[92] for caregivers of patients with cancer[34] and dementia.[64] However, the actual sleep hygiene practices of informal caregivers have never been assessed. Similarly, exploration of over-time or health transition–related changes in caregiver sleep routines is absent. Therefore, a rather theoretical than evidence-based knowledge exists. Whether the relation between sleep hygiene practices and sleep can be extrapolated from other populations to cancer caregivers remains unknown. Even in the studies where sleep interventions for caregivers were tested,[34,64] it is questionable whether their positive effects could also be attributed to their sleep hygiene component.

FACTORS RELATED TO THE CAREGIVING EXPERIENCE

Caregiver Burden. Relevant literature partially confirms caregivers' increased vulnerability to sleep disturbance. Significant differences have been reported in caregivers of patients with cancer[42] or other chronic illnesses[50,62,63,66,67] compared with individuals in noncaregiving roles. There is a possibility, however, that this is a matter of subjectivity, given that objectively evaluated sleep patterns might not differ according to caregiving status.[49,51] Not all caregivers perceive their caring role as burdensome, and even if felt as such, what might be considered as burdensome may not necessarily be linked to sleep disruption. In fact, only weak to moderate[50,67] or even absence of[48,49] associations between subjective caregiver burden and sleep disturbances exists, indicating an increased complexity in underlying mechanisms. That said, stronger triggers such as depression might be responsible, rather than the caregiving experience itself.[53] Even in the cases where a positive relationship was found, the lack of longitudinal data cannot exclude the possibility that caregiver sleep problems observed might have preceded and accounted for burden, rather than resulted from caregiving.[52,53]

As patient needs increase, primary caregivers are expected to provide intensive care, which allows only for minimal periods for rest and sleep.[19,68] Yet, current limited evidence only moderately supports such a hypothesis. Only 1 longitudinal study confirmed baseline objective burden as one of the strongest predictors for sleep problems in the long run.[54] Mainly because of lack of longitudinal data, the extent of caregiver involvement in patient care, as perhaps implied by the number of activities undertaken, has not been found as related to sleep problems other than merely nocturnal sleep disturbances.[71] However, adaptation of the caregiver's sleep-wake schedule to that of the patient's might provide one of several explanatory links,[60] with caregiver narratives providing support to this relationship.[19] The patient's fatigue[48] and own sleeping difficulty[19,28,32,39] might be additional triggers. Despite the inconclusive findings, this seems to apply mainly to cohabiting patient-caregiver dyads and to bed- or room-sharing caregivers.

Fatigue. The extent to which care influences caregivers' daily schedule might be seen as a contributor to perceptions of fatigue.[46,93] This might be perceived as greater during the evening and at night.[40] The interaction between fatigue and nocturnal sleep disruption potentially flows both ways, thus leading to a negative feedback loop.[94,95] Yet, only moderate correlations were reported in 2 widely dissimilar, cross-sectional studies. In these studies, the association between caregiver fatigue and sleep disturbances was explored after the first chemotherapy cycle for gastric cancer[37] and before radiotherapy for prostate cancer.[40] A causal link between the 2 variables has not been established. Admittedly, fatigue and sleep disturbances could coexist and covary without otherwise interacting. Indeed, relatives of patients with cancer in palliative care reported moderate levels of fatigue, even though they were sleeping fairly well.[46] Although sleep disturbances have been proposed as a significant over-time predictor of evening fatigue,[41] whether baseline and ongoing fatigue can be regarded as a predictor of over-time sleep disruptions in this population remains to be confirmed in adequately powered, prospective studies.

Health Deficits. The caregiving situation itself may be associated with negative health effects[96,97] that can adversely impact sleep. This may be true at least at a theoretical level, given that the bidirectionality of this relationship has been examined in cross-sectional studies only.[96,97] In addition, only limited, unclear evidence exists with regard to the effects of physical activity on caregivers' sleep patterns. Objective increases in total sleep time have been positively, whereas increases in WASO have been negatively, associated with caregivers' physical functioning after adjusting for caregiver age.[65] Among female family caregivers of patients with cancer,[43] increased daytime napping was recorded in the group of lower physical activity. Conversely, only marginal subclinical differences were observed in self-reported sleep: women in the active group overall slept approximately 50 minutes more on average than the inactive ones, whereas inactive caregivers reported increased sleep latency (mean, 23.3 vs 11.7 minutes) compared with the active ones. Even so, adjustments for age, level of depression, or concurrent illnesses were not performed.

Sleep Hygiene Deficits. Inadequate sleep hygiene can be an important predisposing factor, but also become a perpetuating cause for caregiver disrupted sleep patterns.[19,28,92] In theory at least, caregivers "might fall into iatrogenic sleep routines (…) to compensate for having their nightly rest disturbed."[28(p145)] However, Aslan et al[29] reported that a mere 7% of the participants consciously attributed their disruptions to their poor sleep routines. Because of the absence of systematic research, the extent of sleep hygiene's contribution to poor sleep is still unclear. What is more, the evident lack of longitudinal sleep assessments also precludes examination of sleep hygiene as a mediator for long-term deficits in the caregivers' sleep.

Emotional Distress. The emotional distress associated with caring for the ill loved one may explain alterations in sleep patterns of informal caregivers.[29,32] Anxiety, depressed mood, stress, nocturnal worry, hyperalertness ("a busy mind"), and physiological arousal can all be related to sleep disruption.[19,39,54] Although superficially examined, some moderate correlations between sleep problems, anger, and anxiety among caregivers of patients with advanced cancer have been reported.[23] A type of "anxiety from exposure to adverse effects of the therapy on the patient" has been mentioned by caregivers themselves as a potential reason for sleep problems.[19,29] Some caregivers with depressive symptoms might wake up crying,[32] and this can lead to feelings of restless or nonrestoring sleep the next morning. Moreover, depressive mood has been associated with decreased total sleep time and sleep efficiency and increased daytime dysfunction in cancer and noncancer caregivers.[23,31–33,52–54,69,71] Depression may be a persistent risk factor for sleep disturbance even after adjusting for differences in caregiver coping strategies, type of personality,[35] caregiver age, and number of sleep aids used.[62] Nevertheless, additional mediating factors such as gender or patient disease status need to be taken into consideration.[32,33]

Coping Strategies. The way caregivers cope with their indirect illness experience can influence manifestation of feelings of anxiety and sadness that interfere with sleep. Those caregivers who avoid and/or deny their situation or are passively resigned to that may be more distressed[98] and depressed[99] and therefore more prone to disrupted sleep. In only 1 study were the linkages between caregiver personality, coping, and sleep problems explored.[35] Significant, yet moderate, positive associations between less functional coping and sleep problems and between neuroticism and sleep problems among caregivers of patients with advanced cancer emerged. However, on further regression analyses, depression was the only significant predictor of caregiver sleep problems. Most probably, in this small sample (n = 51) of overly depressed individuals, the indirect effects of coping and personality on sleep were overshadowed by the high correlations documented between depression and sleep problems.

Social Support. Deficits in caregiver social support have been associated with ineffective ability to cope[100] and with greater depressive symptoms and negative affect.[11,101] Hence, inadequate or unavailable social support can be claimed as indirectly related to perceptions of poor sleep quality among cancer caregivers.[19,29] Absence of a person to share the caregiving responsibility with was associated with poorer subjective sleep quality in individuals supporting women with early-stage breast cancer,[36] yet confounding factors of this relationship were not examined. Using structural equation modeling, Brummett et al[50] demonstrated that dementia caregivers with inadequate social support were more likely to develop sleep problems. This association is possibly mediated by the effects of perceived poor social support on the development of high levels of negative affect.

■ Summary and Critique

The present review confirms the variability of sleep problems evidenced among informal caregivers of people with cancer: at least 4 of 10 individuals may report at least 1 problem. Short sleep duration, nocturnal awakenings, wakefulness after

sleep onset, and daytime dysfunction seem to be the areas most affected irrespective of stage or type of disease, yet circadian activity remains understudied. In addition, despite a wide spectrum of potential triggers, no safe conclusions can be drawn upon that could direct clinicians' attention to factors that can be of definite significance in the onset and maintenance of sleep disturbances.

Current findings share a number of common drawbacks. First, the majority of data are skewed toward the more advanced stages of disease and more prolonged caring periods. Consequently, they mainly target individuals deeply affected by the patient's severity and chronicity of illness and needs. Second, a predominant focus on female spouses in caregiving roles is noted. Third, clarification of the effects of cancer type–specific experiences on caregivers' sleep patterns is lacking. In other words, generalizability is limited only to white spouses older than 50 years, often providing very intense actual care. Inclusion of diverse age, gender, racial, and ethnic groups of informal family and nonfamily caregivers in future exploratory sleep studies is recommended (Figure 3).

An additional point for debate would be whether self-reported prevalence of sleep problems in this population has been reliably measured thus far and whether prevalence rates reflect clinical importance. For instance, Cho et al[37] identified 80% of the caregivers of outpatients with gastric cancer as with poor sleep quality (mean global PSQI score, 5.81 ± 2.20; cutoff score, ≥5). Carter et al[31–33] reported very similar frequencies. However, in the latter studies, mean PSQI scores ranged between 8 and 11, thus indicating greatly disturbed sleep. It is possible that low specificity of the cutoff score selected for this population might have led to an overestimation of sleep disturbance, although actual perceptions might not have pointed to this conclusion. Insufficiently established cutoff scores may in some cases lead to overestimation or underestimation of the overall prevalence of these problems. Indeed, Dhruva et al[38] reported that, within the same sample, 59% and 39% of caregivers were identified as poor sleepers based on cutoff scores from 2 different self-report sleep measures. This underscores the need for more validation studies implementing a combination of subjective and objective measures in this population.

Given the presence of only a limited number of longitudinal studies in caregivers of patients with cancer,[33,34,39] trends of over-time changes in caregiver sleep patterns also remain practically unexplained. This is especially true for major patient health transitions. In addition, a rather secluded terminology to define caregivers was used in the studies, with the focus being on family and mainly spousal caregivers. Even in those studies adopting a broader definition, inclusion of adequate numbers of other family members or nonfamily individuals in caregiving roles was limited.[22,23] This is a clear indication for more comprehensive sampling methods to be pursued in future studies. Finally, a considerable trend can be noted in terms of cultural context. The majority of data derive from the United States or from eastern cultures.[29,36,37] Hence, it is evident the need for the European, Australian, and South American perspectives on cancer caregiver sleep/wake patterns to be explored.

Although the contribution of an array of factors is recognizable, current evidence only partially supports their causal relationship to sleep problems. This is mainly due to the cross-sectional nature of the vast majority of studies conducted. Although links between several factors and disrupted sleep patterns have been reported, it is largely unknown whether this "desirable" direction of relationship is true. In turn, this lack of information often leads researchers to complement cancer-specific data by "borrowing" evidence derived from other caregiving populations; these may also be true for caregivers of people with cancer, but to what extent? In any case, specific data relating to the nature, frequency, severity, or patterns of occurrence of factors affecting sleep regulation when caring for patients in different cancer stages or with different cancer types still remain hidden. For instance, despite the fact that advanced

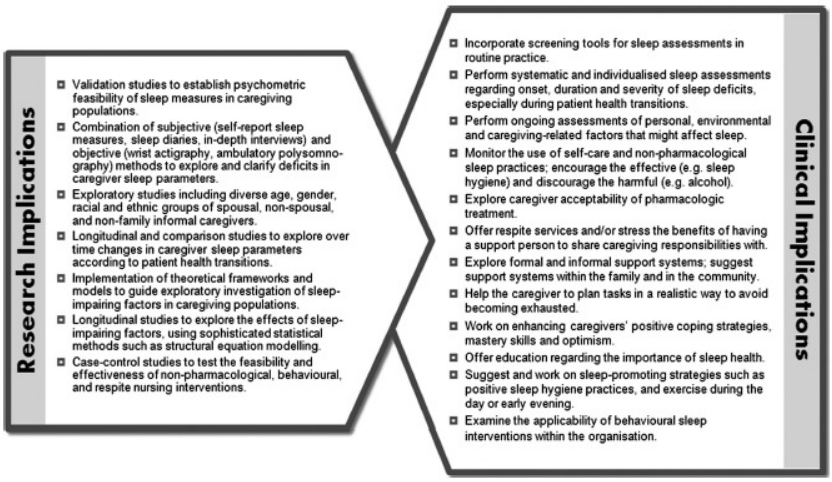

Figure 3 ■ Implications for future research and practice.

cancer has been linked to increased patient needs that may increase caregiver burden, sleep disruption warrants exploration beyond this limited area. Sleep problems experienced by caregivers may manifest themselves irrespective of patient disease severity, but fluctuate according to the overall caregiving situation. In that sense, perceptions of disturbed nocturnal sleep might be greatly associated with additional correlates such as caregiving or other responsibilities, duration of caregiving, or caregiver symptoms and concerns. Such important parameters have scarcely been taken into consideration in the relevant studies. Findings derive from diverse samples of individual, cross-sectional studies only. Whether there is a true prospective impact on sleep problems or evidence is only influenced by different characteristics of these diverse samples remains to be found. More longitudinal, mixed-methods, and comparison studies will need to explore the onset and maintenance of sleep disorders based on the gravity of the caregiving situation in the context of diverse types of cancer and disease severity. In addition, longitudinal data could clarify whether positive coping styles and personality traits can be regarded as truly linked to caregiver sleep quality, through a protective mechanism that possibly leads to reduction of caregiver psychological distress. To this direction, application of a comprehensive theoretical framework or model could effectively guide nursing research to explore the effects of sleep-impairing factors in this population.[102]

Aside from their research projections, findings from this review have important practical implications for nurses and other healthcare professionals. Because caregivers may fail to seek help for their disrupted sleep patterns, clinicians need to be proactive in order to ensure that these persons are adequately supported. That being said, clinicians are encouraged to engage into regular assessments of the caregiver experience to explore its effects on habitual sleep patterns and functioning. Routine use of a brief screening tool could provide valuable information regarding the nature and the severity of sleep deficits and daytime dysfunction. Figure 3 highlights key aspects to be taken into account in cancer care planning for informal caregivers who are poor sleepers.

Some limitations are worth noting. Our search strategy aimed at including all relevant literature. However, it was not exhaustive but limited to the most common databases and to articles published in the English language only. This might have resulted in missing some publications. What is more, as we excluded studies with caregivers during the terminal phases of cancer care or during bereavement, our findings are not indicative of the sleep patterns of these caregiver subgroups, thus rendering further research necessary.

■ Conclusions

Sleep research is only beginning to increase our knowledge on an area of functioning that may be of paramount importance for individuals assuming caregiving roles in the context of cancer. Clearly, more studies are needed to elucidate the experience of sleep disturbances in this growing population. Whereas adequately powered, longitudinal quantitative studies are needed to describe changes and establish associations, well-designed qualitative studies also are warranted to shed light to enhance our understanding on the true meaning of disturbed sleep in the lives of informal caregivers who go through the experience of cancer. Meanwhile, clinicians are encouraged to be vigilant to caregiver complaints of altered sleep patterns and potential triggers and to offer individualized education and intervention strategies that can improve caregivers' sleep quality and quality of life.

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Review Article

Sleep and Sleep-Wake Disturbances in Care Recipient-Caregiver Dyads in the Context of a Chronic Illness: A Critical Review of the Literature

Grigorios Kotronoulas, BSN, MSc, Yvonne Wengström, OCN, PhD, and Nora Kearney, RGN, MSc

School of Nursing & Midwifery (G.K., Y.W., N.K.), University of Dundee, Dundee, United Kingdom; Division of Nursing (Y.W.), Department of Neurobiology, Care Science and Society, Karolinska Institutet, Huddinge, Sweden

Abstract

Context. Alterations in sleep-wake patterns of care recipients and their informal caregivers are common in the context of a chronic illness. Given the current notion that sleep may be regulated within and affected by close human relationships, concurrent and interrelated sleep problems may be present in care recipient-caregiver dyads.

Objectives. To critically analyze evidence regarding concurrent sleep patterns or changes in care recipient-caregiver dyads in the context of a chronic illness and address methodological and research gaps.

Methods. Using a wide range of key terms and synonyms, three electronic databases (Medline, CINAHL, and Embase) were systematically searched for the period between January 1990 and July 2011.

Results. Ten studies met prespecified selection criteria and were included for analysis. Study quality was fair to good on average. Seven studies were conducted in the context of dementia or Parkinson's disease, two in the context of cancer, and one study included a group of community elders with mixed related comorbidities and their informal caregivers. Bidirectional associations in the sleep of care recipient-caregiver dyads seem to exist. Concurrent and comparable nocturnal sleep disruptions also may be evident. Yet, inconsistencies in the methods implemented, and the samples included, as well as uncertainty regarding factors coaffecting sleep, still preclude safe conclusions to be drawn on.

Conclusion. The dyadic investigation of sleep is a promising approach to the development of truly effective interventions to improve sleep quality of care recipients and their caregivers. Nevertheless, more systematic, longitudinal dyadic research is warranted to augment our understanding of co-occurrence and over time changes of sleep problems in care recipient-caregiver dyads, as

Address correspondence to: Grigorios Kotronoulas, BSN, MSc, School of Nursing & Midwifery, University of Dundee, 11 Airlie Place, Dundee, DD1 4HJ, United Kingdom. E-mail: g.kotronoulas@dundee.ac.uk

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well as to clarify covariates/factors that appear to contribute to these problems within the dyad and across time and context of illness. J Pain Symptom Manage 2013;45:579–594.

Key Words

Sleep, sleep-wake disturbances, patient-caregiver dyad, informal caregiving, dyadic approach, chronic illness, critical review

Introduction

The notion that the patient-caregiver relationship is made up of two people, both of whom influence and are influenced by the other, has been stressed as particularly relevant to health care.[1,2] Now more than ever, chronic illness is considered a shared experience that impacts individuals on a level that transcends mere individualistic limits and cannot be understood solely within person-centered models of care[3–5] but in the context of complex networks of relationships.[5] According to social contextual models, health outcomes are likely to covary in close relationships, as in the patient-caregiver relationship.[2,6–17] For instance, any change in the functioning of one individual can affect the functioning of their significant ones.[18] Similarly, although external factors, such as disease severity and social support, may affect patients' and caregiver's physical and psychosocial well-being directly and unidirectionally, interdependence can contribute to a bidirectional situation in which the well-being of each individual in the dyad also affects the well-being of the other.[19] There is general consensus that when patients and caregivers are treated simultaneously, important synergies can be achieved contributing to the well-being of each person.[20,21] Conversely, when these interrelated and often concurrent needs are neglected, patient-caregiver dyads are denied the opportunity to obtain optimal care. Therefore, it has been argued that to provide optimal comprehensive health care, the care plan must focus on these patient-caregiver units.[22]

Sleep is considered a vulnerable state that, in part, occurs, or otherwise is optimized, in the presence of adequate levels of physical comfort and emotional safety, as well as in the relative absence of psychological distress and psychophysiologic arousal.[23–25] An adequate social environment may be particularly important for such feelings to emerge.[26] Hence, for humans, the social projections of sleep are being recognized,[23] as sleep may be regulated within and affected by close human relationships,[23,27] such as the patient-caregiver relationship. Sleep-wake disruptions have been frequently reported in care recipients[28–31] and their informal caregivers[29,32–34] in the context of a chronic illness. However, the fact that the science of sleep has tended to view sleep as an entirely individual phenomenon can be described as a rather confined approach, impeding assessment and management of sleep disorders that might manifest themselves especially during periods of adjustment to illness. Given that interdependence is a defining feature of human relationships, it also might be a defining feature for sleep as seen in the context of a close patient-caregiver relationship.[35]

According to the attachment hypothesis, persons in close relationships may develop expectations from one another that are thought to mediate affect and arousal, particularly in times of real or perceived threat.[23,26,36,37] This theory could, to a certain extent, justify the value of concurrent assessment of sleep patterns of patients and their primary informal caregivers, either in a family[26] or in a wider support context. As care recipients and caregivers go through the experience of illness together, their emotional reactions, distress, and coping strategies also might coaffect their sleep. In a situation involving the copresence of persons, cooperation from each other to achieve their own "sleep ritual" can be of particular importance.[38] This might involve the choice of common bedtimes and complementary sleep conditions.[38] In the context of a chronic illness, however, this "cooperation" can become blurred, given that patient symptom experience, caregiver burden,

and associated frustration can alter sleep habits/rituals or restrict actual sleep of the dyad in a way that concordance might be no longer feasible. Moreover, whereas patient symptom distress can lead to increased caregiving efforts and disrupted caregiver sleep patterns, increasing caregiver burden equally can lead to poor caregiving performance, which in turn might inhibit management of patient symptoms influencing sleep.

Drawing on the above arguments, it can be assumed that such a dyadic approach would augment our understanding of co-occurrence of sleep problems in care recipient-caregiver dyads, trends of concurrent transformation of these sleep problems across time, and covariates/factors that appear to contribute to these patterns within the dyad and across time. Some argue that this is key to the development of truly effective treatment strategies.[23,39,40] Therefore, a systematic search for publications addressing the issue of concurrent examination of sleep-wake disturbances in care recipient-caregiver dyads was conducted in the context of a chronic illness. Specifically, the purpose of this systematic review was to analyze evidence on interrelations in the dyads' sleep-wake patterns or problems, explore potential sleep-impairing factors, and address methodological and research gaps in this body of literature.

Methods

A systematic search was performed to identify original publications in which sleep patterns were concurrently assessed in patient-caregiver dyads in the context of a chronic illness. Studies were identified by systematically searching three electronic databases (Medline, CINAHL, and Embase). A comprehensive search strategy was devised, which implemented a wide range of key terms and synonyms (Table 1). The reference lists of retrieved studies also were examined for any studies that may have been overlooked, as were the reference lists of two topical research reviews.[23,41] Additional literature was sought through the use of the search engine Google Scholar.

Studies were eligible for the review if they were written in the English language, were conducted with adult (>18 years of age) individuals, examined sleep as a primary variable in patient-caregiver dyads irrespective of the context of illness, and were published as original articles in peer-reviewed journals from January 1990 to July 2011, representing the period in which studies of sleep within different clinical populations emerged. Unpublished studies, dissertation studies, or conference presentations were not included in the present review.

A shortlist of studies was initially compiled, and titles and abstracts were screened to assess relevance to the review. Potentially eligible studies were retrieved in full and checked for adherence using the aforementioned selection criteria. Study characteristics were extracted using a systematic scheme. Each study was evaluated for methodological quality using a validated scoring system for the systematic appraisal of empirical studies with varied methodologies.[42] Each study component evaluated (total of 10) was awarded a quality score ranging from 4 (good) to 1 (very poor), which generated a maximum potential score of 40.

Table 1
Electronic Databases Searched and Search Terms Used

Electronic Databases	Search Terms
Medline (1948–2011) CINAHL (1982–2011) Embase (1980–2011)	1. (exp Sleep Disorders, Circadian Rhythm* OR exp Sleep OR exp Sleep Deprivation OR exp Sleep Disorders OR exp "Sleep Initiation and Maintenance Disorders" OR exp Sleep Disorders, Intrinsic OR sleep*) 2. (sleep* OR insomnia OR sleep disturbance* OR sleep disorder* OR sleeplessness OR sleepiness OR circadian rhythm* OR circadian activity OR sleep efficiency OR quality of sleep OR sleep quality OR daytime disturbance OR nap* OR awakening OR sleep latency OR sleep regulation OR sleep architecture OR sleep physiology OR drowsiness OR homeostatic OR sleep propensity OR WASO) 3. 1 *OR* 2 4. (Caregiver* OR carer* OR caregiving OR partner* OR family member* OR significant other* OR friend* OR exp Caregivers/) 5. (dyad* OR dyadic approach OR dyadic context OR couples OR interdepend* OR interpersonal OR patient-caregiver interaction* OR patient-caregiver dyad*) 6. 3 *AND* 4 *AND* 5

Exp = the proposed expansion search method provided by the electronic database.

However, no studies were excluded on the grounds of quality, given the lack of agreement in the application and interpretation of quality criteria.[43] In addition, the evidence categories used by the U.K. Department of Health in the 2001 National Service Framework[44] were used to assess the level of evidence presented according to the type and quality of research (Table 2). Because of the heterogeneity of the studies retrieved, findings were integrated in a narrative synthesis.

Results

Study and Population Characteristics

The searches identified 1114 articles (Fig. 1), 10 of which reported on studies concurrently examining sleep patterns in care recipient-caregiver dyads (Table 3). Seven studies were conducted with patients with dementia[39,40,45,46] or Parkinson's disease[47–49] and their informal caregivers, and one study included a group of community elders (>65 years) with mixed related comorbidities.[50] Two studies included people diagnosed with cancer and their informal caregivers.[51,52]

Where stated, care recipient and caregiver populations were predominantly Caucasian (81%–100% and 67%–100%, respectively). Care recipients had a grand weighted mean ($\overline{X}$) age of 69.2 ± 5.9 years (range of means 64.4–80.7 years), whereas caregivers were slightly younger ($\overline{X} = 63.8 \pm 1.9$ years; range of means 61.7–67.4 years). In most studies, patients were predominantly male (65%–78%) and caregivers were predominantly female (63%–100%). All studies aimed at recruiting family members in caregiving roles, except for one study,[51] where, however, family members accounted for as much as 93% of the total sample. Caregivers were either care recipients' spouses or partners (39%–100%) or children (2%–53%). Most frequently, care recipients and caregivers were living together (54%–100%). However, only four studies explicitly stated percentages (54%–86%) of care recipients and caregivers sharing the same bedroom.[39,45,46,51] Finally, data pertinent to time since patient diagnosis and to caregiving responsibilities were only partly reported. Where stated, people with dementia[39,45,46] and Parkinson's disease[47,48] had been diagnosed at least four and seven years ago on average, respectively.

Assessment of sleep through self-reports only was conducted in three studies,[47–49] one study was based on only objective recordings,[39] and the remainder implemented a combination of subjective and objective sleep measures.[40,45,46,50–52] Only one study was found that used polysomnography for collection of three-day data on caregivers' sleep.[45] Actigraphic measurements were used in seven studies to record sleep-wake patterns of patients and caregivers, where wrist devices were worn for 48,[51] 72,[45] 168,[39,52] 144–192,[50] 214,[40] and 1008[46] consecutive hours. The Pittsburgh Sleep Quality Index[53] was the most frequently used self-report measure in the studies reviewed,[45,46,48,51] assessing quality of sleep over the previous month.

Methodological Quality and Level of Evidence

Overall, studies varied in methodological quality, with scores awarded ranging from 25 to 33 of 40, with a mean score of 28.4 (SD

Table 2

Evidence Categories Used by the U.K. Department of Health in the 2001 National Service Framework[44]

Level of Evidence	Evidence Source
A1	Systematic reviews, which include at least one RCT, for example, systematic reviews from Cochrane or NHS Center for Reviews and Dissemination
A2	Other systematic and high-quality reviews, which synthesize references
B1	Individual RCT
B2	Individual nonrandomized, experimental or intervention studies
B3	Individual well-designed nonexperimental studies, controlled statistically if appropriate. Includes studies using case control, longitudinal, cohort, matched pairs, or cross-sectional random sample methodologies and well-designed qualitative studies and well-designed analytical studies including secondary analysis
C1	Descriptive and other research or evaluation not in B (e.g., convenience samples)
C2	Case studies and examples of good practice
D	Summary review articles and discussions of relevant literature and conference proceedings not otherwise classified

RCT = randomized controlled trial; NHS = National Health Service.

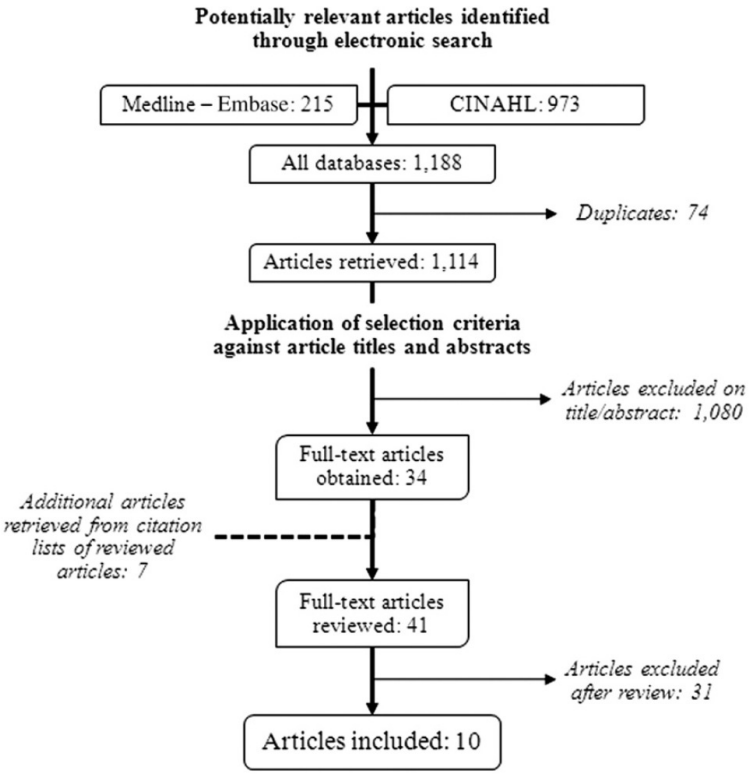

Fig. 1. Flow diagram of the article selection process.

2.7) (Table 3). On average, reporting of the studies was of a fair to good standard. Research bias, ethical issues, and introduction and aims were the areas where the lowest marks were awarded.

In terms of level of evidence, one article[46] reporting on an individual intervention study was identified and classified as level of evidence B2 based on the Department of Health National Service Frameworks hierarchy scheme (Table 2). The remaining nine studies[39,40,45,47–52] were classified as level of evidence B3 as they were matched pairs and/or prospective and/or secondary analysis studies (Table 3).

Major Categories and Findings

Irrespective of the illness context, evidence regarding bidirectional associations in the sleep of care recipient-caregiver dyads is still inconclusive and, in some cases, contrasting. Nevertheless, interesting and promising preliminary findings or associations were reported in the studies reviewed. These findings were organized into two broad thematic categories: sleep-wake patterns or problems and sleep-impairing factors. Table 4 (first two columns) summarizes associations according to the level of clarification established in the relevant literature.

Sleep-Wake Patterns or Problems of Care Recipient-Caregiver Dyads. In agreement with the concept of care recipients and caregivers living in close relationship, similarities in nocturnal and daytime sleep behaviors within dyads were reported in three studies, where close synchronization of bedtimes and wake times,[40,45,51] daytime naps,[40] and sleep duration[45] was found. Caregivers had generally later bedtimes (ranging from 35 to 42 minutes on average)[45,46] and earlier awakening times (ranging from 4 to 36 minutes on average),[45,46,51] thus demonstrating organization of their sleep routines around the patient. What is more, the notion

Table 3
Summary of Methodological Characteristics of the Studies That Met Selection Criteria

Authors, Year (Ref.)	Objective(s) and Population	Study Design, Location, and Participant Characteristics	Sleep and Secondary Outcome Measures	MQS	LE
Carney et al., 2011[51]	To evaluate for differences in the severity of self-reported sleep disturbance and objective measures of nocturnal sleep/rest and daytime wake/activity in oncology patients and their family caregivers at the initiation of primary or adjuvant radiation therapy	Descriptive and correlational; cross-sectional; and part of a larger longitudinal study U.S. $n = 102$ dyads; *Care recipients:* age 64.1 ± 10.2 years; 68.6% male; 95.1% married/partnered; 80.2% white; 42.2% employed; no. of comorbidities 4.6 ± 2.6; and type of cancer: breast, prostate, lung, and brain. *Caregivers:* age 61.7 ± 10.4 years; 71.6% female; 95.1% married/partnered; 78.2% white; 46.5% employed; 91.2% spouse/partner; and 80.8% partner in same bed	Sleep measures: *Objective:* Continuous 48-hour wrist actigraphy (two days before treatment initiation); *Subjective:* PSQI and GSDS (approx. one week before treatment initiation) Outcome measures: —	30	B3
Castro et al., 2009[45]	To explore the correspondence of sleep-wake patterns of patients with dementia in relation to their female caregivers (secondary objective)	Descriptive and exploratory and cross-sectional U.S. $n = 6$ dyads; *Care recipients:* age 79.2 ± 11.4 years and no. of daily activities needing assistance 7.2 ± 1.2. *Caregivers* ($n = 9$): age 62.6 ± 9.7 years; 67% married/partnered; 67% white; 22% employed; 66.7% spouse; 33.3% parent; duration of caregiving 3.6 ± 3.0 years; and ($n = 6$) 66.7% caregiver in same bed	Sleep measures: *Objective:* Continuous 72-hour home PSG—caregivers, continuous 72-hour wrist actigraphy—patients; *Subjective:* PSQI, ESS (Day 1 of PSG data collection), and daily sleep diaries (Days 1–3 during PSG)—caregivers Outcome measures: —	30	B3
Gibbins et al., 2009[52]	To determine the prevalence of sleep-wake disturbances and the amount of daytime spent in activity and rest and to examine the relationship between sleep disturbances, physical and psychological symptoms, and quality of life in patients with advanced cancer and their family caregivers	Descriptive and observational and prospective U.K. $n = 60$ dyads; *Care recipients:* age 67 (32–80) years; 55% female; 71.7% ECOG PS 1–2; no active treatment received within two weeks before participation; and type of cancer: lung, breast, prostate, and colorectal. *Caregivers:* age 66 (27–80) years; 55% male; 100% spouse	Sleep measures: *Objective:* Continuous seven day wrist actigraphy; *Subjective:* Author-constructed sleep history inventory (baseline), daily sleep diaries (seven-day data collection), and ESS (Day 7) Outcome measures: ECOG PS, HADS (Day 7), SF-36 (Day 7), and MSAS (Day 7)	28	B3
Happe and Berger, 2002[47]	To assess the prevalence and causes of sleep problems in caregiving partners of patients with Parkinson's disease	Descriptive and exploratory; cross-sectional; and part of a larger longitudinal cohort study Germany $n = 101$ dyads; *Care recipients:* age 64.6 ± 9.8 years; 63% male; disease duration seven (0–28) years; disease severity: 80% mild and 54% mixed tremor dominant and rigid/akinetic disease. *Caregivers:* age	Sleep measures: *Subjective:* One item from the CES-D 10 short form—patients and caregivers; three items from the Giebener Beschwerdebogen scale—caregivers Outcome measures: UPDRS motor scale, Hoehn & Yahr classification, SF-36 (German version), PDQ-39, CES-D 10 short form, (Instrumental) activities of daily living, Caregiver Burden Inventory	25	B3

		62.3 ± 10.0 years; 63% female; 70% active caregiving; 54% daily caregiving; and 99% lived with the patient	(baseline and follow-up); and Giebener Beschwerdebogen scale for psychosomatic complaints (baseline)		
Lee et al., 2007[46]	To evaluate the sleep-wake patterns of community-dwelling patients with dementia and their primary caregivers before, during, and after two-week periods of institutional respite care	Prospective case series with intervention U.K. $n = 39$ dyads; *Care recipients:* age 76.5 (49–93) years; 67% male; 62% Alzheimer's disease; disease duration 4.8 ± 3.5 years. *Caregivers:* age 67.4 (34–87) years; 67%; 79.5% spouse and 20.5% daughter/son; and 54% caregiver in same bedroom	Sleep measures: *Objective:* Continuous six-week wrist actigraphy—patients and caregivers; *Subjective:* PSQI (baseline), daily sleep diaries, ESS (weekly), and sleep quality five-point Likert scale ratings—caregivers Outcome measures: SF-36 (Mental Health and Vitality subscales)	33	B2
McCurry et al., 2008[39]	To describe the day-to-day variation in sleep characteristics and the concordance between nighttime sleep of persons with Alzheimer's disease and their family caregivers	Descriptive and observational; prospective; and part of a larger longitudinal trial U.S. $n = 44$ dyads; *Care recipients:* age 78.8 ± 7.2 years; 50% male; 87% white; and disease duration 5.7 ± 3.2 years. *Caregivers:* age 64.6 ± 15.2 years; 66% female; 86% white; 100% lived with the patient; 57% spouses; and 57% caregiver in the same bedroom	Sleep measures: *Objective:* Continuous seven-day wrist actigraphy Outcome measures: MMSE, CSDD, CES-D, and SF-36 (Physical Functioning and Physical Role Functioning subscales), DMSS	32	B3
Pal et al., 2004[48]	To evaluate the pattern and determinants of disturbed sleep in patients with Parkinson's disease complaining of sleep disturbances and in their primary caregiver	Descriptive and correlational and cross-sectional Canada $n = 23$ dyads; *Care recipients:* age 67.6 ± 8.5 years; 65% male; disease duration 8.4 ± 6.6 years; and sleep problems' duration 7.8 ± 7.6 years. *Caregivers:* age 65.2 ± 11.3 years; 65% female; and 100% spouses	Sleep measures: *Subjective:* PSQI and General Sleep Questionnaire Outcome measures: ZDRS, ZARS (patients and caregivers), and PIMS (patients)	27	B3
Pollak & Stokes, 1997[40]	To compare sleep and motor activity patterns in older people with and without dementia and their caregivers	Descriptive and observational and prospective U.S. $n = 43$ dyads; *Care recipients:* age 80.7 ± 7.9 years; 50% male—dementia;[25] age 73.7 ± 7.2 years; and 50% male—nondementia.[18] *Caregivers:* age 67.3 ± 10.2 years; 75% female—dementia;[25] age 58.1 ± 16.0 years; 60% female—nondementia;[18] 53% child and 39% spouse; and 60% lived in the same household	Sleep measures: *Objective:* Continuous nine-day wrist actigraphy; *Subjective:* Daily sleep logs completed for 14 days Outcome measures: MDRS (Total score and Memory subscale)	26	B3
Pollak et al., 1997[50]	To quantify nocturnal interactions by cross-correlating motor activity simultaneously recorded in elders (>65 years of age) and their principal caregivers	Descriptive and observational and prospective U.S. $n = 44$ dyads; *Care recipients:* age 77.9 (64–92) years; 55% female; varying health problems: depression, Parkinson's disease	Sleep measures: *Objective:* Continuous nine-day (six to eight days) wrist actigraphy; *Subjective:* Daily sleep logs completed for 14 days Outcome measures: MDRS (Total score and Memory subscale) and CARE depression	26	B3

(*Continued*)

Table 3
Continued

Authors, Year (Ref.)	Objective(s) and Population	Study Design, Location, and Participant Characteristics	Sleep and Secondary Outcome Measures	MQS	LE
		(16%), dementia (36%), and dementia and Parkinson's disease (14%). *Caregivers:* age 61.9 (29–86) years; 73% female; and 52% spouses and 41% daughters	scale		
Smith et al., 1997[49]	To evaluate factors that may influence the prevalence and severity of sleep disturbances in patients with Parkinson's disease and their spouses and compare with a group of healthy adults	Descriptive survey and cross-sectional Germany $n = 153$ dyads; *Care recipients:* 78% male, age 67.0 ± 9.7 years; 22% female, age 67.6 ± 9.1 years; and 59% mixed tremor dominant and rigid/akinetic disease. *Caregivers:* 78% female, age 62.4 ± 9.9 years and 22% male, age 70.8 ± 10.8 years	Sleep measures: *Subjective:* One item (sleep quality from the ZDRS)—patients and caregivers; one item (sleep disruption by disease)—patients; and one item (sleep disruption by patient)—spouses Outcome measures: ZDRS (Psychological and Somatic Symptoms subscales) and Hoehn & Yahr classification	27	B3

MQS = Methodological Quality Score; LE = Level of Evidence; PSQI = Pittsburgh Sleep Quality Index; GSDS = General Sleep Disturbance Scale; PSG = polysomnography; ESS = Epworth Sleepiness Scale; ECOG PS = Eastern Cooperative Oncology Group Performance Status; HADS = Hospital Anxiety and Depression Scale; SF-36 = Medical Outcomes Study Short Form-36; MSAS = Memorial Symptom Assessment Scale; UPDRS = Unified Parkinson's Disease Rating Motor Scale; PDQ-39 = Parkinson's Disease Questionnaire; CES-D = Center for Epidemiologic Studies Depression Scale; MMSE = Mini-Mental State Examination scale; CSDD = Cornell Scale for Depression in Dementia; DMSS = Dementia Management Strategies Scale; ZDRS = Zung Self-Rating Depression Scale; ZARS = Zung Self-Rating Anxiety Scale; PIMS = Parkinson's Impact Scale; MDRS = Mattis Dementia Rating Scale; CARE = Comprehensive Assessment and Referral Evaluation.

that a caregiver's sleep can be a function of the patient's sleep, and vice versa, was investigated and partly verified in the studies reviewed.[40,45,46,48,50,51] Where positive significant correlations emerged, these were moderate to strong,[45,46,51] derived from dyads sharing the same bed/room,[45,46,51] and were pertinent to the objectively recorded nocturnal sleep parameters of sleep onset latency,[51] wakefulness after sleep onset,[51] nighttime activity,[40,50] number of nocturnal awakenings,[51] sleep efficiency,[46,51] and total sleep time.[45,46,51] In a study that involved seven days of actigraphic recordings, however, sleep variables that showed the greatest night-to-night stability and variability were different between patients and caregivers, thus suggesting that sleep deficits within the dyad are not necessarily interrelated.[39] In addition, the frequency and magnitude of correlations between self-reported sleep data were far less in the studies,[48,51] mainly regarding perceived sleep quality,[48,51] sleep duration,[51] and early awakenings.[51] However, daytime behaviors between members of the dyads seemed to be uncoupled, given the consistent absence of significant correlations in their activity levels and total daytime sleep.[40,46,48,50,51]

Where sleep-wake disturbances were investigated,[39,46–49,51,52] patterns of frequency, concurrency, and, in some cases, comparability of nocturnal sleep problems were described in the dyads. Similarities in the occurrence of poor sleep for care recipients and caregivers were reported in most studies,[46–49,51,52] with complaints of poor sleep accounting for approximately 30%–50% in either group. Yet, two studies revealed that in only 20%–23% of the pairs, both parties reported not sleeping well, whereas in 41%–45% only the patient or the caregiver reported not sleeping well.[39,52] Irrespective of whether statistical significance was reached, trends of clinically greater sleep deficits in patients were apparent in all studies. Three studies concluded with no statistical differences between patients' and carers' sleep deficits,[46,51,52] yet others reported on greater sleep dysfunction in the care recipients.[39,48] Even so, nocturnal sleep problems in the caregivers were not unimportant and in some cases comparable with those manifested in the care recipients. On the other hand, despite the absence of perfect agreement,[51] less daytime activity, increased time in immobility, greater daytime

Table 4
Summary of Associations in Sleep Patterns of Care Recipient-Caregiver Dyads According to the Level of Clarification Established in the Literature

Probable/Definite Associations	Possible/Inconclusive Associations	Important Associations Yet to Be Explored
• Nocturnal interactions in coresiding dyads. • Worse daytime activity levels/ greater daytime sleepiness in care recipients vs. caregivers. • Clinically poorer nocturnal sleep in care recipients vs. caregivers. • Close synchronization of bedtime/ wake times in the dyads. • Absence of correlation between care recipient and caregiver daytime activity levels/behaviors. • Infrequent use of sleep medications in the dyads, especially in caregivers.	• Effects of sharing a bed/room on the dyad's sleep. • Organization of a caregiver's sleep around the care recipient. • Frequent/strong correlations between objective nocturnal sleep parameters in the dyads. • Infrequent/weak correlations between subjective nocturnal sleep parameters in the dyads. • Comparability in sleep fragmentation and nighttime movement in the dyads. • Synchronization of the dyad's occurrence of daytime naps. • Occurrence of concurrent sleep disturbances in the dyads. • Dampened circadian rhythms in care recipients vs. caregivers/ infrequent, weak correlations in rhythm activity parameters. • Frequency of use of sleep aids as a predictor of dyads in "sleep distress." • Direction of disruptive nocturnal interactions: patients' sleep deficits affect caregivers' sleep. • Psychological/physical distress, caregiver burden, coping strategies, and disease severity/chronicity as predictors of poor sleep in the dyads.	• Longitudinal effects of the dyad's psychological and/or physical distress on the dyad's sleep-wake patterns. • Longitudinal effects of historical relationship quality on the dyad's sleep quality. • Longitudinal effects of sleep hygiene practices and/or history of poor sleep on the dyad's sleep quality. • Longitudinal effects of the dyad's poor sleep on the dyad's health-related quality of life and functioning. • Longitudinal measurement of daytime/nighttime blood pressure and diurnal cortisol rhythms to understand the effects of sleep deficits on the dyads physical health. • Salient neurobiological mechanisms or pathways that mediate development of poor sleep in the dyads. • Differences in sleep patterns/ problems between dyads of female care recipients/male caregivers vs. dyads of male care recipients/ female caregivers.

dysfunction, and/or higher levels of daytime sleepiness were reported in care recipients than in caregivers in three studies,[40,48,52] which might reflect the consequences of a restless night and/or a severe disease. Two studies revealed dampened circadian rhythms (particularly amplitude), which could explain patterns of excessive daytime inactivity in care recipients.[40,46] Even so, caregiver reports of daytime sleepiness and dysfunction were far from insignificant. Lastly, the infrequent use of sleep medications in care recipients (22%–23%), and also especially in informal caregivers (10%–20%), was highlighted in two studies,[39,52] with a further study confirming patients' greater need to medicate for poor sleep.[51] In any case, McCurry et al.[39] reported that dyads of concurrent poor sleepers were more likely to include a care recipient who was using sleep aids.

Sleep-Impairing Factors in Care Recipient-Caregiver Dyads. With nighttime interactions between care recipients and informal caregivers being apparent,[50] two studies suggested mutuality in the way poor sleep is experienced within these dyads.[45,51] In that sense, each party could be rendered responsible for the sleep disturbance of the other. However, this notion was examined only partially in the studies reviewed, half of which provided some inconclusive evidence suggesting interactions mainly initiated by the care recipients.[39,47,48,50,52] Indeed, although the partner's sleep showed little ability to predict ratings of poor sleep in persons with Parkinson's disease, it was identified as a slight contributor of poor sleep in female caregivers, with a fourfold increase in the relative risk for poor sleep among caregivers whose patients also experienced disrupted sleep.[47] Several significant, moderate-to-high intercorrelations also were reported in a further study in the same population: greater patient sleep disturbance and diminished caregiver sleep duration, as well as poorer patient sleep and

greater caregiver daytime dysfunction.[48] Yet, on spontaneous reports, only a small percentage of caregivers (just below 30%) claimed to have been disturbed by the patient.[52]

Cohabitation and room sharing were examined in four studies as potential mediators of sleep impairments.[39,40,46,50] Findings among the studies were similarly discrepant. One study suggested that especially in dyads who shared the same bed, and in cohabiting pairs, it was mainly the elders who initiated nocturnal interactions; yet, it remained unclear whether such interactions also were truly associated with sleep interruptions in the dyads.[50] In a concurrent study, no significant effects of cohabitation were found for both daytime and nighttime activity, thus implying dissociation between elder nocturnal activity and caregiver sleep disruption.[40] Possible explanations might be caregivers not sharing the same bedroom with the elders and caregivers not spending much time with elders given that most caregivers in this study were adult children of elders.[40] In the context of dementia, two studies also failed to show direct effects of room sharing on the dyads' sleep.[39,46] In the first study, sharing a room was not a significant predictor of dyads of concordant poor sleepers,[39] whereas in the second study, between-group analyses yielded no differences in either self-report or objective baseline sleep measures between caregivers sharing and not sharing a bedroom.[46]

In spite of the absence of findings based on prospective intercorrelations, four studies identified psychological distress in the form of mood disturbance and anxiety as a potential contributor to a dyad's sleep deficits.[39,47,48,52] In three studies, poor sleep was consistently associated to one's own poor psychological well-being,[47,48,52] whereas in dyads of persons with Alzheimer's disease and their family caregivers, patient psychological comorbidity and caregiver ineffective coping strategies were significant predictors of concurrently manifested poor sleep.[39] However, one study concluded with less nocturnal interactions in pairs whose elders reported high levels of depression.[50] One possible, yet unexplored, explanation might be that depressed elders disengaged themselves from their caregivers, which in turn might have led to caregivers experiencing less sleep disruptions overnight.

Disease severity and chronicity, heavily impacting on the patient's physical functioning and rendering the caregiving situation even more demanding, especially where the situation also involves physically affected caregivers, was highlighted—although not explicitly confirmed—as a potential sleep-impairing factor in some of the studies reviewed.[39,47,49,52] One study revealed that approximately 45% of persons with Parkinson's disease and 30% of caregiving spouses claimed that their sleep had been at least moderately affected by the disease itself.[49] Among patients with advanced cancer and their family caregivers, patients' bodily pain and caregivers' global distress were associated with significant sleep deficits, even though potential interactions were not explored.[52] Similarly, McCurry et al.[39] reported that in dyads in which both the patient and the caregiver slept poorly, the overall caregiving situation was more difficult, coaffected by disease chronicity and patients' lower physical functioning. Surprisingly enough, however, caregiver health-related outcomes were not significant predictors of concordant poor sleep,[39] but data on predictive variables were collected only at baseline, thus affecting emergence of associations and limiting reliability of the findings on possible changes across time.

Discussion

Despite the dearth of studies in the field, promising findings have been yielded suggesting bidirectional associations in the sleep of care recipient-caregiver dyads (Table 4). Concurrent and relatively comparable nocturnal sleep disruptions may be evident, where poor sleep quality, decreased sleep duration, and multiple awakenings may correlate with each other within the dyad. However, daytime activity levels may be uncoupled. In any event, care recipients' and caregivers' night and day rest patterns can be synchronized, particularly in coresiding dyads and/or in those in which caregivers organize their sleep around the patient. As a potential consequence, where the illness is more severe, and the overall situation is more intense, distressful, and prolonged, patient-caregiver

dyads may be at greater risk of concurrent sleep disturbances.

On closer inspection, however, this evidence is largely compromised by several limitations, which undermine its generalizability and question its reproducibility. Most studies had relatively small sample sizes, a fact that in itself poses a question as to whether larger sample sizes would allow for emergence of more[40,45,46,52] and/or larger[39,48,50] associations between dyads' sleep variables[39,40,45,46,50,52] and between sleep variables and influential factors.[39,40,46,48,50] Multiple statistical comparisons in the presence of such small sample sizes might have increased the risk for Type I errors, thus rendering unclear whether all associations that emerged are truly significant. Even studies with more than 100 dyads were cross-sectional in nature,[47,49,51] thus precluding causal inferences.

With the exception of one study where assessment spanned a six-week period,[46] prospective assessments took place over a limited period of three days[45] and one[39,52] or approximately one (ranging from six to nine days)[40,50] week. Although the exploratory nature of these studies and the difficulties in obtaining objective data on sleep for extensive periods of time are certainly acknowledged, this narrow time frame of observation may have been inadequate to allow for latent covariances in the sleep of dyads to emerge. Furthermore, in two studies, unavailability of data for all days of assessment was reported, which may have even more confined a true assessment period.[39,45,50] It is reasonable to assume that such inconsistencies also might have interfered with study findings. Moreover, all studies were conducted in a phase of illness experience where no major events were taking place, such as diagnosis, active treatment, health-care transition, or relapse. In at least two studies,[51,52] patients' functional status was overall good to very good, whereas in at least four studies[39,46–48] time since diagnosis exceeded an average of approximately four years. Seen together, these facts might have led to inclusion of dyads who, in the absence of major influential situations, might have found a balance in their sleeping arrangements so as to avoid considerable effect of possible disordered sleep patterns and overall needs on one another.

Longitudinal, repeated-measures research drawing on a combination of objective (wrist actigraphy and ambulatory polysomnography) and subjective (self-report scales and daily sleep logs) sleep measures is therefore warranted[28,54] to meet the goals of future dyadic sleep research as outlined in Table 4. With their ability to record continuously, objective sleep measures have the advantage of providing abundant data on several sleep variables, including sleep latency, sleep duration, nocturnal awakenings, and wakefulness after sleep onset than subjective measures do.[55] Polysomnography remains the "gold standard" for the detection of specific sleep and wake states,[28,41,56] especially with the latest advances of ambulatory devices.[28] Actigraphy has been shown to be particularly good in the evaluation of circadian rhythm disorders[55] and can be useful in examining dyads' habitual sleep patterns in their naturalistic environments for long periods of time.[23] Alternatively, self-reported research instruments measure perceptions,[28] hence they can provide data on the more qualitative features of sleep, such as sleep quality, feelings on arising, or daytime sleepiness and dysfunction.[57] Psychometrically sufficient instruments include the Insomnia Severity Index, the Pittsburgh Sleep Quality Index, the Sleep Assessment Questionnaire, and the Athens Insomnia Scale,[29,58–61] whereas the Pittsburgh Sleep Diary can allow prospective monitoring of sleep parameters in longitudinal studies.[58] In addition, subjective sleep data may correlate more strongly with self-reports of health-related outcomes, thus allowing for intra- and interpersonal relationships to be more thoroughly examined. In any case, specific research hypotheses rather than a priori assumptions of a technique's superiority over another should guide selection of the methods to assess sleep in care recipient-caregiver dyads.[23]

Although it is true that having more sleep interaction data over time would increase the power for looking at care recipient-caregiver sleep relationships (and correlates), some considerable challenges in collecting such data also should be acknowledged. For instance, not all self-report sleep measures have extensively been tested in all patient or caregiver populations and even less are suitable for use as outcome measures given that their ability or sensitivity to detect significant or meaningful changes in sleep patterns has not been established as yet. Similar comments could be

made about daily sleep logs, which also are not always standardized and much harder to keep for prolonged periods than is generally acknowledged in the literature. In addition, given their retrospective nature, self-report sleep measures are prone to introducing recall bias, which when combined with their being influenced by the respondent's situational mood can affect accurate interpretation of a person's—let alone a dyad's—sleep patterns.[28] Objective measurement of sleep can be similarly challenging. Although wrist actigraphy is considered a relatively easy to implement and adhere to method, some care recipients and caregivers cannot tolerate wearing the devices for prolonged periods of time, hence the risk for missing data increases.[41] Also, the use of actigraphy with people with Parkinson's disease has been questioned because of its susceptibility to provide blurred sleep data in the presence of tremor.[62] With in-home polysomnography, participant burden can increase even more.[41] Equipment failures are not insignificant either. Furthermore, simple collection of more data might not completely solve the problem because there are no gold standards for which actigraph type to use or which data collection or scoring protocols to follow.[55] As an example, unclear association of the definition of daytime naps with individuals' inactivity may have led to underestimation of actigraphically recorded daytime wakefulness in one of the studies reviewed.[52] When sleep interaction data are considered, such issues can be of particular importance so as to enhance accuracy in sleep measurement, promote adherence to sleep assessment methods, and prevent unnecessary burden to the dyad.

The investigation of correlates of co-occurring sleep problems in care recipient-caregiver dyads is both intriguing and challenging. In the studies reviewed, this area emerged as a rather understudied one (Table 4). Yet, preliminary findings can be used to form a conceptual model of complex interrelationships between sleep and sleep correlates. This model suggests that a dyad's sleep is a dynamic field of interference of several compounding and interacting variables, which not only affect sleep but also are affected by sleep so that an infinite loop of chronic sleep loss and dysfunction can be established as the dyad moves in time and across health transitions. Whereas the mediating effects of cohabitation and bedroom sharing remain to be explicitly established, a dyad's sleep quality seems to be largely compromised by how parties are coaffected once sleep disturbances are manifested in one or both of them. Hence, frequency and severity of one's sleep deficits can be potentially strong correlates of the other's, possibly mediated by the effects of a history of poor sleep or of an inadequate sleep hygiene. In dyads, then, where physical functioning and/or psychological well-being also are compromised, sleep-wake patterns can be further impacted. Disease severity and chronicity, aging, caregiver burden, dysfunctional coping strategies, and unavailability of external support can pave the way toward this direction by interfering with sleep either directly or through their physical and psychological impact. Although unexplored in this context, historical relationship quality, as influenced by the degree of attachment, the dyad's age, and the impact of a demanding health situation, can possibly affect (and be affected by) the dyad's sleep. A number of psychological, behavioral, and neurobiological mechanisms have been suggested to mediate this relationship in married couples,[23] which may be similar for dyads of care recipients and caregiving spouses but warrant further exploration in a wider caregiving relationship. Alternatively, effects of a dyad's nocturnal sleep loss, especially when this becomes a constant situation, on daytime wakefulness, functional ability, and overall quality of life are not insignificant and may be selected as outcomes for evaluation in other research.

As argued above, to date, data regarding correlates of co-occurring sleep problems in care recipient-caregiver dyads remain scarce and at times discrepant. In several cases, this body of evidence is compromised by several methodological shortcomings involving sampling, research design, data process, and instrumentation issues. Of relevance to the latter, variability (or otherwise, inconsistency) in the use of measures of sleep correlates was apparent in this literature. For example, to assess for the sleep-impairing effects of depression, five different instruments were used across the studies reviewed. Conversely, other constructs were only partially (e.g., burden and coping) or not at all (e.g., attachment) investigated. This lack of standardization in the measurement of key constructs can be seen as

a confounding factor that has hindered comparability of relevant outcomes. On a closely related matter, psychometric insufficiency of some of the instruments implemented may have resulted in compromised findings. Clearly, there is a need for concrete evidence- and research-based guidelines for the use of psychosocial assessment measures in this context. In any case, a wealth of comprehensive literature reviews exists that can assist researchers to select the most sound ones to assess outcomes related to sleep deficits in patient-caregiver dyads according to the disease context.[63–71] Importantly, researchers will need to rely on instruments with proven psychometric properties, preferably those for which responsiveness (i.e, sensitivity to change over time) also has been established. Examination of measures' psychometric properties should lead to a rational approach to selecting those appropriate, as well as promote consistency in their use. This common language will allow for comparable, reproducible, and wide in scope data to be collected. Such data will need to derive from adequately powered longitudinal studies that make use of predictive models of associations. To that end, analysis of dyadic data on sleep patterns and sleep-impairing covariates with more sophisticated, state-of-the-art statistical models, such as the multivariate two-level model for matched pairs' data[72] or the Actor-Partner Interdependence Model,[73] could permit adequate exploration of interdyad effects. In addition, mixed-methods studies integrating quantitative and qualitative data[74] could be particularly useful in the clarification of underlying mechanisms in the development of dyadic sleep disturbances.

Implications for Clinical Practice

Implications for clinical practice are numerous. Evaluation of sleep from a dyadic perspective requires that clinicians engage in a systematic and ongoing assessment of sleep patterns that goes beyond the individual: data are simultaneously taken into account, synthesized, and contrasted to establish a dyad's levels of sleep quality. These will need to be complemented by additional information regarding past sleep problems, present sleeping arrangements, sleep hygiene behaviors, and current use of sleep aids that can help clinicians identify potentially vulnerable dyads for sleep problems. Incorporation of screening tools for organized sleep assessments in routine clinical practice is thus recommended. Screening tools for the detection of sleep-wake disturbances, such as the Insomnia Severity Index, the Clinical Sleep Assessment for Adults, the Medical Outcomes Study Sleep Scale, and the Epworth Sleepiness Scale, are recommended for use in clinical practice.[28,41,58,59]

Once complaints are raised, evaluation of the onset, duration, and severity of sleep deficits, as well as daytime dysfunction, can reveal potentially evolving, co-occurring and/or interrelated problems. Diminished sleep duration, multiple nocturnal awakenings, wakefulness after sleep onset, and daytime sleepiness may put dyads at risk for "sleep distress," particularly those closely interacting. A plan of practical suggestions to reduce disturbing nocturnal interactions can be usefully devised, including use of twin beds or separate rooms for sleep, separation of sleep quarters, use of alarms, readjustment of the patient's caregiving routines, and synchronization of positive sleep hygiene behaviors.[50] Health professionals will need to evaluate the dyad's support environment and advise on the benefits for caregivers of having a support person to share caregiving responsibilities with, whether this person is a family member or a hired attendant. The availability of respite care services also should be explored as it can lead to improvements in sleep quality of both the care recipient and their informal care provider.[46] Moreover, optimizations in symptom control or in pharmacologic sleep therapy can prove beneficial,[41] especially when the shared needs of the dyads are taken into consideration. Referrals to specialist health services could be a useful adjunct for dyads of poor sleepers, where relationship quality is compromised and complicated by dysfunctional coping and psychological distress.[23,24] Lastly, the effectiveness of nonpharmacological interventions for sleep disturbances will need to be reexamined, this time at a dyadic level. Whereas therapeutic interventions, such as cognitive behavioral therapy, bright light therapy, and physical activity, previously have been shown to improve sleep and correlates in patients and informal caregivers,[28,29,75–77] concurrent delivery to dyads rather than merely individuals could be "twice effective," resulting in combined sleep improvements.[47]

Conclusions

To the best of our knowledge, this is the first review to systematically identify and critically appraise evidence derived from studies concurrently investigating sleep parameters in care recipient-caregiver dyads. Results underpin that research has only begun to gain an understanding of the bidirectional associations in the sleep patterns of care recipients and their caregivers and to unravel the complex underlying pathways that lead in the development of sleep disturbances in these dyads. Diversity across the studies reviewed may have precluded safe conclusions to be drawn on, but it poses a clear indication for greater methodological rigor in future studies, while at the same time informs clinicians of a novel perspective on the provision of care. Irrespective of the context of a specific life-threatening illness, more systematic, longitudinal dyadic research is warranted to provide evidence on which relevant theories will be formed and further tested to inform dyadic interventions to prevent sleep disruptions or preserve habitual sleep patterns of care recipients and caregivers and promote their dyadic well-being and adjustment to living with a chronic illness.

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Sleep-wake disturbances in patients with cancer and their informal caregivers: a matter of dyads

Grigorios Kotronoulas[1], Yvonne Wengström[1,2], Nora Kearney[1]

[1]School of Nursing & Midwifery, University of Dundee, Dundee, UK
[2]Department of Neurobiology, Care Science and Society, Division of Nursing, Karolinska Institutet, Huddinge, Sweden

Correspondence:
Grigorios Kotronoulas,
School of Nursing & Midwifery,
University of Dundee,
Dundee, DD1 4HJ, UK,
Tel.: +44 (0) 1382 384963,
Fax: +44 (0) 1382 388533,
e-mail: g.kotronoulas@dundee.ac.uk

ABSTRACT

Background: Changes in habitual sleep are among the most remarkable and important concerns of both patients with cancer and their informal carers. A dyadic approach in the assessment and management of sleep problems in patients and carers is a promising method of exploring concurrent sleep disturbances and establishing associations between sleep and sleep-impairing factors that may co-vary in the members of the dyad. The purpose of the present mini-review article was to discuss the current evidence, as well as highlight areas where future research is warranted.

Patients & Methods: An electronic search for original peer-reviewed articles published between January 1990 and July 2011 in three research and evidence databases (MedLine, CINAHL, EMBASE) was carried out using a wide range of keywords and free-text terms. Cancer care-related evidence was complemented by additional data derived from studies conducted with married couples or in the context of other chronic illnesses.

Results: Concurrent and comparable nocturnal sleep disruptions might be evident, where poor sleep quality, decreased sleep duration, and multiple awakenings may correlate with each other within the dyad. Care recipients' and caregivers' night and day rest patterns can be synchronised, as caregivers organise their sleep around the patient.

Conclusion: More systematic, dyadic research is warranted to enhance development of intervention protocols for the comprehensive management of sleep disorders in this population throughout the illness experience. These interventions will ensure that sleep patterns are assessed in depth and are managed in a concurrent manner to achieve a concurrent increased level of well-being of patient-caregiver dyads.

Key words: sleep; sleep-wake disturbances; cancer; informal caregivers; dyads; interdependence; dyadic approach.

INTRODUCTION

Sleep is a vital human process known to be essential for health, well-being, and optimal physical and psychological functioning [1, 2]. It is therefore reasonable to argue that sleep-wake disturbances may have serious consequences on the equilibrium of life [3, 4]. Sleep difficulties have been reported as a frequent complication of and are associated with various clinical conditions [5]. Over the last fifteen years, the attention of the scientific community has shifted towards systematic investigation of sleep disorders during the experience of cancer as an important aspect of care.

A cancer diagnosis severely disturbs a person's continuum of life. Sudden changes imposed after the diagnosis and during the ensuing anticancer treatment may profoundly affect the person, resulting in several sources of discomfort, among which sleep-wake disturbances and poor sleep quality [3]. Especially throughout the period of diagnosis and treatment, but also during survivorship or, conversely, during palliative care, people with cancer are in great need of support. To a significant extent this support is expected to be provided by their significant others, family members or friends, whom patients feel they receive support from, and are frequently recognized as their informal caregivers [6]. Their practical and emotional involvement, however, often and in other cases considerably affects the caregivers' own lives [7]. Caregiving can be so demanding and stressful that the burden on these persons may lead to disruptions in their sleep as well [6].

This combined situation of sleep deprivation

may be a reality for some patients and their informal caregivers as they strive to survive health care system demands, and also to effectively cope with illness both as individuals and as members of a relationship. As they share closely their everyday concerns, patients and caregivers may be faced with similar challenges and may manifest most of their needs at the same time. Sleep problems may be prominent for both the patients and their caregivers, even at the same time, possibly over a considerable time period and, in other cases, long after treatment is completed, thus posing an additional short-, mid- or long-term burden on their lives.

Therefore, the purpose of the present mini-review article is to discuss the current evidence regarding the added value of a dyadic approach in the assessment and management of sleep disorders, by including both patients with cancer and their informal caregivers, as well as highlighting areas where future research is warranted. In order to facilitate presentation of related concepts, the article has been divided into three major sections. The first section provides evidence on the magnitude of disrupted sleep patterns in people and families affected by cancer. The second section discusses the benefits of a dyadic approach in health research, whereas the final section analyses the application of this dyadic approach in sleep research and synthesises findings from sleep studies conducted concurrently with cancer patients and their caregivers.

THE EXPERIENCE OF DISRUPTED SLEEP IN THE CONTEXT OF CANCER

Changes in habitual sleep are among the most remarkable and important concerns of patients with cancer [8], and among the most prominent and debilitating symptoms of their caregivers [9]. Patients and caregivers identify sleep-related issues as vital aspects of the experience of cancer. Whereas for healthy people sleep provides a needed refuge from everyday demands, for those affected by cancer it constitutes a form of respite from the ongoing physical discomfort and psychological distress, thus allowing them to meet the next day with renewed energy and motivation [5].

The subjective importance patients with cancer and their caregivers attribute to sleep-wake disruptions has potential consequences for behaviours associated with self-care and identification of symptoms, help-seeking strategies and reporting of disturbances to the health care team, as well as acceptance and compliance with recommended therapeutic interventions [10, 11]. On the other hand, objective significance of sleep disorders includes their potential to strongly influence clinical and care-related outcomes in patients with cancer [2], including fatigue [12-16], performance status [17, 18], mood [19-23], immune function [24], quality of life [23, 25, 26], and survival [27-29]. This reported significance warrants and dictates the need for continuing intervention and relief of patients in times of distress.

Sleep patterns of patients with cancer

The empirical observation of disordered sleep in people with cancer has been supported and boosted by systematic research -especially in the last decade. Current knowledge indicates that disordered sleep is one of the commonest (only second to fatigue) [30] symptoms, twice as prevalent compared to the general population [31]. Total sleep time of less than 50 hours per week [32]; fewer than usual hours of sleep [33]; multiple awakenings in the middle of the night; and difficulty falling sleeping have been reported in varying rates in studies with mixed samples of cancer patients [33, 34]. Moreover, decreased sleep duration and efficiency [35]; very early morning awakening; leg restlessness; interruptions of breathing during sleep [34]; as well as drowsiness [36]; daytime sleepiness [8]; and a need to sleep at unusual hours during the day [33] are frequent complaints. There is some evidence that patients with cancer tend to dream more than usual and to have frightening or unpleasant dreams [8, 37], which may be accompanied by not feeling rested the following day [35], urging the need for use of prescribed hypnotics or over-the-counter sedatives [35, 38, 39]. Although much more research is warranted to shed light on different aspects of disrupted sleep and its meaning for people with different types of cancer, stages of disease, or phases of treatment, this evidence is indicative of a problem that requires the attention of health care professionals.

Sleep patterns of cancer patient caregivers

Sleep research in the context of cancer caregiving has gained some interest over the past 15 years; yet, sleep disturbance remains one of the least assessed symptoms as revealed in a recent review [9] and more systematic investigation is required to fully understand the trends of and influences on sleep patterns of cancer caregivers [6]. Despite the absence of a consistent method of assessment, evidence derived mainly from cross-sectional studies with non-homogeneous samples with regard to phase of cancer experience (palliative care, survivorship, active treatment) or duration of caregiving shows that sleep of cancer patient caregivers also becomes disrupted [9]. In general, difficulty falling and staying asleep; experience of restless and non-restorative sleep; as well as development of insomnia and chronic sleep loss may be common complaints raised by cancer patient caregivers [3, 40]. Albeit poorly explained, some evidence exists that cancer patient caregivers might experience restless sleep and problems staying asleep to a greater extent compared to caregivers of patients with other illnesses such as AIDS or age-related dementias [41], but studies evaluating caregivers of patients with Parkinson's [42, 43] or Alzheimer's [43, 44] disease point to the direction of general similarities in sleep disturbance. Yet, occurrence, frequency and/or severity of these sleep problems may vary widely, mainly but not solely depending on the overall caregiving situation [6]. Existent evidence is indicative of this variability, highlighting the need for a

cautious interpretation when more general conclusions are to be drawn [6].

THE PATIENT-CAREGIVER DYAD: BEYOND INDIVIDUALISM

In the previous section, there was a careful distinction in the account of concept-related and sleep-related research data pertinent to patients with cancer and their caregivers. However, in reality, changes in the lives of the person receiving cancer care and the person providing informal care take place in tandem, and illness is often experienced and managed in the context of a complex network of relationships [45]. In that sense, interdependence between parties of close relationships may exist, and has been accounted as the defining feature of human relationships [46]. At the level of a dyad (otherwise, a pair of closely related persons), interdependence and reciprocal influence can characterise the nature of the relationship and influence the ways in which people communicate, grow and thrive, as well as cope in the wake of major events and challenges [47].

By accepting the probability of complex interactions in their relationship, it is reasonable to argue that patients and their caregivers may react to cancer as a unit and, as a result, both have legitimate interrelated needs for help from health care professionals [48, 49]. There is a general consensus among clinicians and researchers that when patients and caregivers are treated simultaneously, important synergies can be achieved contributing to the well-being of each person [50, 51]. Conversely, when these interrelated and often concurrent needs are neglected, patient-caregiver dyads are denied the opportunity to obtain optimal care. Therefore, Northouse *et al.* [48] and Fletcher *et al.* [47] claim that in order to provide optimal comprehensive cancer care and enhance research, the care plan must focus on these patient-caregiver units.

Several health- and quality of life-related variables have been frequently conceptualised in an individualistic way; however, social contextual models argue that health outcomes are likely to co-vary in close relationships, as in the patient-caregiver relationship. For instance, any change in the functioning of one individual can affect the functioning of his/her significant others, and vice-versa [52]. Similarly, although external factors, such as disease severity and social support, may affect patients' and caregivers' physical and psychosocial well-being directly and unidirectionally, patient and caregiver interdependence may contribute to a bidirectional situation, in which the well-being of each individual in the dyad also affects the well-being of the other [53].

The notion that the patient-caregiver relationship comprises two people, both of whom influence and are influenced by the other, has been stressed as particularly relevant to health care in general [54, 55]. To address and confirm this reciprocity, a shift in cancer research is evident towards inclusion of patient-caregiver dyads rather than merely patients or caregivers alone [47]. In turn, this novel approach promises to enhance care by revealing salient aspects of care existing within the mutuality of the patient-caregiver relationship. Albeit logically reasonable, only relevant research evidence will establish the effects of such dyadic approach.

An overview of the most relevant literature reveals a number of studies dyadically exploring the illness experience of patients and their caregivers [56-68], or testing interventions targeting the dyad [69-74] or the caregiver alone [75] to promote dyadic well-being. There is some weak evidence that during survivorship patients' greater psychological distress might predict significantly poorer physical health in their caregivers, and vice versa [58]. Similarly weak evidence indicates that patients' fear of disease recurrence might affect the carers' own fear of recurrence and distress over time [57], but remains unclear whether this association extends beyond six months post-diagnosis; is influenced by dyadic adjustment to illness; or is true for dyads affected by cancers other than head and neck cancer. Along these lines, examination of the intra- and inter-personal consequences of protective buffering among patients and their partners suggests that the more patients hide cancer-related thoughts and concerns from their partners, and the more they feel that their partner hides their own concerns, the lower their concurrent relationship satisfaction and the poorer their mental health might be [59]. Additionally, mutual avoidance and communication withdrawal can be responsible for poor perceived intimacy, ultimately leading to concurrent psychological distress in heterosexual couples in long-term relationships [60, 61]. Due to absence of proven causality, however, the possibility that dissatisfied or distressed partners might exclude each other from their most intimate thoughts cannot be ruled out. Being partially dissatisfied and not feeling privileged in taking care of the sick spouse have been suggested as possible mediators of incongruence in patient and caregiver perceptions of quality of life [56]. Drawing on some of these findings, education interventions [70, 74] and stress-reduction programmes [71] have targeted the dyad for possible joint effects. In spite of some promising concurrent improvements in psychological distress [70, 71], mood [71, 74] and quality of life [74], there is still an outright need to establish superiority of dyadic interventions not only over control groups, but also over groups in which one member of the dyad receives the intervention (four-group designs); as inconclusive findings indicate [74], this can only happen when methodological rigour supersedes the above-mentioned limitations.

Interestingly, the majority of studies have focused only on bidirectional associations of specifically psychological distress with the dyads' well-being, quality of life, or other external predictors, whereas potentially interrelated bio-behavioural symptoms such as sleep or fatigue have not yet been systematically examined in patient-caregiver dyads. Closely related to this, the association between the dyad's long-term adjustment and interrelated health outcomes has yet to be fully explored. This could be facilitated by conducting

longitudinal, repeated-measures studies over extended periods of time, even one or two years after major events or transitions have taken place. Nonetheless, only a limited number of studies have implemented a truly adequate prospective design to test direction of associations, but this strategy does not necessarily ensure that generalisability is feasible. Furthermore, exploration of dyadic changes of outcome variables has very commonly taken place over select time points thereby unlinked to transition to the different phases of cancer experience, such as prospective re-assessments conducted following diagnosis (e.g., 6- or 12-month follow-ups) or during survivorship or remission. It is, however, interesting for interrelated outcomes to be examined at time points where major events occur, such as post-diagnosis and before, during and after active treatment, during transition from one treatment modality to another, at relapse and related health care decisions, or before, during and after hospice or palliative care. Bearing in mind these important limitations, supporting findings need to be treated as only indicative, but certainly not definitive, of a complex interaction between patient- and caregiver-related outcomes in the context of cancer.

DYADIC APPROACH IN SLEEP RESEARCH: A NOVEL CONCEPT

The onset and maintenance of sleep are dependent on meeting a series of physiological conditions including adequate level of physical comfort, and relative absence of psychological distress and psycho-physiological arousal [5]. Therefore, it has been argued that for the vulnerable state of sleep to occur, persons need to feel physically and emotionally safe and secure to down-regulate vigilance and cease alertness [76, 77]. An adequate social environment may be particularly important for such feelings to emerge [78]. Thus, for humans, sleep is regarded as a fundamental attachment behaviour that may be regulated within and affected by close human relationships [76, 79], one of which is the patient-caregiver one. In that sense, the fact that the science of sleep has tended to view sleep as an entirely individual phenomenon can be described as a rather confined approach, impeding assessment and management of sleep disorders that might manifest themselves especially during periods of adjustment to illness [80]. As described earlier, interdependence is a defining feature of relationships and might also be a defining feature for sleep as seen in the context of a close patient-caregiver relationship [81].

Attachment theory has been implemented to provide a perspective of the link between close relationships and sleep [76]. According to this theory, early interactions with caregivers lead to the development of expectations from them to be responsive to one's needs [76, 82]. Especially in times of real or perceived threat, these key expectations are thought to mediate affect and arousal [78, 83]. This might suggest that the closer the relationship, the greater the odds of a good night's sleep, and vice versa [80]. Although attachment theory has been used thus far to guide research in the field of couples' relationship functioning and sleep [76], it could, to a certain extent, justify the value of concurrent assessment of sleep patterns of patients and their primary family or non-family caregiver [78]. Caregivers who, regardless of their actual caregiving tasks, value their role as important to them and the patient they care for, might be more affectionate towards the patient; this in turn could lead to patients feeling more secure in their relationship and sleeping better [80].

On the other hand, as patients and caregivers go through the experience of illness together, their emotional reactions and distress affect one another in a relatively proportionate manner, adding to one's own concerns and worries when they reach a peak, or relieving from additional distress when they simmer down, and possibly resulting in corresponding changes in sleep patterns. In a similar manner, effective or dysfunctional coping strategies of the dyad might co-affect their sleep through a psycho-behavioural mechanism. Moreover, while it is more than obvious that patient symptom distress can lead to increased caregiving efforts, disrupted caregiver sleep patterns and increased fatigue coupled with daytime sleepiness, increased caregiver burden can equally lead to poor caregiving performance, which might in turn inhibit management of symptoms influencing sleep, or disordered sleep itself. Similarly, although not all patients and caregivers share the same bed or the same room, co-sleeping or cohabitating dyads might be co-affected by poor sleep hygiene practices or by disrupted sleep patterns related to the illness experience. Such sleep mediators might well interfere with the prerequisites necessary for a good night's sleep at a level that transcends the individual.

It has been argued that in a situation involving the co-presence of persons, cooperation is required to promote sleep for both parties [84]. In cohabitating or co-sleeping patients and caregivers, this "cooperation" becomes blurred given that patient symptom experience, caregiver burden and associated frustration can alter sleep habits/rituals or restrict actual sleep of the dyad in a way that concordance might be no longer feasible. Drawing on the above arguments, implementation of a dyadic approach can usefully augment our understanding of co-occurrence of sleep problems in patient-caregiver dyads, trends of concurrent transformation of these sleep problems across time, and covariates/factors that appear to contribute to these patterns within the dyad and across time. Such an approach may prove essential in the development of truly effective treatment strategies [76, 85, 86].

Evidence in the context of couples' research

Despite recognition of the dyadic nature of sleep for most adults, there has been surprisingly little investigation of human sleep patterns in a paired manner. To date, relevant sleep research has focused mainly on the nocturnal sleep patterns and daytime impairments of co-sleeping hetero-

sexual couples either in the absence of a medical illness or in the presence of a primary sleep disorder such as obstructive sleep apnoea (OSA). However, insights from research with couples can be fruitfully incorporated into the patient-caregiver-related research [47].

In the general population, Meadows *et al.* [81] reported that the variables showing the most significant couple interdependency in cohabitating heterosexual couples were actual bed time, sleep latency, light/dark movement ratio, and wake bouts (the number of nocturnal awakenings). Despite this interesting -yet inconclusive- evidence suggesting a close interrelation in couples' sleep patterns, presence of a bed-partner has been also viewed as a potential source of sleep disturbances: relevant research has demonstrated significantly lower levels of Stage 4 non-rapid eye movement sleep (NREM) [87], a concomitant increase in REM sleep [87], and a greater number of movements during sleep [87, 88] on the nights when participants slept with their partners rather than when they slept alone. In spite of this reciprocal impact on one another's sleep, participants have reported less satisfaction with their sleep when sleeping alone [87, 88]. In a sample of couples without sleep disorders, Pankhurst and Horne [88] observed more movements in men than in women, with women reporting that their sleep was affected by their partners sleep more than did men. Men are also more often loud snorers [89], and the sound of snoring can be a major disturbing factor of their bed-partner's sleep, who might report symptoms of insomnia, morning headache, daytime sleepiness and fatigue [90]. This might be especially true in the context of OSA. OSA has been referred to as a "disease of listeners" [91]; aside from snoring, increased arousals often adversely affect both the bed-partner's and the individual's sleep [90, 92].

Similarly, several efforts have been made to identify a link between reported or observed sleep disturbances within the couple with relationship functioning or quality [93-95] and attachment behaviours [96-98]. Although a positive unidirectional association has been established, evidence is mainly based on either cross-sectional dyadic studies [95, 96] or single-arm studies [93, 94, 97, 98]. Nonetheless, in a very recent longitudinal study of 29 young adult couples, Hasler and Troxel [99] showed the existence of some bidirectional associations between interpersonal interaction and sleep parameters, specifically sleep efficiency and sleep concordance. Women-reported more positive daytime partner interaction was found to predict higher objective perceived sleep efficiency for themselves, as well as higher perceived sleep efficiency of their male partners [99]. These results imply existence of interdependence in night-time sleep and daytime relationships; however, aside from the small study sample and several inconsistencies in data derived from both objective and subjective sleep measures, findings also seem to be largely confined in the limited context of young, happy and childless couples with no concurrent illnesses, who are good sleepers.

Evidence in the context of cancer research

Albeit promising, evidence regarding sleep patterns and sleep-interfering factors in patient-caregiver dyads, irrespective of the context of medical illness, is rather scarce; disappointingly, this is especially true for cancer care. Our systematic search of the relevant literature revealed only two recently published studies, where sleep patterns of patients with cancer and their informal caregivers were evaluated in a dyadic manner [80].

Gibbins *et al.* [100] examined sleep patterns of sixty patients with advanced cancer (lung, breast, prostate, colorectal) and their co-residing family caregivers over a one-week period. In twenty-three per cent of the pairs both reported not sleeping well, while in 45% of the pairs either the patient or the caregiver reported not sleeping well. Disappointingly, sleep parameters within these differing sleep categories were not explored, nor were group differences examined. Forty-seven per cent of patients and 42% of the caregivers reported overall poor sleep. Yet again, use of sleep medication was reported as low, especially for the caregivers (10%). Interestingly, actigraphic data revealed that in only 12% of the patients and 8.3% of the caregivers sleep efficiency was less than 86% over the seven-night period. Nevertheless, sleep fragmentation and movement was high in both patients and caregivers, with patients having at least clinically higher degrees of sleep fragmentation than caregivers throughout assessment. While the average percentage of time awake was largely similar for the dyads over time, a consistently greater variability was revealed for the caregivers, whose wake times varied by a 4-fold compared to those of the patients. Overall, activity levels were consistently higher for caregivers, whereas time immobile in the daytime was greater for patients. Patient poor sleep was associated with higher anxiety and increased body pain. Similarly, caregiver poor sleep was associated with high levels of anxiety and global distress. However, findings were non-existent with regard to potential interacting factors affecting sleep of the dyads; only 28% of the caregivers spontaneously reported being disturbed by the patient.

Approximately one week prior to primary or adjuvant radiation therapy for non-metastatic breast, prostate, lung or brain cancer, Carney *et al.* [101] explored sleep patterns of 102 patient-caregiver dyads. Subjective occurrence of sleep disturbance was similar in both groups (~40% to ~50%), whereas only partial differences regarding use of sleep aids and mid-sleep awakenings were found based on the perceived severity of sleep disturbance. Similarly, objective data revealed no significant differences, except for less mean sleep efficiency in patients compared to caregivers (81.4% v. 84.1%). On the basis of this data, both patients and family caregivers had a significant and concurrent problem with sleep maintenance, which was depicted in their increased and highly correlated number of nocturnal awakenings (~18 per night in both groups) that lasted 3 to 4 minutes; their less than 7 hours sleep; and their below 85% sleep efficiency.

What is more, dyads seemed to synchronise their sleep and wake patterns, as well as their daytime napping. These findings may suggest that if a patient slept poorly, so did his/her caregiver, and vice versa; however, due to the non-prospective nature of the study it is not possible to rule out the possibility that correlations could be merely accidental, rather than implying a causal link. Then again, potential contributing factors were not explored, rendering future research necessary.

Despite the dearth of studies in the field, promising findings have been yielded suggesting bidirectional associations in the sleep of care recipient-caregiver dyads [80]. Converging evidence complemented by studies conducted in the context of dementia [85, 86, 102, 103], Parkinson's disease [42, 104, 105], or ageing [106] suggest that concurrent and comparable nocturnal sleep disruptions might be evident, where poor sleep quality, decreased sleep duration, multiple awakenings, and daytime dysfunction may correlate with each other within the dyad. Care recipients' and caregivers' night and day rest patterns can be synchronised, as caregivers organise their sleep around the patient [80]. As a potential consequence, where the illness is more severe and the overall caregiving situation is more difficult, intense, and prolonged, patient-caregiver dyads may be at greater risk of concurrent sleep disturbances. Especially in dyads sharing a bedroom, a patient's sleep patterns might be a function of the caregiver's sleep, and vice versa. Yet, the effect of sharing a bedroom remains questionable, a field of interference of several influential variables, and answers can only be provided by adequately powered longitudinal studies using predictive models of associations [80].

CONCLUSIONS AND FUTURE IMPLICATIONS

Neither the patient nor the caregiver goes through the experience of cancer independently, but rather as a pair. Several urgent or constant patient needs can lead to disruption of caregiver sleep patterns, whereas increasing caregiver burden can lead to diminished ability to provide care with that resulting to perpetuated disrupted sleep of patients due to unrelieved symptoms or unmet concerns. Disrupted sleep may be so overwhelming that it undermines patients' well-being as well as caregivers' ability to provide efficient care. With these events occurring at the same time, distress due to disrupted sleep patterns in either person becomes even more unbearable. When disturbed nocturnal sleep or daytime dysfunction is evident or suspected, further assessment is warranted to facilitate timely and dyad-tailored interventions.

Longitudinal, repeated-measures research drawing on a combination of self-report (sleep questionnaires, daily sleep logs) and objective (wrist actigraphy, ambulatory polysomnography) sleep measures also is warranted to establish associations between patient and caregiver sleep patterns, as well as qualitative methodologies to reveal salient characteristics of this relationship and underscore the subjective importance of concurrent sleep problems for patients living with cancer and their caregivers. As the majority of studies have thus far aimed at recruiting partners or family members, future research is required to implement a broader definition of the caregiver [80]. Closely related to this trend, with caregiver samples included being women over a mean age of 55, reports of sleep disturbance incidence may have been influenced, as poor sleep might have been the result of associated menopausal symptoms, hyperarousability or past sleep problems, rather than just the caregiving experience itself or patient sleep patterns [80]. Perhaps the inclusion of predominantly or exclusively male caregivers could result in different associations.

Interestingly, evidence as to the nature of factors that co-affect sleep of patients with cancer and their caregivers still remains close to zero [80]. The aetiology of sleep disorders in cancer patients and their caregivers is multidimensional, since multiple factors are likely to alter the normal regulatory processes of sleep [4, 107]. Onset and maintenance of normal or habitual (the one a person considers as normal and "functions" as normal for him/her) sleep is dependent on a host of person- and environment-related prerequisites. Knowledge of the underlying reasons may guide in-depth assessment and targeted treatment of sleep disorders [108], given that care is specifically rather than vaguely focused on the source of the problem, potentially leading to quicker relief and dramatic improvement in sleep quality and sleep-related outcomes. Processing dyadic data on sleep patterns and sleep-impairing covariates with more sophisticated, state-of-the-art analytic models such as the multivariate two-level model for matched pairs' data [109], or the Actor-Partner Interdependence Model (APIM) [46] could permit adequate exploration of inter-dyad effects [47]. In addition, mixed-method studies integrating quantitative and qualitative data [110] could be particularly useful in the clarification of underlying mechanisms in the development of dyadic sleep disturbances.

It is hoped that future research will enhance development of intervention protocols for the comprehensive management of sleep disorders in people with cancer and their informal caregivers throughout their illness experience. These interventions will ensure that sleep patterns are assessed in depth and are managed in a concurrent manner to achieve a simultaneously increased level of well-being for patient-caregiver dyads.

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Conflicts of interest

The authors declare that there are no financial or personal conflicts of interest with regard to the present study.

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Informal carers: A focus on the real caregivers of people with cancer

Grigorios Kotronoulas[1], Yvonne Wengström[1,2], Nora Kearney[1]

[1]School of Nursing & Midwifery, University of Dundee, Dundee, UK
[2]Department of Neurobiology, Care Science and Society, Division of Nursing, Karolinska Institutet, Huddinge, Sweden

Correspondence:
Grigorios Kotronoulas,
School of Nursing & Midwifery,
University of Dundee, Dundee,
DD1 4HJ, UK,
Tel: +44 (0) 1382 384963,
Fax: +44 (0) 1382 388533,
e-mail: g.kotronoulas@dundee.ac.uk

ABSTRACT

Background: Those who become active caregivers out of their simple need to be included in their loved ones' experience may act as a force in the support and sustenance of the person with cancer. Apart from family members, individuals "considered as family" by the patient may actively participate in the patient's cancer journey. The purpose of this clinical review is to raise clinician awareness on the multiple responsibilities assumed and the impact of active caregiving experienced by informal carers of patients with cancer, also offering a number of practical suggestions to promote person-centred support.

Patients & Methods: An electronic search for original and review articles published between January 1990 and July 2011 in three research and evidence databases (MedLine, CINAHL, EMBASE) was carried out using the terms "caregiver" and "cancer".

Results: Informal caregivers are often required to assume numerous roles and make changes in their lives until they find themselves striving to balance a host of responsibilities. By being practically and emotionally involved, however, caregivers' own lives can be affected, sometimes overwhelmingly. The physical, emotional, social, and financial stress that caregivers can face in this role may result in the neglect of their own needs, adversely affecting their quality of life.

Conclusions: Research-driven support interventions such as peer support groups or psychological/emotional therapy, as well as honest, open and personalised communication with health care professionals and ongoing assessment of their needs can be of utmost importance in supporting those who contribute the most to the patients' cancer journey.

Key words: informal carer; cancer; caregiver roles; caregiving impact; burden; caregiver support.

INTRODUCTION

People diagnosed with a curable cancer may have a transitory care requirement, often before, during and immediately after treatment, whereas those for whom prognosis is less favourable may require long-term palliative care. Whatever the case may be, in their majority people with cancer will rely on families and friends for help and support [1], perhaps over an extended period of time. Regardless of its nature, support provided by persons considered by the patient as significant -often recognised by health professionals as their "informal caregivers"- has been found to be equally or more beneficial than support derived from other sources [2, 3]. Those who become active caregivers out of their simple need to be included in their loved ones' experience [4] may act as a force in the support and survival of the person with cancer. This can be a potentially rewarding experience for the caregiver [5], but mainly a meaningful action to the patient. By providing actual and ongoing care for essential daily tasks to be undertaken and for an acceptable quality of life to be achieved [1], these key holders can play an important part in a patient's ability to respond to and cope with the challenges of living with cancer [2].

From the health system's perspective, the expectation and prevalence of caregiving in significant others is also high. As social welfare costs rise in many nations and medical management of cancer becomes more complex, there are increasing obligations placed on individuals close to the ill person to undertake caregiving responsibilities [6] and deal with extensive coordination of care [7]. Moreover, recent changes in health policy [8] such as shifting the balance of care from hospitals to

the community, coupled with a shortage of health care providers [9] and a reduction in the length of hospital stay [10] have further impacted on the roles and responsibilities of these persons in providing primary and ongoing care at home [11-13]. In fact, the use of outpatient-based cancer treatment means that it is often family members, partners, or friends who provide daily support to the person with cancer, rather than healthcare professionals [14]. According to reports from several organisations for caregivers, over 100 million people in Europe, Australia, and the United States provide care on an unpaid basis for a relative, friend or neighbour in need of support due to old age, disability, frailty or illness [15-20]. By providing approximately 80% of care hours [17], informal caregivers save the world's economy at least €500 billion a year [15, 18-20], and economic considerations form a key element in government policy to support such individuals [15].

Current policy encourages health care professionals to work in partnership with informal caregivers [8]. In order for this cooperation to be effective, an understanding of the significance of the roles caregivers fulfil is required along with recognition of the impact said roles can have on their lives. Therefore, the purpose of this clinical review was to raise clinician awareness on the multiple responsibilities assumed and the impact of active caregiving experienced by informal carers of patients with cancer, also offering a number of practical suggestions to promote person-centred support.

BALANCING A HOST OF ROLES AND TASKS

What the existing literature signals is that *what caregivers do* as individuals and/or as part of caregiver networks can make an essential contribution to the patient's "care package" and that patients' well-being can be profoundly affected by the quality of the informal care they receive [21]. This implies that caregivers can be construed as the "co-caregivers" of formal health care providers [21]. However, Thomas & Morris [21] pose a core question: 'what is the informal caregiver role and how does it contribute to the care of the patient with cancer?' Current knowledge or understanding about what informal caregiving actually involves in cancer contexts, and about the difference that this makes to the overall health care endeavour is based on limited information derived from a few studies. In general, care may be organised into numerous dimensions each possibly consisting of several specific tasks and processes as outlined in the Figure [4, 22-29]. Moreover, it has been suggested that informal caregiving roles and responsibilities:

- may occur in relation to the health transition experienced by the ill person during treatment [22];
- may not necessarily be linear through predictable stages of development; rather they may be fluid and ever changing [22];
- deserve a wider rather than an individualistic focus as care is an area in which *both* the ill person *and* the caregiver participate [22];
- may be novel and never before undertaken [26];
- may be interchangeable, negotiated and adopted as necessary [4, 30]; and
- may depend on the specific moment, setting or patient need [22].

Nonetheless, evidence regarding caregiving roles is confined in terms of generalisability and is inconsistent with regard to type of cancer, stage of disease, phase in the cancer experience, or setting. For instance, it is unclear whether differences in roles assumed are influenced more by the type or stage of the disease, or by who the caregiver might be (family versus non-family member; spouse versus child), whether caregiving tasks are driven more by patient need (caregiving "on demand") or by caregiver attitude towards provision of care, or how (or if) they develop across time, cultures, or socioeconomic status. In that sense, evidence is largely inconclusive and the wide variation in the expression of caregiving tasks remains to be captured. Whereas caregiving might become more significant during periods when patients are in receipt of medical treatments and/or are at later critical moments in the cancer experience [24], what tasks might be involved in different phases have not been explored. Similarly, due to the cross-sectional nature of most studies, a description of transformations or fluctuations in the caregiving tasks across time or across health transitions is practically inexistent. Wagner *et al.* [26] aimed at exploring caregiving responsibilities of husbands of women with breast cancer during active treatment and one year later. Between time points, comparisons indicated relatively stable levels of assistance with daily living activities, despite opposite expectations. Sadly, the specific reasons for this trend were not inquired or explored, thus only hypotheses can be made including the potential impact of disease stage or treatment on women's functioning one year after treatment. However, additional latent reasons may remain unexplained.

On the other hand, the aforementioned broad role categorisation, albeit basically useful, seems too simplistic to depict the array of caregiving tasks, and might imply that caregiving roles are confined only to those that happen to fall into these specific categories, or should be similar in every individual case. One explanation of this wide array of care tasks might be that the majority of patients were more physically impaired and in greater need of support. It can be hypothesized that in the case of patients who might rely more on self-care, caregiving roles might be more limited or even focused on some areas rather than others. Yet, this remains to be established. According to some findings, husbands of women with breast cancer might provide less assistance with more intimate activities such as bathing, toileting, or eating [26]. Still, whether this is a purely gender- or age-related behaviour needs to be confirmed. An important association implied is that caregiving tasks might fluctuate according to the amount of shared involvement of patient and caregiver in the former's care [22]. In other words, what might be important is not only the possible

Figure.
Roles and tasks potentially undertaken by individuals providing informal care for people with cancer.

range of caregiving tasks, but how these tasks fit in each patient-caregiver situation, depending on patients' varying needs and abilities in different time-points, as well as caregivers' capacity to respond to these needs. Studies involving dyads of patients and caregivers can be of particular importance in characterising the dynamics of such interactive processes.

Given the diversity of the caregiving demands, it is equally reasonable to claim that caregivers themselves will possess different skills, capabilities and preferences when performing the different caregiving tasks [1], which to a great extent are influenced or mediated by several endogenous (individual-related) and exogenous (environment-related) factors. In addition, it should be recognized that not all people assume a supportive role in the event of a cancer diagnosis among their loved ones. Becoming a caregiver has been described as an equally demanding process as providing actual care [23], and it has been described as *role tuning* involving engagement, negotiation, and settling of roles between caregiver and care recipient [31]. Age, gender, cultural background, societal beliefs, ethnicity, socioeconomic status, educational level, type of personality, coping style, personal health, as well as family dynamics, quality of relationships, and over time adjustment to cancer diagnosis and illness stage [6, 32-36] may work together as integral factors in predicting a person's involvement in caregiving, the extent of associated tasks, and finally their *reaction* to this demanding role. Along these lines, Fletcher *et al.* [37] urged the need for development and research in areas such as caregiver physical health, culture, and socioeconomic status to enhance conceptualisation of caregiving in the context of cancer.

"I AM ONLY HUMAN": SUFFERING DURING CAREGIVING

It is now recognised that patients' illness experiences cannot be understood as individualised phenomena [35, 38]. A serious illness carries with it a host of physical, psychological and social consequences for everyone close to the ill

person [21]; especially those individuals who assume the short- or long-term role of the caregiver are impacted the most. When cancer becomes a reality, spouses, partners, other family members and friends may actively participate in shaping the cancer experience, and also *share* this experience. However, the practical and emotional involvement in patients' cancer journeys often affects caregivers' own lives [39]. Among others, caregivers may be forced to make changes in their own lives, take on new roles and responsibilities, or give up past activities [26]. These life changes can be viewed as commonalities or *stressors*, which can create burden and strain, especially when extremely high physical and emotional demands are placed on caregivers [11]. It is generally agreed that the concept of caregiver burden has both objective and subjective dimensions [6]. *Objective burden* can be seen as the effort required to attend to the needs of an ill person. Thus, it may include the amount of time spent in caregiving, the type of caregiving services provided, and financial resources expended on behalf of the "dependent" person [34, 40, 41], which can have economic implications, as well as a personal and social impact [42]. On the other hand, *subjective burden* consists of the beliefs, assumptions, and feelings with regard to the caregiver role. Studies in the context of cancer care have included such elements as the extent to which caregiving causes strain with regard to work productivity, finances, physical well-being, family relationships and social life, or emotional distress associated with caregiving [6, 35, 43-45].

The physical, emotional, social, and financial stress that caregivers can face in this role may result in the neglect of their individual needs [15, 42, 45], whereas a diminished immune response may increase their susceptibility to physical illness and infection. Where caregiving is intense, providing round-the-clock care can also leave a caregiver feeling exhausted with little opportunity to socialise and engage in social pursuits [36]. This may not only create social stress as caregivers fail to meet other obligations beyond the patient, such as work and other family responsibilities, but also a sense of isolation. Often informal caregivers face continual and concurrent challenges: apart from caring for the ill person, they at the same time have to meet family responsibilities, work commitments, and household duties [36]. A feeling that care is never enough might emerge, whereas daily priorities may be continually juggled within narrow time limits [15].

Caregivers may be more likely to report anxiety, depression, loss of confidence and self-esteem than non-caregivers [46]. Current hypotheses suggest that patients with cancer and their informal caregivers react to cancer as a single emotional system [47, 48]. Based on this assumption there may be a significant reciprocal relationship between each person's response to the illness, with caregivers often reporting similar [49, 50] or greater [51] emotional distress, anxiety, or depression than patients do. The risk of psychological distress may increase both with the intensity and the duration of caregiving [15]. Some studies report that caregivers' psychological distress reduces over time after diagnosis [52], but others suggest it increases and becomes prolonged [7, 53, 54]. The latter might be the case for caregivers who disregard their own problems in order to focus exclusively on fulfilling patients' needs; however, this is only one of several possible explanations. Distress, anxiety and anger may be experienced while patients' symptoms manifest; appearance changes; and functioning declines [36]. The ongoing emotional distress may be part of a cascading process that may lead caregivers to disheartenment and exhaustion [55]. Along these lines, caregivers may be less likely than patients to disclose their concerns and worries, and up to only half of those with serious psychological problems may actively seek help [33]. Similarly, caregivers' family and social well-being might become affected, especially in relation to talking about the illness; dealing with deficits in sexual well-being; changing roles and assuming new responsibilities; as well as maintaining support systems [9]. Difficulty communicating their feelings and negotiating their roles can hinder patients' and caregivers' ability to support one another and decrease intimacy within the dyad [56]. In addition, cultural and societal beliefs about cancer may pose additional burdens on both patients and caregivers [42, 57]. Belief in the inevitability of death once cancer is diagnosed can lead to an early withdrawal from life. This fatalistic or deterministic view of cancer can lead to inactivity [42]. As a result, anger and resentment may arise when, despite the caregiver's efforts, the patient is giving up.

Caregivers of patients with cancer may also experience a decline in their physical well-being [9, 58]. Notably, caregivers may be more than twice as likely to suffer from poor health compared to people without caring responsibilities [16]. Although caregivers' health status is initially similar to that of the normal population, they often report more problems with fatigue, sleep disturbances, and impaired cognitive function than non-caregivers [49]. Over time, as caregiver burden and strain increase, caregivers' physical well-being might be at stake including -while not limited to- possible reasons such as little time to rest; engagement in fewer self-care behaviours (e.g. physical activity); poor dietary habits; or failure to seek medical care for themselves when sick [9, 45, 53]. Indeed, relevant research suggests that, as a direct result to new caregiving tasks, an increase in alcohol consumption and smoking; sleep deprivation; lack of exercise; and infrequent use of preventive health services may be noted [45, 59]. A considerable proportion of informal caregivers have chronic health problems of their own, such as excessive body weight, heart disease, hypertension, and arthritis [9], and these health problems can be exacerbated by the stress of caregiving [34]. Presence or worsening of pre-existing symptoms, as well as the development of new ones may interfere with caregivers' ability to assume roles and/or fulfill those already assumed. Furthermore, adjustments caregivers may be forced to make in their way of life

[60] can result in added strain on their physical well-being. Eventually, both unrelieved symptoms and ongoing demands of caregiving may adversely affect both their functional status and quality of life [7].

Is this evidence enough to exhaustively describe the impact caregiving has on persons in caregiving roles? Given the methodological limitations of studies conducted thus far, the most probable answer is no, which subsequently renders additional questions unavoidable. What precipitating (e.g. blood relationship, hours of caregiving, number of roles, cohabitation etc.) or protective (e.g. coping strategies, relationship quality etc.) factors predict or mediate prediction of levels of perceived burden? For instance, what is the impact of cultural caregiving demands on caregiver burden? And then, how closely inter-related patient-specific and caregiver-specific factors affect caregiver burden? Moreover, how do predictors of caregiver burden change over time as changes occur in a patient's condition or as caregivers adapt or become fatigued? On the other hand, what are the differences in levels of caregiver burden in different caregiving situations as determined by type or stage of cancer; setting of care provision (hospital or home); treatment modality; or changes in stereotypically assumed roles? Notably, what is the inter-related impact of increased burden on caregiver and patient health variables over time and across joint transitions? Studies implementing a dyadic approach [37], drawing on a multiple-measures design across major transitions, using an adequate sampling methodology to recruit representative samples of our multi-cultural, multi-caregiving society, and assessing multiple facets of burden could prove to be helpful towards clarification of these issues.

IMPLICATIONS FOR CLINICAL PRACTICE

Nowadays, caregivers are not only legitimised as persons affected by cancer in profound ways, but also construed as actual or potential "co-users" of health services in addition to being "co-caregivers" [21]. Key cancer service policy documents [61, 62] reflect this acceptance, acknowledging the presence of these 'significant others' and legitimising their interests as service users alongside patients: "Patients, families and carers need access to support from the time that the cancer is first suspected through to death and into bereavement" (p. 62) [62]. In practice, however, health care professionals only rarely pay attention to the situation of informal caregivers, to the extent that they may feel neglected by the health care system [63]. Although informal caregivers constitute a vulnerable population, often their needs may not be adequately addressed, and resources to assist them may be extremely limited and fragmented [42].

There is a need for informal caregivers to be recognised as "care recipients" in their own right, and their right to having their own support acknowledged [36, 42]. Given their documented general lack of preparation to respond to the demands of providing informal care [64], more and better resources and emotional support for caregivers are of the utmost importance. Availability of sufficient resources, acknowledgement of their burden, and active engagement in social roles can lead to more positive perspectives on caregiving [42]. Within hospital clinics, participation in small informal groups can offer caregivers the opportunity to discuss and validate their experiences and feelings with similarly affected individuals [36]. Moreover, education sessions and individualised training for family and friends could very well assist those caring for a person with cancer to develop their skills, enhance their self-efficacy, and increase their understanding of the situation they are in [36, 65]. In the home setting, provision of non-clinical social support services [66] or clinical community nursing services [36], or participation in computer-mediated interactive social support groups [67] may be beneficial towards caregiver reassurance and emotional and practical support. Informal family conferences can offer the opportunity for caregivers to assess their responsibilities and jointly plan their actions [68]. When palliative and end-of-life care is required, dyadic emotional and psychological interventions [69], as well as the support services of a hospice may be vital in relieving caregivers from their physically demanding and emotionally exhausting responsibilities [36, 70].

Even individually, health care professionals can make a significant difference in caregivers' lives by being present and by actively engaging in caregiver support [36, 70, 71]. With caregivers being in a constant pursuit for information across all stages of their indirect illness experience, honest, open and personalised communication is the cornerstone of a supportive relationship [36, 72]. Health care professionals should always consider the needs of informal caregivers as they develop and change. Careful evaluation and re-evaluation of caregiver experiences is vital in ensuring that mounting burden is assessed and interventions are provided in a timely manner. For instance, in many cultures caregivers may be reluctant to seek help or accept assistance provided by health care services outside the family [36]. Caregiver willingness to reach out and accept help from others may be a significant factor to mediate caregiver experiences [73]. Health care professionals are expected to show respect and support such choices, but also encourage caregivers to request assistance from "support persons" such as other family members or friends, or from health care services whenever they feel overwhelmed in their roles [72].

A holistic understanding of the caregiver's unique situation, views, and desired outcomes can enable limited resources to be targeted appropriately [42]. Caregivers may suffer in silence. Some may have difficulty accepting the diagnosis of cancer, whereas others may feel guilt or being punished, or even question their purpose in life in the face of a life-threatening illness in their loved one [74, 75]. Strategies caregivers of people with cancer may employ to help them cope in their role can predict their ability to survive the challenges they face. Positive coping styles such as problem-solving deserve reinforcement; whereas negative

strategies such as avoidance or denial require attention and intervention to avoid interference with caregivers' psychological well-being [13]. For a significant part of informal caregivers, being present with the patient can be seen as an irreplaceable means towards fulfilling their role, or achieving a personal connection that will help us cope with the anticipatory grief they experience [36, 70, 76]. Especially in the hospital setting, those who are denied this "healing presence" may perceive it as a sense of personal failure, which can add to their emotional burden. Informal caregivers rely on what they perceive as "meaningful actions" to endure potentially distressing experiences in this role. If this motivation source is depleted, caregivers may question their contribution and become frustrated or withdraw. Ongoing assessment and consideration of psychological and cognitive interventions can be useful in supporting individuals in need [36, 77]. Apart from being aware of and open to such reactions or beliefs, health care professionals should also act towards making time and space for informal caregivers to accompany patients, and find a meaningful way to share in the patients' cancer journey.

Finally, significant transitions in the caregiving experience need to be addressed and evaluated in a rigorous prospective manner. Caregiver transitions encompass not only the patient's phases of illness, but also the daily adjustments made by significant others in response to the patient's needs [42]. During transitional times, the presence of health care professionals can encourage and support caregivers to continue functioning [36], thus supporting the whole patient-caregiver dyad. Seen in the context of a whole-systems framework that allows interpersonal relationships to be understood [12], caregiver experiences can be addressed in conjunction to the patients' responses to their joint illness journey. In that sense, implementation of a dyadic approach, where both the patient and the caregiver are seen as the core of one unit in which they share the same challenges, can lead to improving supportive interventions for those affected by cancer.

CONCLUSIONS

Be they spouses, partners, siblings, children, or friends, informal caregivers not only unconditionally invest an immeasurable amount of energy in caring for their loved ones with cancer [36], but also greatly contribute to the sustainability of the health care system in general. When, however, caregivers feel overwhelmed in their roles, both their and patients' needs may become hampered, and their well-being as a dyad may be threatened. The least health care professionals can offer in turn to this "caregiving force" is acknowledgement of their rights and needs, adequate assistance in their tasks, and effective, tailored support and respite services when -but preferably before- their experiences become difficult to handle.

Credits/Acknowledgements

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Appendix 8. Ethics and R&D Approval Documentation

EoSRES

NHS SCOTLAND

East of Scotland Research Ethics Service (EoSRES) REC 1
(formerly Tayside Committee on Medical Research Ethics A/B)
Tayside Medical Sciences Centre (TASC)
Residency Block C, Level 3
Ninewells Hospital & Medical School
George Pirie Way
Dundee DD19SY

Mr Grigorios Kotronoulas
PhD Student
University of Dundee
11 Airlie Place
Dundee
DD1 4HJ

Date: 18 October 2011
Your Ref:
Our Ref: LR/AG/10/S1401/41
Enquiries to: Mrs Lorraine Reilly
Extension: Ninewells extension: 40099
Direct Line: 01382 740099
Email: lorraine.reilly@nhs.net

Dear Mr Kotronoulas

Study title:	**Sleep quality & key predictors for sleep disturbances in patients with early stage breast cancer and their informal caregivers during adjuvant chemotherapy**
REC reference:	**10/S1401/41**
Protocol number:	**N/A**

This study was given a favourable ethical opinion by the Committee on 06 September 2010.

Research Ethics Committees are required to keep a favourable opinion under review in the light of progress reports and any developments in the study. You should submit a progress report for the study 12 months after the date on which the favourable opinion was given, and then annually thereafter. Our records indicate that a progress report is overdue. It would be appreciated if you could complete and submit the report by no later than one month from the date of this letter.

Guidance on progress reports and a copy of the standard NRES progress report form is available from the National Research Ethics Service website.

The NRES website also provides guidance on declaring the end of the study.

Failure to submit progress reports may lead to the REC reviewing its opinion on the study.

10/S1401/41: Please quote this number on all correspondence

Yours sincerely

Arlene Grubb

Arlene Grubb
Administrative Assistant
E-mail: agrubb@nhs.net

Copy to: NHS Tayside R & D Office

POSITIVE ABOUT DISABLED PEOPLE

NHS Tayside

EC/LH

21 October 2010

Mr Grigorios Kotronoulas
PhD Student
School of Nursing and Midwifery
University of Dundee
11 Airlie Place
DUNDEE
DD1 4HJ

Dear Mr Kotronoulas,

NHS TAYSIDE MANAGEMENT/GOVERNANCE APPROVAL

Tayside R&D Project ID: 2010ON10

Title: Sleep quality and key predictors for sleep disturbances in patients with early stage breast cancer and their informal caregivers during adjuvant chemotherapy.

Main REC Ref: 10/S1401/41 **Main REC Approval Date: 03/09/10**

Funder: Unfunded

Sponsor: University of Dundee

NHS Support Costs: No

The above project has been registered on the NHS Tayside R&D database, as required by the Research Governance Framework. Medical Research Ethics approval has been obtained and there are no local NHS Support Costs associated with this research project.

NHS Tayside has no objection to the project proceeding, provided all necessary approvals are in place and all amendments to the protocol, personnel involved and funding be notified to the R&D Office and all appropriate personnel. **Please note notification of end of study and a copy of the end of study report is also required by the NHS R&D office.**

It is important to note that all research must be carried out in compliance with the Research Governance Framework for Health & Community Care, GCP and the new EU Clinical Trials Directive (for clinical trials involving investigational medicinal products).

Kind Regards

Elizabeth Coote
R&D Manager

Research and Development

Foresterhill House Annexe
Foresterhill
Aberdeen
AB25 2ZB

NHS Grampian

Dr Ravi Sharma
NHS Grampian
Aberdeen Royal Infirmary
Clinic D
Aberdeen
AB25 2ZN

Date 14/06/11
Our Ref 2011on005

Enquiries to Fiona White
Extension 51121
Direct Line 01224 551121

Dear Dr Sharma,

Management Approval for Non-Commercial Research

MREC Ref: 10/S1401/41
NRS Ref: NRS11/ON156
Project title: Sleep quality and key predictors for sleep disturbances in patients with early stage breast cancer and their informal caregivers during adjuvant chemotherapy

Thank you very much for sending all relevant documentation. I am pleased to confirm that the above project is now registered with the NHS Grampian Research & Development Office. The project now has R & D Management Approval to proceed locally. This is based on the documents received from yourself and the relevant Approvals being in place.

All research with an NHS element is subject to the Research Governance Framework for Health and Community Care (2006, 2nd edition), and as Chief or Principal Investigator you should be fully committed to your responsibilities associated with this.

It is particularly important that you inform us when the study terminates.

The R&D Office must be notified immediately and any relevant documents forwarded to us if any of the following occur:

- A change of Principal Investigator, Chief Investigator or any additional research personnel
- Premature project termination
- Any amendments (particularly a study extension)
- Any change to funding or any additional funding

We hope the project goes well, and if you need any help or advice relating to your R&D Management Approval, please do not hesitate to contact the office.

Yours sincerely

Susan Ridge
Business Development Officer

Professor Nora Kearney, University of Dundee
Mr Grigorios Kotronoulas, University of Dundee
NRS PCC

Operational Division
Victoria Hospital

Hayfield Road
Kirkcaldy
Fife KY2 5AH
Telephone 01592 643355
www.show.scot.nhs.uk/faht

NHS Fife

Mr Grigorios Kotronoulas
PhD Student
University of Dundee
11 Airlie Place
DUNDEE
DD1 4HU

Date: 15 March 2011
Our ref: 11-018 NRS11/ON156
10/S1401/27
Enquiries to: Aileen Yell
Direct Dial: 01383 565110
Fax No:
E-mail: aileenyell@nhs.net

Dear Mr Kotronoulas

Project Title: Sleep quality & Key predictors for sleep disturbances in patients with early stage breast cancer and their informal caregivers during adjuvant chemotherapy

Thank you for your application to carry out the above project. Your project documentation (detailed below) has been reviewed for resource and financial implications for NHS Fife Operational Division and I am happy to inform you that NHS permission for the above research has been granted on the basis described in the application form, protocol and supporting documentation. The documents reviewed were:

Document	Version	Date
Protocol	5.0	31 July 2010
Investigator CV		3 August 2010
Letter from REC with provisional favourable opinion		3 September 2010
Letter to REC – response to request for further information		14 September 2010
IRAS R&D Form	3.0	23 September 2010
REC letter confirming evidence of compliance with approval conditions		24 September 2010
NRS-CC Certificate of Compliance		18 February 2011
IRAS SSI Form	3.0	10 March 2011

The terms of the approval state that you are the investigator authorised to undertake this study within NHS Fife with assistance from Mrs Maureen Devaney, Oncology Research Nurse. Site Specific Assessment review has not been required in this case.

The sponsors for this study are the University of Dundee.

Details of our participation in studies will be included in annual returns we are expected to complete as part of our agreement with the Chief Scientist Office. Regular reports of the study require to be submitted. Your first report should be submitted to Dr A Wood, R&D Manager, R&D Resource Centre, Lynebank Hospital, Halbeath Rd, Dunfermline, KY11 4UW (Amanda.wood3@nhs.net) in 12 months time and subsequently at yearly intervals until the work is completed. A Lay Summary will also be required upon completion of the project.

In addition, approval is granted subject to the following conditions, where applicable:-

- All research activity must comply with the standards detailed in the Research Governance Framework for Health & Community Care (http://www.cso.scot.nhs.uk/publications/resgov/resgov.htm)

- Health & safety regulations, data protection principles, other appropriate statutory legislation and in accordance with Good Clinical Practice (GCP).

- Any amendments which may subsequently be made to the study should also be notified to Aileen Yell, Research Governance Officer (aileenyell@nhs.net), as well as the appropriate regulatory authorities. Notification should also be given of any new research team members post approval and/or any changes to the status of the project.

- This organisation is required to monitor research to ensure compliance with the Research Governance Framework and other legal and regulatory requirements. This is achieved by random audit of research. You will be required to assist with and provide information in regard to monitoring and study outcomes (including provision of recruitment figures to the R&D office when required).

- As custodian of the information collated during this research project you are responsible for ensuring the security of all personal information collected in line with NHS Scotland IT Security Policies, until the destruction of this data.

- Permission is only granted for the activities for which a favourable opinion has been given by the REC (and which have been authorised by the MHRA where applicable).

- The research sponsor or the Chief Investigator or local Principal Investigator at a research site may take appropriate urgent safety measures in order to protect research participants against any immediate hazard to their health or safety. The R&D office (aileenyell@nhs.net) should be notified that such measures have been taken. The notification should also include the reasons why the measures were taken and the plan for further action. The R&D office should be notified within the same time frame of notifying the REC and any other regulatory bodies.

I would like to wish you every success with your study and look forward to receiving a summary of the findings for dissemination once the project is complete.

Yours sincerely

Dr Gordon G Birnie MD FRCP
Medical Director, Operational Division

Cc : Aileen Yell, Research Governance Officer, NHS Fife, Lynebank Hospital, Dunfermline
Pamela Shand, NHS Research Scotland C, R&D Office, Foresterhill House Annex, Foresterhil, AberdeenAB25 2ZB
Maureen Devaney, Oncology Research Nurse, R&D Resource Centre, Lynebank Hospital, Dunfermline

NHS
Forth Valley

Date: 22 July 2011
Your Ref:
Our Ref:
Direct Line: 01324 677564
Email: allyson.bailey@nhs.net
R&D ref: FV 602

Mr. Grigorios Kotronoulas
University of Dundee
11 Airlie Place
Dundee
DD1 4HJ

Dear Mr. Kotronoulas

Study title: Sleep quality and key predictors for sleep disturbances in patients with early stage breast cancer and their informal caregivers during adjuvant chemotheray
NRES number: 10/S1401/41

Following the favourable opinion from the Tayside Committee on Medical Researhc Ethics A on 24 September 2010, I am pleased to confirm that I formally gave Management Approval to the study above on 22 July 2011. I note that Fiona Galbraith is acting as your Clinical Supervisor for this project in NHS Forth Valley

This approval is granted subject to your compliance with the following:

1. Any amendments to the protocol or research team must have Ethics Committee and R&D approval (as well as approval from any other relevant regulatory organisation) before they can be implemented. Please ensure that the R&D Office and (where appropriate) NRS are informed of any amendments as soon as you become aware of them.

2. You and any local Principal Investigator are responsible for ensuring that all members of the research team have the appropriate experience and training, including GCP training if required.

3. All those involved in the project will be required to work within accepted guidelines of health and safety and data protection principles, any other relevant statutory legislation, the Research Governance Framework for Health and Community Care and IHC-GCP guidelines. A copy of the Framework can be accessed via the Chief Scientist Office website at: http://www.cso.scot.nhs.uk/Publications/ResGov/Framework/RGFEdTwo.pdf
and ICH-GCP guidelines may be found at http://www.ich.org/LOB/media/MEDIA482.pdf

4. As custodian of the information collected during this project you are responsible for ensuring the security of all personal information collected in line with NHS Scotland IT security policies, until the destruction of this data.

5. You or the local Principal Investigator will be required to provide the following reports and information during the course of your study:

- A progress report **annually**

- Recruitment numbers on a **monthly** basis (if your study should be added to the NIHR research Portfolio you will receive a separate letter from the R&D Office detailing the steps to be taken)
- Report on SAEs and SUSARs if your study is a Clinical Trial of an Investigational Medicinal Product
- Any information required for the purpose of internal or external audit and monitoring
- Copies of any external monitoring reports
- Notification of the end of recruitment and the end of the study
- A copy of the final report, when available.
- Copies of or full citations for any publications or abstracts

The appropriate forms will be provided to you by the Research and Development office when they are needed. Other information may be required from time to time.

Yours sincerely

DR. IAIN WALLACE
Medical Director

CC: NRS Permissions Coordinating Centre (NRS Permissions CC)
Research & Development Office
Foresterhill House Annexe
Foresterhill
ABERDEEN
AB25 2ZB

Prof. Nora Kearney
University of Dundee
11 Airlie Place
Dundee
DD1 4HJ

Appendix 9. Study Documentation

Sleep Quality in Patients and Caregivers during Adjuvant Chemotherapy for Breast Cancer

Invitation to Research Study

Sleep Quality and Key Predictors for Sleep Disturbances in Patients with Early Stage Breast Cancer and their Informal Caregivers during Adjuvant Chemotherapy

A good night's sleep is highly important for everyone as it improves quality of life.
A good night's sleep is equally important for those who have breast cancer and for those who give care to a person with breast cancer.

Therefore, we are inviting you to take part in this study, which aims to give us a better understanding about your quality of sleep and how your sleep might be affected during this period.
By knowing more about your sleep, we aim to provide better care in the future.

You have received this leaflet because **you are about to begin chemotherapy** for early stage breast cancer.

This study is interested in the sleep patterns of **both** you and the person, family member or friend, who you feel supports and cares for you at this time. We would like you to identify your caregiver so as to also give him/her information about the study, as taking part will involve **both** of you.

If you decide to take part in this study, you will be asked to complete a set of questionnaires at four (4) different time-points: before, during and after chemotherapy.

These questionnaires will ask you to give information about your sleep, symptoms you might have, your mood, and how you cope during this period. You can complete the questionnaires at home and they will only require around 40 minutes of your time.

If you are interested in taking part in this study, please tell the member of the clinical team who gave you this leaflet today.

Many thanks for taking time to read this leaflet.

You can always contact the researcher directly:
Mr. Greg Kotronoulas
School of Nursing & Midwifery, University of Dundee
Tel: 01382 384963; Mob: 07587 050388; Email: g.kotronoulas@dundee.ac.uk

Participant Information Sheet (PIS) – Patient *Version 4.1P 080910*

Hospital/Institution
Ninewells Hospital, NHS Tayside

STUDY TITLE
Sleep Quality and Key Predictors for Sleep Disturbances in Patients with Early Stage Breast Cancer and their Informal Caregivers during Adjuvant Chemotherapy

INVITATION
My name is Grigorios Kotronoulas and I am a PhD student at the University of Dundee. I am required to undertake a project as part of my course and invite you to take part in the following study. However, before you decide to do so, I need to be sure that you understand firstly why I am doing it, and secondly what it would involve if you agreed. I am therefore providing you with the following information. Please read it carefully and be sure to ask any questions you might have and, if you want, discuss it with others including your friends and family. I will do my best to explain the project to you and provide you with any further information you may ask for now or later.

What is the purpose of this study?
You have been scheduled to receive chemotherapy for breast cancer after initial breast surgery. You may have some symptoms before or during your treatment, among them disrupted sleep.

The purpose of the study is to gather knowledge on sleep quality during chemotherapy by exploring sleep patterns of patients with breast cancer and their informal caregivers during chemotherapy.

Another purpose of the study is to consider other factors that may affect sleep over time in both patients and caregivers.

The aim of the study is to inform and educate health care professionals caring for women with breast cancer and their caregivers in regard to sleep-related problems so as to increase the standard of care being delivered and improve patients' and carers' well-being.

Why have I been chosen?
You have been chosen because you were diagnosed with early stage breast cancer and you were initially treated with breast surgery, and now you will receive chemotherapy treatment for breast cancer. A total of 136 participants (68 patients – 68 carers) from one clinical site in Scotland will participate in this study.

Do I have to take part?
Participation in this study is entirely voluntary and you are free to refuse to take part or to withdraw from the study at any time without having to give a reason and without this affecting your future medical care or your relationship with medical staff looking after you.

What will happen to me if I take part?
You will participate in the study at several time points before and during your treatment (at least 6 chemotherapy cycles).

If you do decide to take part, you will be first asked to nominate your primary caregiver (i.e. a family member, friend or neighbour, who you feel provides care and support to you) as they will also be invited to take part in the study.

Secondly, during the study, you will be asked to complete a set of questionnaires at four (4) time points. These time points will be the following: before starting chemotherapy, before the 2nd chemotherapy cycle, before the 5th chemotherapy cycle, and 3 weeks after your chemotherapy treatment has finished.

The questionnaires will ask you questions about your sleep, other symptoms you experience and methods of coping with the disease at each time point. The questionnaires will be the same at all time points and for you both. You can complete the questionnaires at home and they will require approximately 40 minutes of your time. Questionnaires will be given or mailed to you and, after you complete them, you will be able to return them to the researcher via pre-paid post.

For the purposes of the study, the researcher will contact you either at the hospital or at your home.

What will my responsibilities in the study be?
Throughout your participation you will only be asked to give information about your sleep and your experiences during chemotherapy.

What are the side effects or disadvantages of taking part?
As this study does not affect the treatment and care you receive, there are no real side effects of taking part. Also, in no way will it affect your ability to receive treatment, nor will incur any additional expenses to you (or your carer).

However, giving information about your personal experience might become upsetting. In addition, as you will be asked to reflect on your symptoms by completing the set of questionnaires, you may be thinking about your symptoms more than you might if you were

not asked to complete the questionnaires. Although some people may find it upsetting to focus on their symptoms so much, others find this helpful or don't notice any difference. If you feel too uncomfortable completing the questionnaires, you do not need to continue. If you feel that taking part in the study may make you think too much about your symptoms, then you can withdraw without having any effect on your future treatment and care. You should discuss these feelings or concerns with your doctor on nurse.

What are the possible benefits of taking part?
Although you may not directly benefit from taking part, you may benefit in an indirect manner. This study aims to inform and educate the health professionals involved in your care (i.e. doctors, nurses etc.) about your (and your carer's) experience of sleep problems during chemotherapy so as to provide better care to you both. Therefore, your health care team will be able to treat you in the best way possible in case you complain of sleep problems. In addition, by completing the set of questionnaires you will have the opportunity to reflect on your experience, which may urge you to discuss this with your doctor or nurse to get help, should you need it.

What if new information becomes available?
Sometimes during the course of a research project new information becomes available about the procedures being tested. If this happens, the researcher will tell you about it and discuss with you whether you want to continue in the study. If you decide to withdraw, your treatment and care will continue as normal. This will not be affected in any way. If you decide to continue in the study you might be asked to sign an updated informed consent form. Also, on receiving new information, the researcher might consider it to be in your best interests to withdraw you from the study. He will explain the reasons.

Are there any circumstances and/or reasons under which my participation in the study may be terminated?
Your participation is solely based on your free willingness. If however you become upset while completing the questionnaires, your participation in the study will be re-evaluated for your own benefit.

Will I be paid to take part?
No.

What happens when the research study stops?
This study will continue until you have completed all cycles of chemotherapy and 3 weeks after your last chemotherapy cycle. You will continue to receive standard care as is normal at your hospital.

What if something goes wrong?
Any complaints that you have about this study should be addressed initially to your doctor or nurse. If you do not get a satisfactory response from them you are free to contact the sponsor of this research at the address below.

Catrina Forde, PhD
Research Governance Manager
Tayside Academic Health Sciences Centre
Ninewells Hospital & Medical School
TAHSC Research & Development Centre
Residency Block, Level 2
George Pirie Way
Dundee, United Kingdom
DD1 9SY
c.forde@dundee.ac.uk
Ph. 01382 740125

If you are harmed due to someone's negligence, then you may have grounds for legal action to **claim compensation** but you may have to pay for it. Regardless of this, if you wish to complain about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints procedure mechanisms may be available to you. Your doctor will give you further information if necessary.

Will my taking part in this study be kept confidential?
All information that is collected about you during the course of the study will be kept strictly confidential. Any information about you, which leaves the hospital, will have your name and address removed from it so that you cannot be recognised from it. Your personal data will be identified only by a randomly generated number.

Your medical records may be inspected by the team organising the research for purposes of checking data. If you provide your consent, your General Practitioner (GP) will be sent a letter, telling him/her that you are taking part in this study.

If you decide to take part, the signed Informed Consent Form will be kept separately from any other information you provide and will be stored in a locked drawer for the Researcher's use only and will not be shared with anyone else.

What will happen to the results of the study?
The information you provide will be used to draw general conclusions on sleep-related issues during chemotherapy. The results of the study will then be used for research and education

purposes (including reports, publications and presentations) with strict preservation of your anonymity.

Who is organising and funding the study?
The study is being organised by the University of Dundee. It is being funded by a PhD Student Grant.

Who has reviewed this study?
The Tayside Committee on Medical Research Ethics, which has responsibility for scrutinising all proposals for medical research on humans in Tayside, has examined the proposal and has raised no objections from the point of view of medical ethics. It is a requirement that your records in this research, together with any relevant medical records, be made available for scrutiny by the University of Dundee, NHS Tayside and the Regulatory Authorities, whose role is to check that research is properly conducted and the interests of those taking part are adequately protected.

Contact for further information?
Should you wish any further information about the study, please contact one of the researchers below:

Researcher – PhD Student
Grigorios Kotronoulas
School of Nursing & Midwifery
University of Dundee
11 Airlie Place, Dundee, DD1 4HJ
Tel: 01382 384963
Fax: 01382 388533
Email: g.kotronoulas@dundee.ac.uk

1st Supervisor
Professor Nora Kearney
School of Nursing & Midwifery
University of Dundee
11 Airlie Place, Dundee, DD1 4HJ
Tel: 01382 388532
Fax: 01382 388533
Email: n.kearney@dundee.ac.uk

2nd Supervisor
Professor Yvonne Wengström
Department of Neurobiology, Care Science and Society, Division of Nursing
Karolinska Institutet
23300, 141 83 Huddinge, Sweden
Tel: +46 8 524 83683
Email: yvonne.wengstrom@ki.se

If you would like to speak about a problem or a complaint you have to someone who knows about this study who is an independent advisor, please contact:

Dr. Bridget Johnston
School of Nursing & Midwifery
University of Dundee
11 Airlie Place, Dundee, DD1 4HJ
Tel: 01382 385062
Fax: 01382 388533
Email: b.johnston@dundee.ac.uk

Thank you for taking the time to read this Information Sheet and for considering taking part in this study.

Participant Information Sheet *Version 4.1C 080910*

Hospital/Institution
Aberdeen Royal Infirmary, NHS Grampian

STUDY TITLE
Sleep Quality and Key Predictors for Sleep Disturbances in Patients with Early Stage Breast Cancer and their Informal Caregivers during Adjuvant Chemotherapy

INVITATION
My name is Grigorios Kotronoulas and I am a PhD student at the University of Dundee. I am required to undertake a project as part of my course and invite you to take part in the following study. However, before you decide to do so, I need to be sure that you understand firstly why I am doing it, and secondly what it would involve if you agreed. I am therefore providing you with the following information. Please read it carefully and be sure to ask any questions you might have and, if you want, discuss it with others including your friends and family. I will do my best to explain the project to you and provide you with any further information you may ask for now or later.

What is the purpose of this study?
You have been nominated as the informal caregiver of the patient scheduled to receive chemotherapy for breast cancer after initial breast surgery. You may have some symptoms while caring for this person, among them disrupted sleep.

The purpose of the study is to gather knowledge on sleep quality during chemotherapy by exploring sleep patterns of patients with breast cancer and their informal caregivers during chemotherapy.

Another purpose of the study is to consider other factors that may affect sleep over time in both patients and caregivers.

The aim of the study is to inform and educate health care professionals caring for women with breast cancer and their caregivers in regard to sleep-related problems so as to increase the standard of care being delivered and improve patients' and carers' well-being.

Why have I been chosen?
You have been chosen because you were nominated as the informal caregiver of a patient with early stage breast cancer, who will receive post-surgery chemotherapy treatment. A total of 136 participants (68 patients – 68 carers) from different clinical sites in Scotland will participate in this study.

Do I have to take part?
Participation in this study is entirely voluntary and you are free to refuse to take part or to withdraw from the study at any time without having to give a reason and without this affecting the future medical care of the person you care for or your relationship with medical staff looking after that person.

What will happen to me if I take part?
You will participate in the study at several time points before and during patient's treatment (at least 6 chemotherapy cycles).

During the study, you will be asked to complete a set of questionnaires at four (4) time points. These time points will be the following: before starting chemotherapy, before the 2nd chemotherapy cycle, before the 5th chemotherapy cycle, and 3 weeks after your chemotherapy treatment has finished.

The questionnaires will ask you questions about your sleep, burden you experience and methods of coping with patient's disease at each time point. The questionnaires will be the same at all time points and for you both. You can complete the questionnaires at home and they will require approximately 40 minutes of your time. Questionnaires will be given or mailed to you and, after you complete them, you will be able to return them to the researcher via pre-paid post.

For the purposes of the study, the researcher will contact you either at the hospital or at your home.

What will my responsibilities in the study be?
Throughout your participation you will only be asked to give information about your sleep and your experiences during patient's chemotherapy.

What are the side effects or disadvantages of taking part?
As this study does not affect your physical condition, there are no real side effects of taking part. Also, in no way will it affect your ability to provide care to the patient, nor will incur any additional expenses to you (or the patient).

However, giving information about your personal experience might become upsetting. In addition, as you will be asked to reflect on your experience by completing the set of questionnaires, you may be thinking about your experience more than you might if you were not asked to complete the questionnaires. Although some people may find it upsetting to focus on their experience caring for a cancer patient so much, others find this helpful or don't notice any difference. If you feel too uncomfortable completing the questionnaires, you do

not need to continue. If you feel that taking part in the study may make you think too much about your experience, then you can withdraw without having any effect on your legal rights. You should discuss these feelings or concerns with a member of the health care team.

What are the possible benefits of taking part?
Although you may not directly benefit from taking part, you may benefit in an indirect manner. This study aims to inform and educate the health professionals involved in your care (i.e. doctors, nurses etc.) about your (and the patient's) experience of sleep problems during chemotherapy so as to provide better care to you both. Therefore, your health care team will be able to treat you in the best way possible in case you complain of sleep problems. In addition, by completing the set of questionnaires you will have the opportunity to reflect on your experience, which may urge you to discuss this with a member of health care team to get help, should you need it.

What if new information becomes available?
Sometimes during the course of a research project new information becomes available about the procedures being tested. If this happens, the researcher will tell you about it and discuss with you whether you want to continue in the study. If you decide to withdraw, your legal rights will remain unaffected. If you decide to continue in the study you might be asked to sign an updated informed consent form. Also, on receiving new information, the researcher might consider it to be in your best interests to withdraw you from the study. He will explain the reasons.

Are there any circumstances and/or reasons under which my participation in the study may be terminated?
Your participation is solely based on your free willingness. If however you become upset while completing the questionnaires, your participation in the study will be re-evaluated for your own benefit.

Will I be paid to take part?
No.

What happens when the research study stops?
This study will continue until the patient has completed all cycles of chemotherapy and 3 weeks after her last chemotherapy cycle. She will continue to receive standard care as is normal at your hospital.

What if something goes wrong?

Any complaints that you have about this study should be addressed initially to a member of the health care team. If you do not get a satisfactory response from them you are free to contact the sponsor of this research at the address below.

Catrina Forde, PhD
Research Governance Manager
Tayside Academic Health Sciences Centre
Ninewells Hospital & Medical School
TAHSC Research & Development Centre
Residency Block, Level 2
George Pirie Way
Dundee, United Kingdom
DD1 9SY
c.forde@dundee.ac.uk
Ph. 01382 740125

If you are harmed due to someone's negligence, then you may have grounds for legal action to **claim compensation** but you may have to pay for it. Regardless of this, if you wish to complain about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints procedure mechanisms may be available to you. A member of the health care team will give you further information if necessary.

Will my taking part in this study be kept confidential?
All information that is collected about you during the course of the study will be kept strictly confidential. Any information about you, which leaves the hospital, will have your name and address removed from it so that you cannot be recognised from it. Your personal data will be identified only by a randomly generated number.

If you decide to take part, the signed Informed Consent Form will be kept separately from any other information you provide and will be stored in a locked drawer for the Researcher's use only and will not be shared with anyone else.

What will happen to the results of the study?
The information you provide will be used to draw general conclusions on sleep-related issues during chemotherapy. The results of the study will then be used for research and education purposes (including reports, publications and presentations) with strict preservation of your anonymity.

Who is organising and funding the study?
The study is being organised by the University of Dundee. It is being funded by a PhD Student Grant.

Who has reviewed this study?
The Tayside Committee on Medical Research Ethics, which has responsibility for scrutinising all proposals for medical research on humans in Tayside, has examined the proposal and has raised no objections from the point of view of medical ethics. It is a requirement that your records in this research, together with any relevant medical records, be made available for scrutiny by the University of Dundee, NHS Grampian and the Regulatory Authorities, whose role is to check that research is properly conducted and the interests of those taking part are adequately protected.

Contact for further information?
Should you wish any further information about the study, please contact one of the researchers below:

Researcher – PhD Student
Grigorios Kotronoulas
School of Nursing & Midwifery
University of Dundee
11 Airlie Place, DUNDEE DD1 4HJ
Tel: 01382 384963
Fax: 01382 388533
Email: g.kotronoulas@dundee.ac.uk

1st Supervisor
Professor Nora Kearney
School of Nursing & Midwifery
University of Dundee
11 Airlie Place, DUNDEE DD1 4HJ
Tel: 01382 388532
Fax: 01382 388533
Email: n.kearney@dundee.ac.uk

2nd Supervisor
Professor Yvonne Wengström
Department of Neurobiology, Care Science and Society, Division of Nursing
Karolinska Institutet
23300, 141 83 Huddinge, Sweden
Tel: +46 8 524 83683
Email: yvonne.wengstrom@ki.se

If you would like to speak about a problem or a complaint you have to someone who knows about this study who is an independent advisor, please contact:

Dr. Bridget Johnston
School of Nursing & Midwifery
University of Dundee
11 Airlie Place, DUNDEE DD1 4HJ
Tel: 01382 385062
Fax: 01382 388533
Email: b.johnston@dundee.ac.uk

Thank you for taking the time to read this Information Sheet and for considering taking part in this study.

PARTICIPANT INFORMED CONSENT FORM – PATIENT
Version 3.1P 080910

Please take time to read the following statements. If you agree with the statement, please put your initials in the box, thus providing your consent to take part in the study.

STUDY TITLE
Sleep Quality and Key Predictors for Sleep Disturbances in Patients with Early Stage Breast Cancer and their Informal Caregivers During Adjuvant Chemotherapy

Statement	Your initials
I confirm that I have read and understand the Study Information Sheet dated 080910 (version 4.1P) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	
I understand the prospective nature and purpose of the study.	
I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical treatment, care or legal rights being affected.	
I understand that no personally identifiable information will be collected and my data will be identified only by a randomly generated number.	
I understand that if I choose to withdraw from the study, any information provided till this moment will be included in the study, with my personal data remaining confidential.	
I understand that this form will be kept separately from any other information that I provide and will be stored in a locked drawer for the Researcher's use only and will not be shared with anyone else.	
I understand that any information I provide will be treated in the strictest confidence. The information will be held securely for 5 years and will only be available to the researcher. The information will be destroyed after this time.	
I give permission for the information I provide to be used for research purposes (including reports, publications and presentations), with strict preservation of anonymity.	
I agree to my Consultant being notified by letter of my participation in this project.	

Please turn over

Statement			**Your initials**
I agree to take part in the above-mentioned study.			
Consent section			
Participant *(print name)*	Date:	Signature:	
Researcher *(print name)*	Date:	Signature:	

UNIVERSITY OF DUNDEE

NHS Forth Valley

PARTICIPANT INFORMED CONSENT FORM

Version 3.1C 080910

Please take time to read the following statements. If you agree with the statement, please put your initials in the box, thus providing your consent to take part in the study.

STUDY TITLE

Sleep Quality and Key Predictors for Sleep Disturbances in Patients with Early Stage Breast Cancer and their Informal Caregivers During Adjuvant Chemotherapy

Statement	Your initials
I confirm that I have read and understand the Study Information Sheet dated 080910 (version 4.1C) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	
I understand the prospective nature and purpose of the study.	
I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my legal rights being affected and without my decision affecting the medical treatment, care or legal rights of the patient I care for.	
I understand that no personally identifiable information will be collected and my data will be identified only by a randomly generated number.	
I understand that if I choose to withdraw from the study, any information provided till this moment will be included in the study, with my personal data remaining confidential.	
I understand that this form will be kept separately from any other information that I provide and will be stored in a locked drawer for the Researcher's use only and will not be shared with anyone else.	
I understand that any information I provide will be treated in the strictest confidence. The information will be held securely for 5 years and will only be available to the researcher. The information will be destroyed after this time.	
I give permission for the information I provide to be used for research purposes (including reports, publications and presentations), with strict preservation of anonymity.	

Please turn over

Statement			**Your initials**
I agree to take part in the above-mentioned study.			
Consent Section			
_____ Participant *(print name)*	_____ Date:	_____ Signature:	
_____ Researcher *(print name)*	_____ Date:	_____ Signature:	

Mr. G. Kotronoulas
School of Nursing & Midwifery
University of Dundee
11 Airlie Place
Dundee, DD1 4HJ

Letter to Consultant/GP
Version: 3.0 010710

[add details]

Study Title

Sleep quality & key predictors for sleep disturbances in patients with early stage breast cancer and their informal caregivers during adjuvant chemotherapy

Patient Details

Name: **Mrs** .....

Dear Dr.....,

The aforementioned patient is participating in the above study on early stage breast cancer. The study will involve patients and caregivers, who will be asked to complete a set of questionnaires in four distinct time points during adjuvant chemotherapy, but does NOT involve any changes in standard treatment.

A copy of the Patient Information Study Sheet is enclosed.

Yours sincerely,

Grigorios Kotronoulas, BSN, MSc, PhD student
School of Nursing & Midwifery
University of Dundee
Email: g.kotronoulas@dundee.ac.uk
Tel: 01382 384963

Appendix 10. Data Collection Forms and Questionnaires

Sleep Quality in Patients and Caregivers during Adjuvant Chemotherapy for Breast Cancer

Demographic Characteristics Form (DCF)

Age *(in years)*:	

Educational Background	High School	☐
	University	☐

Employment	Not employed	☐
	Employed	☐

Marital Status	Married/partnered	☐
	Single	☐
	Divorced	☐
	Widowed	☐

Yearly Household Income	< £ 10,000	☐
	£ 10,001 – 20,000	☐
	£ 20,001 – 50,000	☐
	> £ 50,000	☐

Demographic Characteristics Form (DCF)

Age *(in years)*:	

Gender	Male	☐
	Female	☐

Educational Background	High School	☐
	University	☐

Employment	Not employed	☐
	Employed	☐

Marital Status	Married/partnered	☐
	Single	☐
	Divorced	☐
	Widowed	☐

Yearly Household Income	< £ 10,000	☐
	£ 10,001 – 20,000	☐
	£ 20,001 – 50,000	☐
	> £ 50,000	☐

Relation to patient	Family member	☐	*Please specify:*
	Partner *(other than husband)*	☐	
	Friend	☐	
	Neighbour	☐	
	Other	☐	*Please specify:*

Duration of relationship *(in months)*: *Note: Except for parent-to-child relationship*	

Clinical Characteristics Form (CCF)

Use of dexamethasone over the past 2 weeks	Yes	☐
	No	☐

Use of pain control over the past 2 weeks	Yes	☐	*Please specify analgesic:*
	No	☐	

Use of alternative/complementary therapies over the past 2 weeks	Yes	☐	*Please specify type:*
	No	☐	

ECOG Performance Status

Please indicate the level of your performance for the PAST 2 WEEKS by circling the most appropriate statement.

		Grade
Fully active, able to carry on all pre-disease performance without restriction	Excellent	0
Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work	Good	1
Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours	Average	2
Capable of only limited self-care, confined to bed or chair more than 50% of waking hours	Poor	3
Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair	Very poor	4

Source: Oken MM et al. (1982. American Journal of Clinical Oncology 5(6): 649-655.

Clinical Characteristics Form (CCF)

Physical Activity
What has your leisure time physical activity level been during the PAST 2 WEEKS? *(walking to work counts as leisure time.)*

Please respond to both categories by marking your answer in the box.

	Hours per week			
Categories	No	< 1	1-2	≥ 3
Low-level activity (not becoming sweaty/breathless; e.g. reading, light housework, walking for pleasure)				
High-level activity (becoming sweaty/breathless; e.g. using stairs, heavy housework, exercising)				

Source: Oldervoll LM, et al. (2007). BMC Cancer, 7: 210.

Clinical Characteristics Form (CCF)

Present illnesses	Yes	☐	*Please specify:*
	No	☐	

Use of prescribed medications over the past 2 weeks	Yes	☐	*Please specify:*
	No	☐	

Use of non-prescribed medications over the past 2 weeks	Yes	☐	*Please specify:*
	No	☐	

ECOG Performance Status

Please indicate the level of your performance for the PAST 2 WEEKS by circling the most appropriate statement.

		Grade
Fully active, able to carry on all pre-disease performance without restriction	Excellent	0
Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work	Good	1
Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours	Average	2
Capable of only limited self-care, confined to bed or chair more than 50% of waking hours	Poor	3
Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair	Very poor	4

Source: Oken MM et al. (1982. American Journal of Clinical Oncology 5(6): 649-655.

Clinical Characteristics Form (CCF)

Physical Activity
What has your leisure time physical activity level been during the PAST 2 WEEKS? *(walking to work counts as leisure time.)*

Please respond to both categories by marking your answer in the box.

	Hours per week			
Categories	No	< 1	1-2	≥ 3
Low-level activity (not becoming sweaty/breathless; e.g. reading, light housework, walking for pleasure)				
High-level activity (becoming sweaty/breathless; e.g. using stairs, heavy housework, exercising)				

Source: Oldervoll LM, et al. (2007). BMC Cancer, 7: 210.

Welstein, L.; Dement, W.C.; Redington, D.; and Guilleminault, C. Insomnia in the San Francisco Bay Area: A telephone survey. *Sleep/Wake Disorders: Natural History, Epidemiology, and Long-Term Evolution.* New York: Raven Press, 1983. pp. 73-85.

Appendix. Pittsburgh Sleep Quality Index (PSQI)

Name _____ ID # _____ Date _____ Age _____

Instructions:

The following questions relate to your usual sleep habits during the past month *only*. Your answers should indicate the most accurate reply for the *majority* of days and nights in the past month. Please answer all questions.

1. During the past month, when have you usually gone to bed at night?
   USUAL BED TIME _____
2. During the past month, how long (in minutes) has it usually take you to fall asleep each night?
   NUMBER OF MINUTES _____
3. During the past month, when have you usually gotten up in the morning?
   USUAL GETTING UP TIME _____
4. During the past month, how many hours of *actual sleep* did you get at night? (This may be different than the number of hours you spend in bed.)
   HOURS OF SLEEP PER NIGHT _____

For each of the remaining questions, check the one best response. Please answer *all* questions.

5. During the past month, how often have you had trouble sleeping because you...

(a) Cannot get to sleep within 30 minutes

Not during the past month _____	Less than once a week _____	Once or twice a week _____	Three or more times a week _____

(b) Wake up in the middle of the night or early morning

Not during the past month _____	Less than once a week _____	Once or twice a week _____	Three or more times a week _____

(c) Have to get up to use the bathroom

Not during the past month _____	Less than once a week _____	Once or twice a week _____	Three or more times a week _____

(d) Cannot breathe comfortably

Not during the past month _____	Less than once a week _____	Once or twice a week _____	Three or more times a week _____

(e) Cough or snore loudly

Not during the past month _____	Less than once a week _____	Once or twice a week _____	Three or more times a week _____

(f) Feel too cold

Not during the past month _____	Less than once a week _____	Once or twice a week _____	Three or more times a week _____

(g) Feel too hot

Not during the past month _____	Less than once a week _____	Once or twice a week _____	Three or more times a week _____

(h) Had bad dreams

Not during the past month _____	Less than once a week _____	Once or twice a week _____	Three or more times a week _____

(i) Have pain

Not during the past month _____	Less than once a week _____	Once or twice a week _____	Three or more times a week _____

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(j) Other reason(s), please describe _____

_____

How often during the past month have you had trouble sleeping because of this?

Not during the past month _____	Less than once a week _____	Once or twice a week _____	Three or more times a week _____

6. During the past month, how would you rate your sleep quality overall?

Very good _____
Fairly good _____
Fairly bad _____
Very bad _____

7. During the past month, how often have you taken medicine (prescribed or "over the counter") to help you sleep?

Not during the past month _____	Less than once a week _____	Once or twice a week _____	Three or more times a week _____

8. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?

Not during the past month _____	Less than once a week _____	Once or twice a week _____	Three or more times a week _____

9. During the past month, how much of a problem has it been for you to keep up enough enthusiasm to get things done?

No problem at all _____
Only a very slight problem _____
Somewhat of a problem _____
A very big problem _____

10. Do you have a bed partner or roommate?

No bed partner or roommate _____
Partner/roommate in other room _____
Partner in same room, but not same bed _____
Partner in same bed _____

If you have a roommate or bed partner, ask him/her how often in the past month you have had...

(a) Loud snoring

Not during the past month _____	Less than once a week _____	Once or twice a week _____	Three or more times a week _____

(b) Long pauses between breaths while asleep

Not during the past month _____	Less than once a week _____	Once or twice a week _____	Three or more times a week _____

(c) Legs twitching or jerking while you sleep

Not during the past month _____	Less than once a week _____	Once or twice a week _____	Three or more times a week _____

(d) Episodes of disorientation or confusion during sleep

Not during the past month _____	Less than once a week _____	Once or twice a week _____	Three or more times a week _____

(e) Other restlessness while you sleep; please describe _____

_____

Not during the past month _____	Less than once a week _____	Once or twice a week _____	Three or more times a week _____

Sleep-related Questions

The following questions relate to some features of your sleep. Your answers should indicate the most accurate reply for the majority of days and nights in the PAST 2 WEEKS. Please answer all questions.

1. During the past 2 weeks have you felt the need of taking naps during the day?
   - Yes ☐
   - No ☐
   - If yes, what was their average total duration (*in minutes)* per day? ☐

2. During the past 2 weeks, when you were getting up in the morning how were you feeling?
   - Not at all rested ☐
   - A little bit rested ☐
   - Quite a bit rested ☐
   - Very rested ☐

3. During the past 2 weeks, how often did you feel kicking or twitching your legs while you were sleeping?
   - Not during the past 2 weeks ☐
   - Once a week ☐
   - Twice a week ☐
   - Three or more times a week ☐

4. During the past 2 weeks, how sleepy did you feel during the day?
   - Not at all sleepy ☐
   - A bit sleepy ☐
   - Quite sleepy ☐
   - Very sleepy ☐

5. During the past 2 weeks, how many times (on average) did you wake up during the night?
   - None ☐
   - 1-2 times ☐
   - 3-5 times ☐
   - 6 or more times ☐

6. During the past 2 weeks, how often did you wake up earlier than planned and couldn't get back to sleep?
   - Not during the past 2 weeks ☐
   - Once a week ☐
   - Twice a week ☐
   - Three or more times a week ☐

Brief Sleep History

The following questions are related to your sleep habits and current life-style habits. Please answer all questions.

1. Have you had problems with your sleep in the past?
   - Yes ☐
   - No ☐

2. Has your sleep been affected in any way by the diagnosis of cancer?
   - Yes ☐
   - No ☐

3. Do you smoke?
   - Yes ☐
   - No ☐

4. Do you drink alcohol?
   - Never ☐
   - Only occasionally ☐
   - Everyday ☐

Brief Sleep History

The following questions are related to your sleep habits and current life-style habits. Please answer all questions.

1. Have you had problems with your sleep in the past?	Yes	☐
	No	☐
2. Has your sleep been affected in any way by the diagnosis of cancer?	Yes	☐
	No	☐
3. Do you smoke?	Yes	☐
	No	☐
4. Do you drink alcohol?	Never	☐
	Only occasionally	☐
	Everyday	☐
5. Do you and the person you are caring for sleep in the same room?	Yes	☐
	No	☐
6. Do you and the person you are caring for sleep in the same house?	Yes	☐
	No	☐

Sleep Hygiene Index (SHI)

This questionnaire helps us to know about your sleep habits. Read every sentence.

During the PAST 2 WEEKS, I was...		Never	Rarely	Sometimes	Frequently	Always
1	Taking daytime naps lasting two or more hours	0	1	2	3	4
2	Going to bed at different times from day to day	0	1	2	3	4
3	Getting out of bed at different times from day to day	0	1	2	3	4
4	Exercising to the point of sweating within 1 hour of going to bed	0	1	2	3	4
5	Staying in bed longer than I should two or three times a week	0	1	2	3	4
6	Making use of alcohol, tobacco or caffeine within 4 hours of going to bed or after going to bed	0	1	2	3	4
7	Doing something that may wake me up before bedtime (e.g. play video games, use the internet, or clean)	0	1	2	3	4
8	Going to bed feeling stressed, angry, upset or nervous	0	1	2	3	4
9	Making use of my bed for things other than sleeping or sex (e.g. watch television, read, eat or study)	0	1	2	3	4
10	Sleeping on an uncomfortable bed (e.g. poor mattress or pillow, too much or not enough blankets)	0	1	2	3	4
11	Sleeping in an uncomfortable bedroom (e.g. too bright, too stuffy, too hot, too cold, or too noisy)	0	1	2	3	4
12	Doing important work before bedtime (e.g. pay bills, schedule, or study)	0	1	2	3	4
13	Thinking, planning, or worrying when I was in bed	0	1	2	3	4

Source: Martin DF et al. (2006). *Journal of Behavioural Medicine* 29(3): 223-227.

(a)

MEMORIAL SYMPTOM ASSESSMENT SCALE

NAME: DATE:

SECTION 1:

INSTRUCTIONS: We have listed 24 symptoms below. Read each one carefully. If you have had the symptom during this past week, let us know how OFTEN you had it, how SEVERE it was usually and how much it DISTRESSED OR BOTHERED you by circling the appropriate number. If you DID NOT HAVE the symptom, make an "X" in the box marked "DID NOT HAVE".

DURING THE PAST WEEK. Did you have any of the following symptoms?	DID NOT HAVE	IF YES, How OFTEN did you have it?				IF YES, How SEVERE was it usually?				IF YES, How much did it DISTRESS or BOTHER you?				
		Rarely	Occasionally	Frequently	Almost constantly	Slight	Moderate	Severe	Very severe	Not at all	A little bit	Somewhat	Quite a bit	Very much
Difficulty concentrating		1	2	3	4	1	2	3	4	0	1	2	3	4
Pain		1	2	3	4	1	2	3	4	0	1	2	3	4
Lack of energy		1	2	3	4	1	2	3	4	0	1	2	3	4
Cough		1	2	3	4	1	2	3	4	0	1	2	3	4
Feeling nervous		1	2	3	4	1	2	3	4	0	1	2	3	4
Dry mouth		1	2	3	4	1	2	3	4	0	1	2	3	4
Nausea		1	2	3	4	1	2	3	4	0	1	2	3	4
Feeling drowsy		1	2	3	4	1	2	3	4	0	1	2	3	4
Numbness/ tingling in hands/feet		1	2	3	4	1	2	3	4	0	1	2	3	4
Difficulty sleeping		1	2	3	4	1	2	3	4	0	1	2	3	4
Feeling bloated		1	2	3	4	1	2	3	4	0	1	2	3	4
Problems with urination		1	2	3	4	1	2	3	4	0	1	2	3	4

(b)

DURING THE PAST WEEK. Did you have any of the following symptoms?	DID NOT HAVE	IF YES, How OFTEN did you have it?				IF YES, How SEVERE was it usually?				IF YES, How much did it DISTRESS or BOTHER you?				
		Rarely	Occasionally	Frequently	Almost constantly	Slight	Moderate	Severe	Very severe	Not at all	A little bit	Somewhat	Quite a bit	Very much
Vomiting		1	2	3	4	1	2	3	4	0	1	2	3	4
Shortness of breath		1	2	3	4	1	2	3	4	0	1	2	3	4
Diarrhoea		1	2	3	4	1	2	3	4	0	1	2	3	4
Feeling sad		1	2	3	4	1	2	3	4	0	1	2	3	4
Sweats		1	2	3	4	1	2	3	4	0	1	2	3	4
Worrying		1	2	3	4	1	2	3	4	0	1	2	3	4
Problems with sexual interest or activity		1	2	3	4	1	2	3	4	0	1	2	3	4
Itching		1	2	3	4	1	2	3	4	0	1	2	3	4
Lack of appetite		1	2	3	4	1	2	3	4	0	1	2	3	4
Dizziness		1	2	3	4	1	2	3	4	0	1	2	3	4
Difficulty swallowing		1	2	3	4	1	2	3	4	0	1	2	3	4
Feeling irritable		1	2	3	4	1	2	3	4	0	1	2	3	4

Figure 1. (a) Page 1, (b) page 2. The revised version of the Memorial Symptom Assessment Scale.

The Memorial Symptom Assessment Scale

(c)

SECTION 2:

INSTRUCTIONS: We have listed 8 symptoms below. Read each one carefully. If you have had the symptom during this past week, let us know how SEVERE it was usually and how much it DISTRESSED OR BOTHERED you by circling the appropriate number. If you DID NOT HAVE the symptom, make an "X" in the box marked "DID NOT HAVE".

DURING THE PAST WEEK. Did you have any of the following symptoms?	DID NOT HAVE	IF YES, How SEVERE was it usually?				IF YES, How much did it DISTRESS or BOTHER you?				
		Slight	Moderate	Severe	Very severe	Not at all	A little bit	Somewhat	Quite a bit	Very much
Mouth sores		1	2	3	4	0	1	2	3	4
Change in the way food tastes		1	2	3	4	0	1	2	3	4
Weight loss		1	2	3	4	0	1	2	3	4
Hair loss		1	2	3	4	0	1	2	3	4
Constipation		1	2	3	4	0	1	2	3	4
Swelling of arms or legs		1	2	3	4	0	1	2	3	4
"I don't look like myself"		1	2	3	4	0	1	2	3	4
Changes in skin		1	2	3	4	0	1	2	3	4
**IF YOU HAD ANY OTHER SYMPTOMS DURING THE PAST WEEK, PLEASE LIST BELOW AND INDICATE HOW MUCH THE SYMPTOM HAS DISTRESSED OR BOTHERED YOU.										
Other:						0	1	2	3	4
Other:						0	1	2	3	4
Other:						0	1	2	3	4

Figure 1. (c) Page 3. The revised version of the Memorial Symptom Assessment Scale.

Brief COPE Scale

These items deal with ways you've been coping with the stress in your life since you have been diagnosed with cancer. We want to know to what extent you've been doing what the item says; how much or how frequently.

Don't answer on the basis of whether it seems to be working or not – just whether or not you're doing it. **USE THESE RESPONSE CHOICES:**

1 = I haven't been doing this at all

2 = I've been doing this a little bit

3 = I've been doing this a medium amount

4 = I've been doing this a lot

Try to rate each item separately in your mind from the others. Make your answers as true FOR YOU as you can for the PAST 2 WEEKS.

During the PAST 2 WEEKS I have been...		**Circle your response**			
1.	Turning to work or other activities to take my mind off things.	1	2	3	4
2.	Concentrating my efforts on doing something about the situation I'm in.	1	2	3	4
3.	Saying to myself "this isn't real".	1	2	3	4
4.	Using alcohol or other drugs to make myself feel better.	1	2	3	4
5.	Getting emotional support from others.	1	2	3	4
6.	Giving up trying to deal with it.	1	2	3	4
7.	Taking action to try to make the situation better.	1	2	3	4
8.	Refusing to believe that it has happened.	1	2	3	4
9.	Saying things to let my unpleasant feelings escape.	1	2	3	4
10.	Getting help and advice from other people.	1	2	3	4
11.	Using alcohol or other drugs to help me get through it.	1	2	3	4
12.	Trying to see it in a different light, to make it seem more positive.	1	2	3	4
13.	Criticizing myself.	1	2	3	4
14.	Trying to come up with a strategy about what to do.	1	2	3	4
15.	Getting comfort and understanding from someone.	1	2	3	4
16.	Giving up the attempt to cope.	1	2	3	4
17.	Looking for something good in what is happening.	1	2	3	4
18.	Making jokes about it.	1	2	3	4
19.	Doing something to think about it less, such as going to movies, watching TV, reading, daydreaming, sleeping, or shopping.	1	2	3	4
20.	Accepting the reality of the fact that it has happened.	1	2	3	4
21.	Expressing my negative feelings.	1	2	3	4
22.	Trying to find comfort in my religion or spiritual beliefs.	1	2	3	4
23.	Trying to get advice or help from other people about what to do.	1	2	3	4
24.	Learning to live with it.	1	2	3	4
25.	Thinking hard about what steps to take.	1	2	3	4
26.	Blaming myself for things that happened.	1	2	3	4
27.	Praying or meditating.	1	2	3	4
28.	Making fun of the situation.	1	2	3	4

Source: Carver CS (1997). *International Journal of Behavioral Medicine* 4(1): 92-100.

Brief COPE Scale

These items deal with ways you've been coping with the stress in your life since you have been caring for a person diagnosed with cancer. We want to know to what extent you've been doing what the item says; how much or how frequently.

Don't answer on the basis of whether it seems to be working or not – just whether or not you're doing it. **USE THESE RESPONSE CHOICES:**

1 = I haven't been doing this at all

2 = I've been doing this a little bit

3 = I've been doing this a medium amount

4 = I've been doing this a lot

Try to rate each item separately in your mind from the others. Make your answers as true FOR YOU as you can for the PAST 2 WEEKS.

During the PAST 2 WEEKS I have been...	Circle your response			
1. Turning to work or other activities to take my mind off things.	1	2	3	4
2. Concentrating my efforts on doing something about the situation I'm in.	1	2	3	4
3. Saying to myself "this isn't real".	1	2	3	4
4. Using alcohol or other drugs to make myself feel better.	1	2	3	4
5. Getting emotional support from others.	1	2	3	4
6. Giving up trying to deal with it.	1	2	3	4
7. Taking action to try to make the situation better.	1	2	3	4
8. Refusing to believe that it has happened.	1	2	3	4
9. Saying things to let my unpleasant feelings escape.	1	2	3	4
10. Getting help and advice from other people.	1	2	3	4
11. Using alcohol or other drugs to help me get through it.	1	2	3	4
12. Trying to see it in a different light, to make it seem more positive.	1	2	3	4
13. Criticizing myself.	1	2	3	4
14. Trying to come up with a strategy about what to do.	1	2	3	4
15. Getting comfort and understanding from someone.	1	2	3	4
16. Giving up the attempt to cope.	1	2	3	4
17. Looking for something good in what is happening.	1	2	3	4
18. Making jokes about it.	1	2	3	4
19. Doing something to think about it less, such as going to movies, watching TV, reading, daydreaming, sleeping, or shopping.	1	2	3	4
20. Accepting the reality of the fact that it has happened.	1	2	3	4
21. Expressing my negative feelings.	1	2	3	4
22. Trying to find comfort in my religion or spiritual beliefs.	1	2	3	4
23. Trying to get advice or help from other people about what to do.	1	2	3	4
24. Learning to live with it.	1	2	3	4
25. Thinking hard about what steps to take.	1	2	3	4
26. Blaming myself for things that happened.	1	2	3	4
27. Praying or meditating.	1	2	3	4
28. Making fun of the situation.	1	2	3	4

Source: Carver CS (1997). *International Journal of Behavioral Medicine* 4(1): 92-100.

Caregiver Reaction Assessment Scale (CRAS)

This questionnaire helps us to know how caregiving impacts on your life. Read every sentence. Circle the answer that best describes how caregiving has impacted on each life situation during the PAST 2 WEEKS.

Statement	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
1. My activities are centered around care for my patient.	1	2	3	4	5
2. I am healthy enough to care for my patient.	5	4	3	2	1
3. My family works together at caring for the patient.	5	4	3	2	1
4. Caring for my patient is important to me.	1	2	3	4	5
5. It takes all my physical strength to care for my patient.	1	2	3	4	5
6. I enjoy caring for my patient.	1	2	3	4	5
7. I have to stop in the middle of my work or activities to provide care.	1	2	3	4	5
8. My health has gotten worse since I've been caring for my patient.	1	2	3	4	5
9. Since caring for my patient, I feel my family has abandoned me.	1	2	3	4	5
10. Caring for my patient makes me feel good.	1	2	3	4	5
11. It is very difficult to get help from my family in taking care of my patient.	1	2	3	4	5
12. I feel privileged to care for my patient.	1	2	3	4	5
13. Others have dumped caring for my patient onto me.	1	2	3	4	5
14. I have eliminated things from my schedule since caring for my patient.	1	2	3	4	5
15. I resent having to care for my patient.	5	4	3	2	1
16. The constant interruptions make it difficult to find time for relaxation.	1	2	3	4	5
17. My family (brothers, sisters, children) left me alone to care for my patient.	1	2	3	4	5
18. Since caring for my patient, it seems like I'm tired all of the time.	1	2	3	4	5
19. I really want to care for my patient.	1	2	3	4	5
20. I visit family and friends less since I have been caring for my patient.	1	2	3	4	5
21. I will never be able to do enough caregiving to repay my patient.	5	4	3	2	1
22. Financial resources are adequate	5	4	3	2	1
23. It is difficult to pay for my patient	1	2	3	4	5
24. Caring my patient puts a financial strain on me	1	2	3	4	5

Source: Nijboer C, et al. (1999). *Social Science & Medicine* 48: 1259-1269.