Sleep disturbances and the experience of pain: a multi-methodological approach

by

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Table of Contents

List of figures and tables

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This thesis is submitted to the University of Warwick in support of my application for the degree of Doctor of Philosophy. It has been composed by myself and has not been submitted in any previous application for any degree.

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Abstract

Poor sleep and pain conditions present a major public health challenge due to their pervasive impact on well-being. Using a mix of experimental and observational methodologies, this thesis assesses sleep disruptions and its potential associations with the experience of pain. Chapter 4 comprises two experimental studies in healthy young adults (n = 57; n = 118) revealing that impairment in central pain inhibitory processes (conditioned pain modulation response) may be associated with self-reported sleep disruptions. The studies also support the validity of the conditioned pain modulation response as a physiological marker of pain inhibition. Chapter 5 presented a quasi-experimental study comparing chronic pain groups (Fibromyalgia n = 9; Chronic Back Pain n = 8) with healthy controls (n = 9) across range of self-reported and objective sleep and pain-related parameters. Findings revealed differences in patterns of self-reported sleep but not objective sleep between the two chronic pain conditions compared with healthy controls. The study also provided some extension of the findings from Chapter 4 by exploring the associations of objective sleep disturbance with less efficient pain inhibitory processes. To expand on these findings, the thesis adopted an epidemiological approach to explore the long-term interrelationship between sleep and pain-related outcomes in the general population. A systematic literature review (Chapter 6) of 16 longitudinal studies involving 61,000 participants consolidated evidence that changes in sleep are associated with several dimensions of the pain experience (risk of developing a pain condition, elevations in levels of inflammatory markers, and a decline in self-reported physical health status). Finally, Chapter 7 presents an analysis of a sample of the UK population and revealed the association between four-year changes in different insomnia symptom (sleep onset latency, awakenings, and daytime sleepiness) and perceived physical and psychological well-being in the general population (n = 30,594) and a subgroup with arthritis (n = 4,300). Overall, the findings from this thesis provide support for the associations of sleep disturbances with the processes underlying and shaping the experience of pain. The thesis highlights future research and beneficial interventions aimed at improving sleep and addressing associated pain-related health outcomes.

Abbreviations

AASM – American Academy of Sleep Medicine
ACC – Anterior Cingulate Cortex
AHRQ – Agency for Healthcare Research and Quality
AMYG – Amygdala
APSQ – Anxiety and Preoccupation about Sleep Questionnaire
BDI – Beck Depression Index
BG – Basal ganglia
BHPD – British Household Panel Survey
BHT – Bag holding task
BHTd – Bag holding task distractor
BM – Body Manikin
BMI – Body Mass Index
BPI – Brief Pain Inventory
CAP - Cyclic Alternating Patterns
CAPI – Computer Assisted Personal Interviewing
CBP – Chronic Back Pain
CBT-I – Cognitive Behavioral Therapy for Insomnia
CI – Confidence Intervals
CNS – Central Nervous System
CPT – Cold pressor task
CPTd – Cold pressor task distractor
CRP – C-reactive protein
CPPC – Chronic Painful Physical Conditions
CPM – Conditioned Pain Modulation
ΔCPM – Conditioned Pain Modulation effect
CSD – Consensus Sleep Diary
DALYs – Disability Adjusted Life Years
DBAS-16 – Dysfunctional Beliefs & Attitudes about Sleep
DCML – Dorsal Column Medial Leminscal
DNIC – Diffuse Noxious Inhibitory Control
DRt – Dorsal Reticular Nucleus
DSM-5 – Diagnostic and Statistical Manual of Mental Disorders, Fifth edition
ECG – Electrocardiography
EEG – Electroencephalography
EMG – Electromyography
EOG – Electrooculography
EMB – Ethnic Minority Booster sample
FM – Fibromyalgia
GHQ-12 – 12-item General Health Questionnaire

GP - General Population sample
HIPP – Hippocampus
HR – Hazard Ratio
HRQoL – Health-Related Quality of Life
hsCRP – High sensitivity C-Reactive Protein
HYP – Hypothalamus
IBS – Irritable Bowel Syndrome
ICC – Intraclass Correlation Coefficient
ICD-11 – The International Classification of Disease, Eleventh revision
ICSD-3 – The International Classification of Sleep Disorders, Third edition
IL-Iβ – Interleukin 1 beta
IL-6 – Interleukin-6
KPa – Kilopascal
MC – Manipulation Check
MCS – Mental Component Summary
MQS – Medication Quantification Scale
MSLT – Multiple Sleep Latency Test
M1 – Primary Motor Cortex
N1 – Stage 1 sleep
N2 – Stage 2 sleep
N3 – Stage 3 sleep
NKCA – Natural Killer Cells Activities
NREM – Non-rapid Eye Movement Sleep
OA – Osteoarthritis
OR – Odds Ratio
PAG – Periaqueductal Grey
PCS – Physical Component Summary
PCS – Pain Catastrophising Scale
PEBL – The Psychology Experiment Building Language
PFC – Prefrontal Cortex
POMS – Profile of Mood States
PPTh – Pressure Pain Threshold
PSAS – Pre-Sleep Arousal Scale
PSG – Polysomnography
PSQI – Pittsburgh Sleep Quality Index
PSWQ – Penn State Worry Questionnaire
PVAQ – Pain Vigilance & Awareness Questionnaire
PVT – Psychomotor Vigilance Task
QALY – Quality Adjusted Life Year
QST – Quantitative Sensory Testing
RA – Rheumatoid Arthritis

RCT – Randomised Controlled Trials
REM – Rapid Eye Movement Sleep
RT – Reaction Time
RVM – Rostral Ventromedial Medulla
S1 – Primary Somatosensory Cortex
S2 – Secondary Somatosensory Cortex
SCN – Suprachiasmatic Nuclei
SE – Sleep Efficiency
SF-12 – 12-item Short-Form Health Survey
SF-36 – 36-item Short Form Health Survey
SMD – Standardised Mean Differences
SOL – Sleep Onset Latency
SQ – Sleep Quality
STAI – State Trait Anxiety Inventory
STROBE – Strengthening the Reporting of Observational studies in Epidemiology
SSS – Stanford Sleepiness Scale
SWS – Slow Wave Sleep
TIB – Time in Bed
TMD – Temporomandibular Joint Disorder
TNF-α – Tumour Necrosis Factor Alpha
TST – Total Sleep Time
UKHLS – UK Household Longitudinal Survey
VLPO – Ventrolateral preoptic nucleus (VLPO)
WASO – Wake after Sleep Onset
YLD – Years Lived with Disability
YLL – Years of Life Lost Due to Premature Mortality

1 Introduction

"Both symptoms are attributable to the same cause in the majority of cases. They are nature's danger signals, and he who would aim at merely relieving them by drugs may be compared to him who would cover up the red flag of danger on the railway with a white one, while the danger continued"

John Haddon (1905) on pain and sleeplessness.

The processes of sleep and pain are both intrinsic and essential for our survival as humans. The ability to perceive and react to pain is one of the most basic and beneficial physiological, psychological, and evolutionary response that we possess. Without this ability, the body becomes easily susceptible to different manners of physical threats and dangers. Sleep is also key to human survival and while it may be a behaviour that renders the individual into an unconscious state, it has evolved regardless to serve various important functions and we continue to depend on good sleep for optimum functioning. Neurobiological evidence shows that the systems regulating these two processes are overlapped and inextricably linked (Foo & Mason, 2003). This sets up an eventuality where problems in one system would affect or at least justify malfunction in the other. Dysregulation in the function of pain can alter and impede the ability of sleep to serve its necessary physiological function. Similarly, impaired sleep may lead to malfunction in the ability to perceive and manage pain.

1.1 The process of sleep

Sleep is a complex process regulated by various biological systems, which in turn can also impact different physiological processes in the body. Sleep depends on a network of brain activities across different neurobiological, neurophysiological, and

neuroanatomical levels and engages numerous neurotransmitters, cellular and molecular interactions within the brain (Carskadon & Dement, 2011). Borbely, Daan, Wirz-Justice, and Deboer (2016) explains that sleep regulation depends on the action of two mechanisms that drives sleep and wakefulness; the body's 24-hour circadian clock (Process C) which drives the timing of biological propensity to sleep and wakefulness and an arousal-dependent homeostatic system to drive sleep propensity, duration and intensity of sleep pressure build-up, and which measures and monitors sleep debt (Process S). The two processes usually work in a complimentary manner to drive wakefulness during the day and sleep at night. Other factors such as light, social activities, meal times and other behavioural and environmental factors can also regulate the two processes and drive sleep-wake activities (Dijk & Lazar, 2012). All these factors come together to bring about sleep through the activities of multiple brain regions. The suprachiasmatic nuclei (SCN) of the hypothalamus houses the internal 24-hour body clock and the ventrolateral preoptic nucleus (VLPO) which drives the action of associated genes, neurotransmitters, and the orexin, monoaminergic and cholinergic neurons (Dijk & Lazar, 2012). Also involved in the control of sleep are modulation hormones such as melatonin from the pineal gland, which regulates levels of alertness (Borbely et al., 2016; Peigneux, Urbain, & Schmitz, 2012).

Why we sleep is still not known. There is no grand overarching explanation, but several theories have suggested a role of sleep in maintaining optimal physiological and mental functioning. A set of theories propose that sleep allows us to function most efficiently during waking hours by carrying out tasks of neuronal maintenance

and memory consolidation during sleep (Harrison, 2012). There is also evidence to support that sleep is required for the process of learning, converting short-term to long-term memory and improving already existing long-term memories (Stickgold, 2005). This is thought to be achieved by enhancing neuroplasticity and consolidation of neuronal circuity involved in learning, promoting learning-dependent synapse formation, and regulation of other higher cortical brain regions (Harrison, 2012; Stickgold, 2005; Yang et al., 2014). Another emerging theory is that deep slow wave sleep is when sleep-dependent hormones such as growth hormone and thyroid stimulating hormones are released and hence plays a role in ensuring cellular repair, maximal cell division, and protein synthesis (Tononi & Cirelli, 2014; Tung, Takase, Fornal, & Jacobs, 2005). Furthermore, it is thought that sleep is critical in ensuring metabolic homeostasis by engaging in the metabolic clearance task of ridding the central nervous system of potential neurotoxic by-products that accumulate during wakefulness, in particular proteins linked to neurodegenerative diseases such as β-amyloid (Xie et al., 2013). Immune signalling molecules and cytokines also interact within neurochemical systems in the brain influencing the regulation of normal sleep (Imeri & Opp, 2009). Regardless of the function sleep may serve, it appears that the process is key to both optimum physiological and cognitive functioning. A disruption in the normal process would subsequently impact both physiological and psychological well-being.

1.2 What is chronic pain?

International Association for the Study of Pain defines pain as 'an unpleasant sensory and emotional experience associated with actual or potential tissue damage

or described in terms of such damage' (Merskey & Bogduk, 1994). The most notable concept that has emerged from this definition is that pain is very much an affective emotional experience as well a physical one. Pain is inherently a subjective phenomenon and evidence reveals that perception of pain is not restricted to just localised sensations in body sites but rather a sum of various cortical processes and complex neurobiological pathways involving the somatosensory cortices, insula, limbic system, cingulate gyrus and prefrontal cortex (Apkarian et al., 2005). Pain invoked by injury or disease is generally perceived through a cumulative interaction of peripheral nocipceptive activation and different biochemical, physiological and psychological mechanisms involving a majority of the central nervous system. Ascending pathways are comprised of specialised sensory receptors responsible for the detection of noxious stimuli and the transformation of these stimuli into signals conducted to the central nervous system (Brooks & Tracey, 2005). From then on, the central nervous system can take on a pain inhibitory or facilitatory role in a number of ways. This can be at the spinal cord level, but there are also neural pathways that descend from the central structures of the nervous system and diminish pain signals (Brooks & Tracey, 2005). The outcome of the balance of these activities consequently determine the perception of pain by the individual.

Acute feeling of pain serves an important bodily function of signalling injury and damage. In contrast, chronic pain persists beyond the expected time of healing from injury, illness or tissue damage, lasts beyond 3-6 months, and lacks the adaptive warning function that acute pain serves (Merskey & Bogduk, 1994). Chronic pain conditions are usually accompanied by notable emotional distress and/or significant

disabilities and interference with daily functioning and activities. The International Classification of Disease (ICD-11) categorisation for chronic pain (Treede et al., 2015), classifies chronic pain disorders into seven main categories. This includes chronic cancer pain (malignant cancer-related pain), chronic postsurgical and posttraumatic pain, chronic neuropathic pain (e.g., diabetic neuropathy), chronic headache and orofacial pain (e.g., migraines, temporomandibular joint disorder), chronic visceral pain (e.g., ischemia and thrombosis), chronic musculoskeletal pain that arises as part of a disease process directly affecting any bone, joint, muscle, or related soft tissues (e.g., specific lower back pain, osteoarthritis, and rheumatoid arthritis), and chronic primary pain persisting or recurring in 1 or more anatomic regions for longer than 3 months and not better explained by another chronic pain condition (e.g., fibromyalgia and conditions with idiopathic origin).

Chronic pain further involves various degrees of dysfunction in peripheral and central sensitisation. Edwards (2005) explained that peripheral sensitisation is increased nociceptive input and dysfunction of pain regulating nociceptive signal in a way that heightens sensation of pain. Although compared to conditions such as osteoarthritis and back pain, idiopathic chronic pain conditions such as fibromyalgia and irritable bowel syndrome do not necessarily engage tissue or any peripheral damage to begin with. It is thought that in these cases, chronic pain is possibly rooted in dysfunction in central processes underlying pain functioning. Central sensitisation in chronic pain conditions refers to hypersensitivity that arise from a reduced threshold for pain facilitation and abnormal amplification of sensory signalling within the central nervous system, as well as reduced central pain inhibitory abilities

(Pergolizzi et al., 2013). Chronic pain may also result from neuroplastic changes over time at both spinal and supraspinal level, which results in amplified pain signal, surges in pain neurotransmitters, and dampened pain inhibitory responses (Edwards, 2005).

1.3 Chronic pain conditions

The discussions in this thesis focus on some of the most prevalent conditions (fibromyalgia, chronic back pain, and arthritis) in order to highlight and reflect the reality of pain and sleep disturbances as prevalent health burdens. These common primary and musculoskeletal pain conditions often account for the most primary care doctor's visits and health care costs (Hoy, Brooks, Blyth, & Buchbinder, 2010; Marcus, 2009) and are very briefly introduced below:

1.3.1 Fibromyalgia

Fibromyalgia (FM) is condition that typically presents with a combination of symptoms; pain at contralateral tender points all over the body, fatigue, memory problems, and sleep and mood disturbances. Global prevalence of FM is around 3% - 8%, with 75% of affected individuals being women and aged between 30 – 50 years old (Clauw, 2014; Won & Kirsch, 2017). Diagnosis of FM is made according to the 2011 Modification of the American College of Rheumatology Preliminary Diagnostic Criteria for Fibromyalgia. This diagnosis is based on an assessment of tender points, widespread pain index, and severity of accompanying symptoms (Wolfe et al., 2011; Wolfe & Hauser, 2011; Wolfe et al., 1990).

1.3.2 Chronic back pain

Chronic back pain (CBP) is defined as back pain that lasts for longer than 3 – 6 months and is commonly associated with a host of socioeconomic, work-related, psychological and psychosocial dysfunctions (Andersson, 1999). According to the latest findings from the Global Burden of Disease study, CBP is the leading cause of years lived in less than ideal health, measured as years lived with disability (YLDs). It also ranks among the top five illnesses contributing to disability-adjusted life years (DALYs) which combines data on mortality, measured as years of life lost due to premature mortality (YLLs) and YLDs (Institute for Health Metrics and Evaluation (IHME), 2016). This highlights the enormous global burden of low back pain as a prominent pain condition. The condition has a global prevalence estimated to be 11.9%, with the highest prevalence among female individuals and those aged 40–80 years (Buchbinder et al., 2013; Hoy et al., 2012; Hoy et al., 2010). A report based on Global Burden of Disease study findings revealed that in the UK, a third of all long-term sickness absence from work, and nearly a fifth of any sick leave, is caused by musculoskeletal disorders such as chronic back and neck pain (Vos et al., 2016). A recent article also showed the increasing healthcare costs of chronic back pain. The condition costs the USA about $88bn a year in personal healthcare which is the third highest bill for any health condition yet the prevalence, complaints, and burden of the condition persists for most individuals (Dieleman et al., 2016).

1.3.3 Arthritis

Arthritis is a common chronic pain condition and a leading cause of health-related disability worldwide and years lost to disabilities (YLD) (Institute for Health Metrics and Evaluation (IHME), 2016). It has two most common forms; rheumatoid (RA) and osteoarthritis (OA). RA is an inflammatory and autoimmune pain condition characterised by joint pain and joint swelling. Incidence of sleep problems in RA ranges from 54 to 70% (Abad, Sarinas, & Guilleminault, 2008). OA on the other hand is not associated with immune problems but is similarly characterised by musculoskeletal problems, joint pain, and joint stiffness. It is estimated that some 8.75 million in the UK have sought treatment for OA and around 400,000 have been diagnosed with RA (Arthritis Researh UK, 2013).

1.4 The prevalence and impact of sleep and pain problems in the population

Poor sleep and pain disorders are two of the biggest global health problems and present a major public health challenge with great economic and societal costs and burden to healthcare systems worldwide. Yet, understanding of the interrelationship between the two remains incomplete. Estimations and measures of health-related quality of life (HRQoL) and quality-adjusted life-year (QALY) also show that pain disorders in the general population are highly associated with disabilities. Namely, inability to engage in activities in daily living, limitations in social functioning, increased health-care utilisation, and risk of other comorbid disorders, morbidity and pre-mature mortality (Fernandez et al., 2010).

A diagnosis of insomnia often encompasses poor sleep quality. Insomnia is characterised by having difficulty initiating sleep, difficulty maintaining sleep and/or early morning awakenings with inability to return to sleep with those difficulties occurring despite adequate opportunity for sleep, and with accompanying daytime dysfunction (DSM-5, 2013; ICSD-3, 2014). Insomnia can either be a cause or consequence of poor physical and mental health. Studies have highlighted the negative association of both problems with insomnia (sleep quality) and problems with sleep quantity on morbidity and overall poor physical health. The implication of this can be seen on the biggest public health problems in society; sleep problems are linked to the development of depression (Riemann & Voderholzer, 2003), cardiovascular diseases (Cappuccio, Cooper, D'Elia, Strazzullo, & Miller, 2011), stroke (Leng et al., 2015), Type II diabetes (Cappuccio, D'Elia, Strazzullo, & Miller, 2010a), premature mortality (Cappuccio, D'Elia, Strazzullo, & Miller, 2010b), suicide and overall life satisfaction (Bernert, Turvey, Conwell, & Joiner, 2014), and chronic pain (Mork & Nilsen, 2012). Prevalence of insomnia symptoms in the general population ranges from 10 – 30% (Ohayon, 2002; Roth, 2007). Chronic pain prevalence can also range from 10 – 20% depending on different conditions and on how chronic pain is defined, if present for over three or six months (Breivik, Collett, Ventafidda, Cohen, & Gallacher, 2006; Goldberg & McGee, 2011).

Sleep problems are a common presentation in individuals suffering from chronic pain. Data suggests that the prevalence of sleep complaints in chronic pain patients can be anything up to 50% in chronic back pain patients, 90% in those with

fibromyalgia, and 65 – 70% in other mixed chronic conditions (Atkinson, Ancoli-Israel, Slater, Garfin, & Gillin, 1988; Morin, Gibson, & Wade, 1998; Pilowsky, Crettenden, & Townley, 1985; Tang, Wright, & Salkovskis, 2007; Theadom & Cropley, 2008). The National Health Interview Survey in America also revealed that 10.2 million of those with arthritis report insomnia, sleep disturbance, sleep duration of less than 6 hours and/or excessive daytime sleepiness (Louie, Tektonidou, Caban-Martinez, & Ward, 2011). Ohayon (2005) 's telephone survey of over 18,980 residents living in UK, Germany, Italy, Portugal, and Spain revealed a snapshot of the state of insomnia and painful conditions across Europe. This study assessed chronic painful physical conditions (CPPC) defined by pain lasting for at least six months and insomnia symptoms (difficulty initiating sleep, difficulty maintaining sleep, early morning awakening and non-restorative sleep, occurring for at least 1 month, more than three times a week and with daytime consequences). More than 40% of individuals with insomnia symptoms also reported at least one CPPC. Presence of a pain condition such as backaches and joint/arthritic diseases was a strong predictor of the presence insomnia symptoms with odds ratio (OR) ranging from 3.0 to 5.0. This relates to up to 5 times higher the risk of reporting insomnia compared with those with no pain condition. Sivertsen, Krokstad, Overland, and Mykletun (2009) also reported the prevalence of insomnia in Norway from the HUNT-2 survey to be at 17% - 39.8% amongst individuals with a chronic pain condition. In addition, amongst the 47,700 respondents, those with insomnia were more likely to report a co-occurring pain condition (mean ORs ranging from 1.24 – 2.75 across pain conditions). Since chronic pain is by definition intractable, focus has been on factors such as poor sleep quality that are either risk factors for developing long-lasting painful conditions, might

contribute to greater pain-related disability, or may be changeable factors that determine pain management and quality of life.

1.5 Interrelationship between sleep and pain in chronic pain patients

Not all patients with chronic pain have trouble sleeping, for example, in one study up to 35% of 105 chronic pain sample with high pain intensity still sleep normally and describe themselves as good sleepers (Morin et al., 1998). However, in those that do report problems, pain is believed by the patients to interfere with the ability to obtain adequate sleep and this disrupted sleep consequently worsens the experience of pain and related problems (Theadom & Cropley, 2008). Pain causes arousal and this arousal interferes with the ability to either initiate or maintain sleep, maintaining a vicious cycle of physical limitations and mental frustration (Drewes & Arendt-Nielsen, 2001; Vitiello, Rybarczyk, Von Korff, & Stepanski, 2009). Notably, findings from recent studies using varied and sophisticated research designs are suggesting that sleep disturbance may have a stronger contributory effect on the experience, development, maintenance and perception of chronic pain than vice-versa. Research designs examining the temporal day-to-day variations have revealed the associations of poor sleep quality with next-day pain (Tang, Goodchild, Sanborn, Howard, & Salkovskis, 2012). Healthy women whose sleep continuity was disrupted using overnight forced awakenings reported decreased pain threshold and self-reported spontaneous painful somatic symptoms the next morning (Smith, Edwards, McCann, & Haythornthwaite, 2007). Notably, prospective data in healthy populations have also revealed that complaints of non-restorative sleep or sleep disturbances are risk factors for the onset

and exacerbation of a host of chronic pain conditions (Campbell et al., 2013; McBeth, Lacey, & Wilkie, 2014; Mork & Nilsen, 2012; Nitter, Pripp, & Forseth, 2012).

Finan, Goodin, and Smith (2013) expanded on these findings in their comprehensive review and urged more research to elucidate the directionality and potential mechanisms of the sleep and pain relationship. Aside from these initial findings, there is an overall lack of both extensive experimental and observational data in the area to substantiate the evidence that poor sleep and sleep disruptions activates symptoms of pain and contributes to the experience of chronic pain. It is possible that sleep problems may not just simply be a consequence of pain. Poor sleep itself may even alter central pain mechanisms and immune process implicated in the processing of pain and the pathophysiology of chronic pain. Disrupted sleep may also play a role in influencing not just the biological but also behavioural and psychological mechanisms that may perpetuate the pain experience.

On the whole, sleep is emerging as an important aspect of the chronic pain condition; however, sleep is not currently routinely considered as a therapeutic target in chronic pain management. Proactive management of sleep disturbance would be beneficial to those individuals whose sleep quality may put them at greater risk for developing chronic pain conditions (Tang, 2009). Additionally, recent evidence also suggests that improving sleep quality may also alleviate the pain experience and consequently enhance health outcomes and quality of life for those living with chronic pain conditions (Tang, Lereya, et al., 2015).

1.6 Background and aim of thesis

The aim of the thesis is to assess the specific mechanisms of sleep disruptions and its associations with pain processes. Additionally, the thesis aimed to explore if changes in sleep status are associated with pain-related health outcomes. Finan et al. (2013) and Smith and Haythornthwaite (2004) suggest the use of an integrated biopsychosocial model to investigate the different mechanisms, antecedents, and sequelae of the association between sleep and pain. They encourage basic and clinical research incorporating systematic and thorough measures of sleep and pain across both experimental and observational designs. Salkovskis (2002) also supports this manner of approach in clinical sciences; a model that incorporates a varied evidence base to support the biological understanding of health conditions and development of novel approaches to treatment. This further emphasises that the empirical basis of clinical interventions must come from validated theories and linked research studies. In light of this, this thesis adopted a multi-methodological approach that allows for a detailed multi-level investigation of the biological and psychological contingencies underlying the association between sleep disturbances and the pain experience. Notably, the thesis considers how much sleep contributes to the experience of pain and chronic pain *both* at the individual within-person and at the general population level. At the individual level, we need a deeper and better understanding of the biological interaction between impaired sleep and pain, to establish individual variations in sleep behaviours and pain processing in heathy individuals and clinical pain patients. At the population level, we need evidence to also demonstrate the long-

term association of sleep and pain symptoms, in order to tackle and contain the societal impact of sleep and pain problems and their comorbidities.

Using a mix of experimental and observational methodologies, this thesis seeks to:

- Characterise sleep disturbances, pain inhibitory processes, and bio-psychological functioning in healthy and clinical pain populations.
- Explore the long-term association of changes in sleep status and pain-related health outcomes and general wellbeing in the general population and subgroups with chronic pain.

The thesis is structured and presented as follows:

Chapter 2 – An overview of measures and assessment of sleep (polysomnography and actigraphy), pain (quantitative sensory testing), and physiological biomarkers (inflammatory cytokines) discussed and explored in subsequent chapters.

Chapter 3 – A brief overview of existing literature and research evidence on the different bio-behavioural aspects and mechanisms underlying the association between sleep and pain.

Chapter 4 – An experimental study which assesses the validity of conditioned pain modulation (CPM) as a measure of central pain inhibitory processes and the association of CPM with self-reported sleep disturbances in healthy young adults.

Chapter 5 – A quasi-experimental study using self-report, actigraphy, and polysomnography to identify the characteristics of pain, sleep disturbance, inflammation, and psychological functioning in two chronic pain conditions (fibromyalgia and chronic back pain) compared with healthy controls. Specifically, with a focus on polysomnography assessment to examine both overnight sleep macroarchitecture and micro architecture. In addition, it forms a further exploration of the association of sleep disturbance with pain inhibitory processes in those with chronic pain.

Chapter 6 – A systematic review and meta-analysis of prospective studies that have evaluated changes in sleep quality, sleep quantity, and insomnia symptoms, as well as their associations with pain-related health outcomes in the general population.

Chapter 7 – A study to examine whether changes in sleep and insomnia symptoms over a four-year period are associated with psychological wellbeing and perceived physical functioning and mental health assessed at baseline and follow-up (four years). This was investigated in the general population and a subset of individuals with chronic pain within the general population.

Chapter 8 – A summary and general discussion on the unique contributions of the thesis to the mechanisms and processes that shape the associations between sleep disturbance and pain experience. This chapter brings together results of all the studies, strengths and weaknesses of the thesis, and discusses general recommendations emerging from the findings.

2 Assessment of sleep, pain, and inflammation biomarkers

This chapter provides an overview of measures and assessments applied in this thesis. The chapter considers the measurement of sleep (including polysomnography, actigraphy, and self-reported measures). The chapter then addresses the mechanism of human pain perception and use of quantitative sensory testing in the assessment of pain. Finally, the chapter presents an overview of physiological biomarkers (inflammatory cytokines) implicated in sleep and pain processes which are discussed and explored in subsequent chapters.

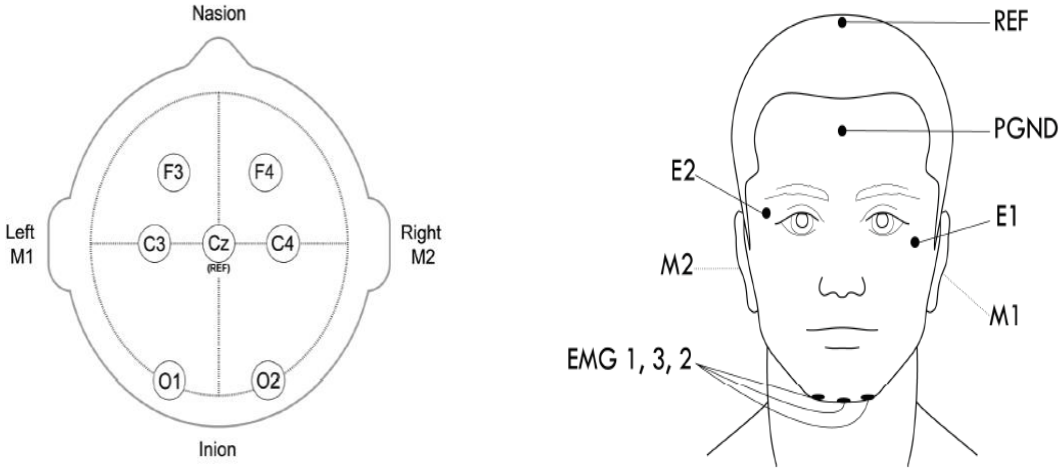
2.1 Assessment of sleep

2.1.1 Polysomnography

Sleep is a dynamic process involving changing electrical activity within the brain and accompanying physiological characteristics (Carskadon & Dement, 2011). Polysomnography (PSG) comprises of electroencephalography (EEG), electromyography (EMG), electrooculography (EOG), respiration measures, heart rate, and sometimes body temperature and is the gold standard method for the assessment of measuring sleep and sleep disturbances. PSG is an electrophysiological marker reflecting the sleep process and allows for analysis of both macrostructure (sleep continuity and sleep architecture, sleep stages) and microstructure (EEG wave form distribution using spectral analysis) of sleep. PSG recording montage (Berry et al., 2017) typically consists of six electroencephalography (EEG) electrodes attached to the scalp near the frontal (F3, F4), central (C3, C4), and occipital (O1, O2) cortices. Additional EEG electrodes are used as reference electrodes – these include Ground

(PGND) placed on the forehead (FPz) to maintain amplifier inputs within a small voltage range relative to the amplifier's zero voltage level, Reference (REF) placed near the centre of the scalp (Cz) and M1 and M2 placed on the mastoid bone behind the left and right ear. The EEG channels are referenced to each mastoid on the opposite side of the head (e.g., F3/M1, C4/M2). EEG electrodes are placed according to the 'International 10-20 system' for describing the location and application of scalp electrodes (Berry et al., 2017). Electrode sites are usually cleaned with a mild abrasive cream (e.g. Weaver NuPrep skin prep gel) and electrode application completed using GRASS 30" 78in/200cm gold EEG electrodes fixed with a conductive paste such as the Natus Grass EC2 electrode paste. See Figure 1 for electrodes placement and location used in this thesis.

Figure 1 Sleep EEG Electrodes placement and location



Notes: Electrode placement for standard EEG and PSG recording
Figure reproduced from Embla® S4500 clinical manual with permission.

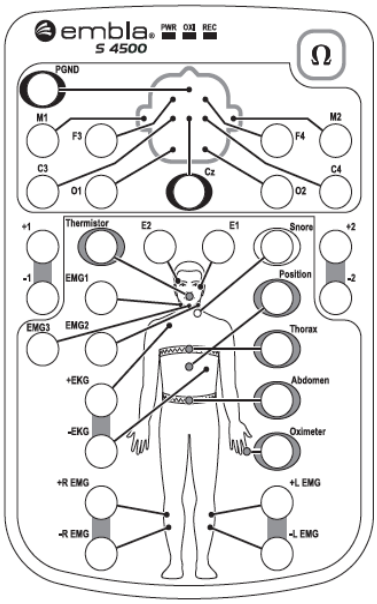
For the rest of PSG set up, electrooculography (EOG) electrodes E1 and E2 are placed around the eyes to detect eye movements during sleep.

Electromyography (EMG) electrodes are used to detect electrical activity in the muscles. Three EMG electrodes are placed around the chin and two further electrodes on muscle of each leg to measure leg movements. Two electrocardiography (ECG) electrodes are placed under the collarbone on each side of the chest to detect heart rate and cardiac activity. Nasal and oral airflow and respiration rate are measured using a nasal cannula and airflow thermistor placed around the nostrils. In addition, respiratory effort is measured using belts placed around the chest and the abdomen, which expand and contract upon breathing effort. Pulse oximetry assesses blood oxygen levels and is measured using a pulse oximeter placed over the fingertip. Snoring can also be recorded using a snore microphone placed over the neck. In addition, for polysomnography recording, participants are usually monitored visually during the night using infra-red CCTV camera for sleep behavioural observations. Any sleep disruptions such as periodic limb movement disorder or parasomnias can thus be detected as part of PSG assessment.

For the study described in Chapter 5 of this thesis, overnight sleep assessment was conducted to determine sleep macro- and micro-structure. The first night of PSG recording was used for screening and adaptation to the new sleeping environment and was not included in the analysis as per standard recommendations (Berry et al., 2017). Embla REMLogic 3.4 PSG software was used for PSG data recording, acquisition and later analysis, scoring and spectral analysis. Impedance test and bio calibrations were carried out on the RemLogic software before each recording to check the amplifier settings and integrity of the electrodes and sensor. All impedance was kept below 5Ω or less to lessen the chances of noisy traces during the night. Acquisition of

the data on was relayed to the RemLogic PSG software via the M-Drive communication unit and Embla S4500 system. EEG traces and PSG signals were digitised, transmitted and viewed in real time on a Lenovo ThinkVision LT2934z 29-inch display computer monitor with a 2560 x 1080 resolution, minimum resolution for sleep scoring as per AASM recommendations is 1600 x 1200.

Figure 2 Embla unit for PSG recording



Notes: Embla® S4500 bedside unit and channel inputs for standard EEG and PSG recording used in the study. Figure reproduced from Embla® S4500 clinical manual with permission.

2.1.1.1 Sleep Scoring

Outputs from PSG recording is normally scored and summarised by a polysomnography technician according to standardised AASM criteria (Berry et al., 2017). Scoring involves analysing each 30-second period of sleep (epochs) and the brain electrical wave patterns in each epoch for amplitude and frequency, as well as distinct markers of brain activity, eye movements, and muscle activity.

As described by the AASM (Berry et al., 2017), in adults, sleep typically consists of non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep periods. These parameters make up normal sleep architecture and macro-structure. In normal sleep physiology, transitions through these states of sleep occur approximately every 90 minutes and it is usual for an individual to pass through 4-5 cycles overnight. Wakefulness with eyes closed is characterised by fast frequency alpha waves (8-12 Hz) seen on the EEG. NREM sleep has three distinct sleep stages and the initial short period following sleep onset is known as stage 1 (N1). This initial stage marks the disappearance of alpha waves and emergence of theta (4-7 Hz) waves. This is followed by stage 2 (N2) sleep which is characterised by a variety of wave frequency and distinct bursts of activities such as sleep spindles and K-complexes. Sleep spindles are short burst of oscillatory electrical activity of beta and sigma frequency waves (12–16 Hz) and K-complexes precede sleep spindles. K-complexes are large amplitude (>75 μV), low-frequency (0.5–2.0-Hz) biphasic wave-forms with a brief negative high-voltage peak, followed by a slower positive electrical component. Following N2, Stage 3 (N3) sleep, also known as slow wave sleep (SWS) emerges and is characterised by low amplitude delta frequency (0.5-4.5 Hz) wave formations (Berry et al., 2017).

REM sleep is characterised by mixed frequency theta and beta wave patterns with distinct sawtooth shapes, rapid eye movements picked up by EOG electrodes and decrease in muscle tone detected by EMG electrodes (Berry et al., 2017). During normal sleep in healthy individuals, REM sleep episodes come at the end of each sleep

cycle and become increasingly longer as the night progresses and as SWS conversely becomes less dominant especially in the last 2 sleep cycles (Carskadon & Dement, 2011). Typically for an adult, a normal night of sleep would comprise approximately 5% of N1, 50% of N2, 20% of N3 (SWS), and 25% of REM sleep.

For the study described in Chapter 5, PSG sleep scoring was performed for the second night of PSG monitoring. Each night of data was analysed using the Embla RemLogic 3.4 software, traces were viewed and scored in 30-s epochs by the researcher using the AASM criteria (Berry et al., 2017). Variables derived from PSG and their definitions are displayed in Table 1. The beginning of sleep scoring was determined by 'lights out' time and this was when participants depressed the light when going to sleep and 'lights on' was when they turned on the light in the morning to indicate getting out of bed. The scored sleep period was used for the definition of the values of: sleep onset latency, wake after sleep onset, sleep efficiency, total sleep time, time spent in each sleep stages, awakenings, and arousals. Arousals were computed automatically by the system; the sensitivity of detection was calibrated to be in accordance with AASM defined criteria; an abrupt shift in frequency lasting for at least 3 seconds with 10 seconds of stable sleep preceding (Berry et al., 2017).

2.1.1.2 Spectral analysis

Sleep macrostructure refers to the organisation of sleep stages as described above, whilst sleep microarchitecture focuses more on the EEG features and subtle alterations occurring during the course of sleep. This approach provides a deeper and more dynamic characterisation of the sleep process not reflected by simple

macrostructure sleep scoring. Spectral analysis involves mathematical transformation of EEG signals into representations of power bands of different frequencies (Campbell, 2009) and provides a way to quantify EEG activity. For the study described in this thesis, spectral analysis was applied to the second night of sleep EEG data. Additionally, the C4 - M1 channel was selected for spectral analysis as it was deemed to produce the most robust signal, C3 – M2 were also used in some cases when C4 – M1 was noisy and with a lot of artefacts (Campbell, 2009; Spiegelhalder et al., 2012). Analysis was conducted using the RemLogic 3.4 software. The software has an algorithm for artefact rejection and to discard outlier epochs with a lot of noise and artefacts from the computation of average spectral power. The software protocol for spectral analysis involves Fast Fourier Transform (FFT) as per Spiegelhalder et al. (2012). Each analysis window equates to 512 points (2.56 seconds) long, giving a frequency resolution of 1/2.56 = 0.39Hz and 22 overlapping windows cover each 30 second epochs. Spectral power values were obtained from FFT bins with frequency within the frequency bands of Delta-1 (0.1-1Hz), Delta-2 (1-3.5Hz), Theta (3.5-8Hz), Alpha (8-12Hz), Sigma-1 (12- 16Hz), Beta-1 (16-24Hz), Beta-2 (24-32Hz) and Gamma (32-48Hz). These power bands were averaged over the whole night of sleep across all artefact-free epoch of scored sleep stages. The values were then log transformed (log10) for analysis. Frequency bands were analysed separately for NREM and REM periods and for sleep stages N2 and N3. Analysis was separated and examined separately for N2 and N3 to eliminate the influence of different frequencies of NREM sleep stage distribution across participants (Feige et al., 2013).

Table 1 Polysomnography (PSG) variables and definition

PSG variables	Definition
Time in Bed	Analysis period from 'lights off' to 'lights on', beginning to end of sleep period
Sleep onset latency	Time (minutes) from start of analysis until first occurrence of 30secs of consecutive sleep events
Sleep efficiency	Total sleep time/Time in bed*100
Wake after sleep onset duration	Time (minutes) spent awake during sleep period
Total sleep time	Total amount of time spent sleeping during sleep period
Awakenings	A duration of awakening during the sleep period that equates to 60 seconds or greater
Arousal	Automatic arousal analyser, based on criteria set by AASM, duration of 3 seconds or longer, abrupt shift in EEG frequency greater than frequency band thresholds. RemLogic algorithm uses the following frequency bands: Delta 0.5-4.0Hz, Theta 4.0-8.0Hz, Alpha 8.0-12.0Hz, Sigma 12.0-16.0Hz, Beta 16.0-20.0Hz
Stage N1%	Time (minutes) and percentage of time (as a function of total sleep time) spent in Stage N1
Stage N2%	Time (minutes) and percentage of time (as a function of total sleep time) spent in Stage N2
Stage N3%	Time (minutes) and percentage of time (as a function of total sleep time) spent in Stage N3
Stage REM%	Time (minutes) and percentage of time (as a function of total sleep time) spent in Stage REM
Power Spectral Analysis Trace used (C4 – M1)	Power bands: Delta-1 (0.1-1Hz), Delta-2 (1-3.5Hz), Theta (3.5-8Hz), Alpha (8-12Hz), Sigma-1 (12- 16Hz), Beta-1 (16-24Hz), Beta-2 (24-32Hz) and Gamma (32-48Hz). Power spectrum computed in logarithmic scale and synced with predefined 30sec scoring epochs. A 512-point Fast Fourier Transform (FFT) was used and overlapped by 50% and average over 30sec epoch duration.

2.1.2 Actigraphy

Actigraphy is a non-invasive method of sleep assessment that uses a wristwatch like device with an accelerometer to detect movements. The devices usually come with an event marker with which the wearer can indicate time in bed, overnight awakenings, and wake time. The data collected is downloaded unto a computer and a corresponding analysis software can then use validated algorithms to provide information on sleep and wake patterns. This provides an interpretation and overview of participants' sleep schedule and sleep pattern over a period of days and weeks. Actigraphy is relatively inexpensive and more convenient than PSG assessment. It can provide an ecologically valid assessment and estimate of sleep amounts and sleep continuity in the individual's normal sleeping environment (Ancoli-Israel et al., 2003). Another advantage of actigraphy is that it can be used over a period of weeks (depending on battery length) as a non-invasive assessment of sleep and activity across different sleep disorders including insomnia and circadian rhythm disorders. However, unlike PSG, actigraphy does not provide an assessment of sleep architecture and cannot provide a specific diagnosis of a sleep disorder such as sleep apnoea. Actigraphy sensitivity and specificity for sleep detection is usually good and often shows high agreement rates with PSG data for total sleep time and sleep efficiency variables in healthy individual but is more limited in detecting sleep onset latency for example (Kushida et al., 2001). It is often recommended to use self-reported data as a supplement to actigraphy data (Ancoli-Israel et al., 2003).

For the study described in Chapter 5, actigraphy monitoring involved the use of CamNTech Actiwatch 4 and corresponding activity and sleep analysis software. Each

participant's recording was set up and anonymised according to their study identification number. The actigraph was set up to capture one week of baseline data and set up again for the laboratory session. The devices were set up to record continuously 30-second epochs of activity. Table 2 provides the actigraphy definitions for sleep variables as computed by the software.

Table 2 Actigraphy variables and definition

Actigraphy variables	Definition
Time in bed	Period from bedtime – waketime, determined by markers/sleep diary
Sleep onset latency	The latency before sleep onset following bedtime
Total sleep time	The amount of sleep as determined by software algorithm and is equivalent to assumed sleep minus wake time
Wake time	The amount of time spent awake after sleep onset as determined by software algorithm
Sleep efficiency	The percentage of time spent asleep relative to time in bed
Fragmentation index	Indicator of restless as determined by software algorithm, percentage of time spent moving during assumed sleep period relative to percentage of immobility phases in 1 minute

2.1.3 Structured clinical interview, self-reported measure, and sleep diary

Structured clinical interviews can also be used to gain an insight into an individual's sleep patterns, and especially as a baseline screening measure before the start of a research study. One such interview is the Duke Structured Interview for Sleep Disorders Schedule for Insomnia Screening [DSM-IV and ICSD-2] (Edinger et al., 2009). Since there is not currently an updated or another interview schedule for the current DSM-V and ICSD-3 classifications, an adapted version of the Duke Structured Interview was used in this thesis to reflect the most recent DSM-V and ICSD-3 classification for

sleep disorders. This interview usually lasts for an hour. It can form part of a participants' social, physical and mental health history, medication and alcohol use. It also has specific questions regarding the timing and onset of sleep and can even delve deeper to assess that individuals have no other medical illnesses, psychiatric conditions, sleep disorders (e.g., sleep apnoea, narcolepsy, restless leg syndrome/periodic limb movement syndrome), or dependency on and abuse of medication and substances that could be contributing to any reported or unknown sleep disturbance (Buysse, Ancoli-Israel, Edinger, Lichstein, & Morin, 2006). It is worth noting that use of clinical interviews such as this is open to lack of standardisation and requires other concurrent measures of sleep to be meaningful and interpretable within the context of the study.

There are also many standardised and validated self-report questionnaires through which participants can report sleep-related cognitions, beliefs, behaviours, attitudes, perceived mental and physical health, and quality of life. These are presented as used in subsequent chapters. The sleep diary is also a credible standard for self-reported assessment of sleep (Carney et al., 2012). Sleep diaries are key to understanding an individual's self-reported sleep patterns and disturbances. Self-monitoring of sleep using a sleep diary enables the participants to estimate and report their overnight sleep quality, the time it takes to fall asleep (sleep onset latency), how many times and for how long they wake up overnight (wake after sleep onset times and duration), the time spent in bed and total sleep time and from this, their sleep efficiency can be calculated which is the percentage of time spent asleep relative to the amount of time spent in bed. The diary is usually completed upon waking and

refers back to sleep the prior night and can be completed over a period of one to two weeks to get a reliable estimate of sleep pattern. It is recommended and proposed by the AASM that the Consensus Sleep Diary developed by Carney et al. (2012) be used as a template for a standard sleep diary across research studies. The sleep diary is fairly easy to use, however, to ensure the accuracy and completeness of the data, participants need to be trained on how to complete the diary properly. Although there is often good correlation between the objective and self-reported sleep measures, self-reported sleep from the sleep diary may also differ from PSG measures (Lockley, Skene, & Arendt, 1999; Westerlund, Lagerros, Kecklund, Axelsson, & Akerstedt, 2016). Recent studies have also suggested that derived PSG sleep measure may be less predictive of an individual's perception of the quality of their overnight sleep (Kaplan et al., 2017).

2.2 Assessment of pain

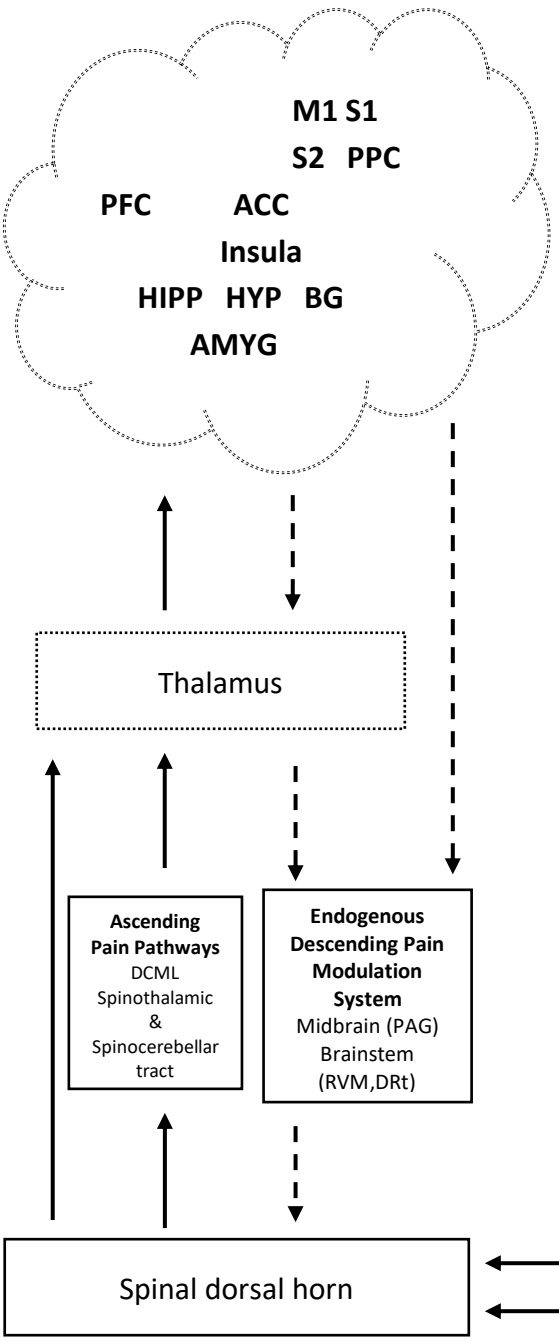
2.2.1 Pain pathways in the brain

Pain is a personal and private experience. The awareness of pain is a multidimensional process in that it commands a wide range of different sensory, physiological and cognitive processes. This thesis utilises methods to quantitatively assess pain perception. To appreciate how the experience of pain can be assessed quantitatively beyond self-report, it is important to understand the physiological, sensory, and evaluative nature of pain. Specifically, how the central nervous system engages several actions to reduce, and sometimes increase perception of pain. The awareness of a painful event first starts with contact with a noxious stimuli, a signal is then sent to the central nervous system and relayed to be processed by the brain's

pain related cortices, including the primary (S1) and secondary (S2) somatosensory cortex, primary motor cortex (M1), anterior cingulate cortex (ACC), insula, prefrontal cortex (PFC), hippocampus (HIPP), basal ganglia (BG), hypothalamus (HYP) and amygdala (AMYG) (Brooks & Tracey, 2005; Bushnell et al., 2013; Bushnell et al., 1999). Structures within the midbrain, brainstem, and spinal cord consequently modulate and construe the actual physical perception of pain. Ascending pathways comprised of spinothalamic tract, dorsal column medial leminscal pathway (DCML), and spinocerebellar tract work together for the detection of noxious stimuli and the transformation of these stimuli into pain signals (Apkarian et al., 2005; Brooks & Tracey, 2005).

The midbrain periaqueductal grey (PAG), brainstem rostral ventromedial medulla (RVM) and dorsal reticular nucleus (DRt) are key structures of the endogenous descending pain modulation system. The PAG is the source of the descending opioid-mediated inhibition of pain. The RVM and DRt alter inhibition and facilitation of pain and enable the PAG to project directly to the spinal dorsal horn for regulating nociceptive input at the spinal level (Ossipov, Morimura, & Porreca, 2014). Since these structures send and receive projections to and from different cortical sites within the central nervous system, this allows the potential for varying cognitive (e.g., attention, distraction, beliefs, appraisal, catastrophising), affective (mood), behavioural (activity), physiological (inflammation) influences to regulate activity within this pain inhibition system and contribute to the overall experience of pain (Bushnell et al., 2013; Ossipov, Dussor, & Porreca, 2010). See Figure 3 for an overview of brain structures and pathways involved in the perception of pain.

Figure 3 Pain pathways in the brain



Primary and secondary somatosensory cortex (S1 & S2), primary motor cortex (M1) – pain transmission, modality, duration, intensity, and location of pain

Anterior cingulate cortex (ACC), insula, prefrontal cortex (PFC) – pain perception, unpleasantness, and cognitive evaluation

Hippocampus (HIPP) – pain-related spatial memory and mood

Basal ganglia (BG) – integration of motor, emotional, autonomic, cognitive pain responses

Hypothalamus (HYP) – regulation of visceromotor and motivation pain responses

Amygdala (AMYG) – pain-related fear, anxiety and pain modulation

Thalamus – pain recognition, processes and relays transmission of nociceptive information to the cerebral cortices

Periaqueductal gray (PAG) – descending opioid-mediated pain inhibition

Rostral ventromedial medulla (RVM) – receives input from PAG, bidirectional descending pain modulation

Dorsal reticular nucleus (DRt) – interacts with PAG and RVM and projects pain modulatory signals to spinal cord

Dorsal column medial leminscal pathway (DCML) – ascending pain pathway through spinothalamic and spinocerebellar tract

Input from peripheral to CNS through C and A nociceptive fibres. Local gating control of pain and modulation through different neurotransmitters and synaptic mechanisms.

Notes: Schematic diagram of pain pathways within the central nervous system. Black arrows represent transmission of pain signals from the periphery; nociceptive information enters the brain from the spinal cord through C and A nociceptive fibres, the information is recognised by the thalamus and projected to the cerebral cortices involved in the different experience of pain – primary (S1) and secondary (S2) somatosensory cortex, primary motor cortex (M1), anterior cingulate cortex (ACC), insula, prefrontal cortex (PFC), hippocampus (HIPP), basal ganglia (BG), hypothalamus (HYP) and amygdala (AMYG). Black arrows represent direction of ascending pain pathway; spinothalamic tract, dorsal column medial leminscal pathway (DCML), and spinocerebellar tract. Dashed arrows represent the direction of descending pain modulation pathways; the midbrain periaqueductal grey (PAG), brainstem rostral ventromedial medulla (RVM) and dorsal reticular nucleus (DRt) are key structures of the endogenous descending pain modulation system. They receive input from spinal cord and cerebral cortices and alter inhibition but also facilitation of pain at the spinal level. *Adapted from:* (Apkarian, Bushnell, Treede, & Zubieta, 2005; Brooks & Tracey, 2005; Bushnell, Čeko, & Low, 2013; Zhuo, 2008)

This effect of the central nervous system to modulate pain perception is reflected in theories of pain control. One such theory is the gate control theory of pain proposed by Melzack and Wall (1965) to describe the process of pain modulation at the spinal cord level. The theory also provides the physiological basis to allow such explanations how cognitive and affective influences could control sensory outputs and regulate pain perception. They explained that small 'C' (nociceptive) and 'A' large (non-painful) nerve fibres transmit unto 'inhibitory' or 'transmission' cells within the spinal cord. The interplay between these fibres and cells control when pain signals are sent to the brain; when there's no input, the inhibitory cells prevent sending of signals to the brain (gate closed), normal somatosensory input means large 'A' fibres activations and both inhibition and transmission cells are facilitated but inhibitory cells prevent sending of signals to the brain (gate still closed).

Pain perception occurs with small fibres activation, this inactivates the inhibitory cells and enables the transmission cells to send nociceptive pain signals to the brain (Melzack & Wall, 1965). The concept of pain threshold reflects how open the gates must become to enable a greater number of small nociceptive fibre signals to pass through. Descending pathways from the brain can either help close or keep the gate open by sending signals to pain control centres within the midbrain and brainstem, from which descending messages are then sent to the spinal cord (Coons & Steglitz, 2013). These messages either facilitate pain by amplifying incoming nociceptive signals from the body or diminish pain perception by reducing or inhibiting the nociceptive signals.

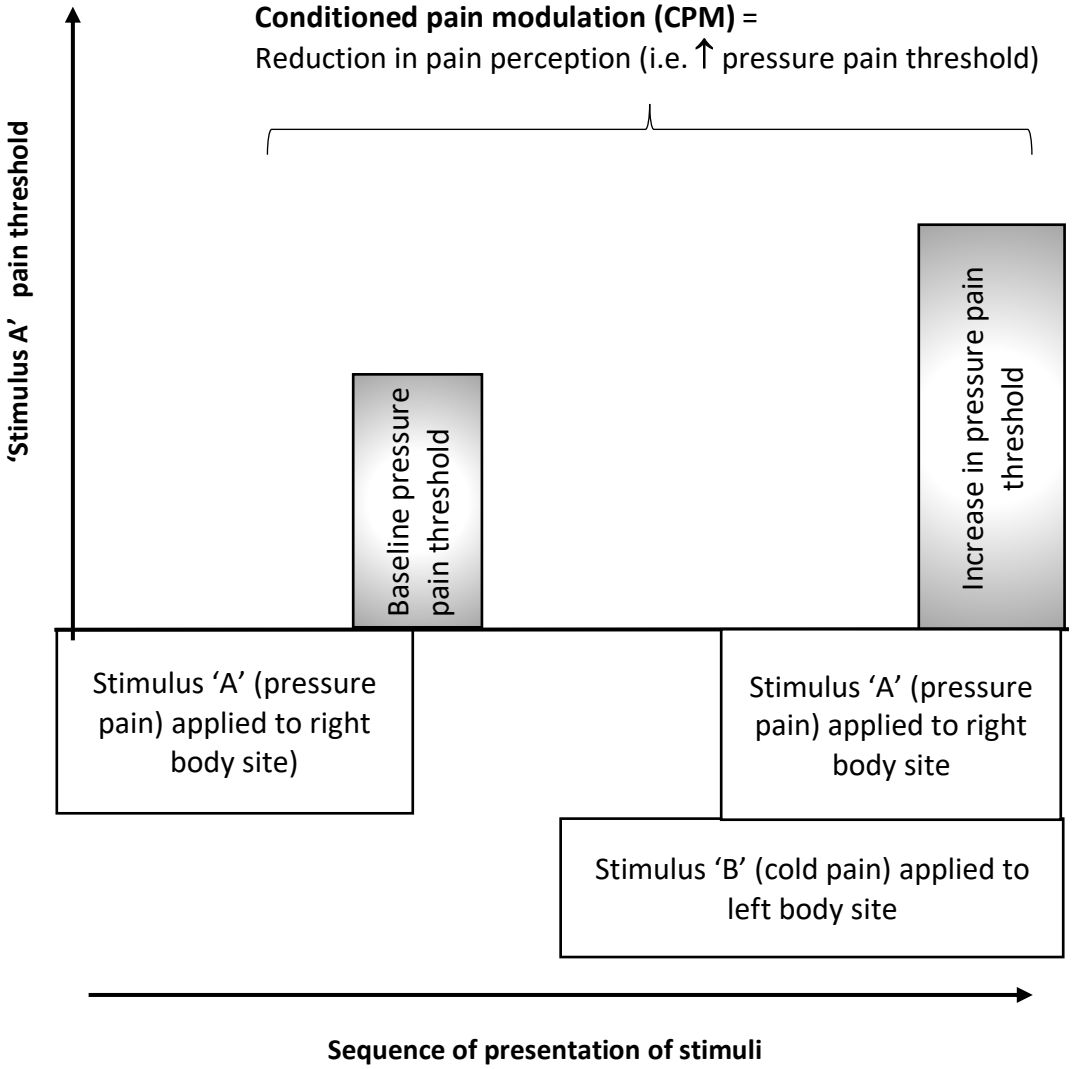
2.2.2 Quantitative sensory testing and Conditioned pain modulation

Quantitative sensory testing (QST) is a psychophysical testing method to measure these responses to sensory stimuli and can thus be used as an indicator of neural function or altered pain processing. Dysfunction of the peripheral nerves or ascending and descending pain pathways within central nervous system may give rise to abnormalities in QST. A QST protocol can be used to assess minimum sensory threshold perceived, localisation of pain, threshold perceived as painful, pain tolerance, or differentiation between sensory inputs. It can reflect relevant aspects of the somatosensory system, including large and small fibre functions, and signs of central sensitisation (Uddin & MacDermid, 2016). Stimulus modality for QST can include electrical, thermal (heat or cold), mechanical (pressure, touch, vibration), and chemical (capsaicin) (Arendt-Nielsen & Yarnitsky, 2009). QST assesses the subjective responses (within a psychophysical parameter) by measuring perception magnitude to a controlled quantitative stimulus intensity (Uddin & MacDermid, 2016).

Conditioned pain modulation (CPM) is a quantitative sensory testing paradigm and one of the most studied mechanisms of descending endogenous pain control in humans (Yarnitsky et al., 2015). The descending pain inhibition that underlies CPM is integrated within the DRt, which interacts with the PAG and RVM, projects to the spinal cord and involves opioid, serotonergic and noradrenergic neurotransmission systems to enhance or attenuate pain input at the spinal level (Ossipov et al., 2010; Piché, Arsenault, & Rainville, 2009; Tracey & Dunckley, 2004). It engages pain signals arriving at the brainstem, activates the descending pain inhibitory pathways, projects pain modulatory signals to the spinal cord and exerts an inhibitory effect on incoming

concurrent pain signals (Staud, 2013). This modulation prevents excessive pain by attenuating successive and simultaneous painful stimuli, and limits processing of nociceptive signals not concerned in processing of the strongest pain stimulus (Le Bars, 2002). In other words, it is based on the "pain inhibits pain" phenomenon, where a painful stimulus inhibits or subdues the perception of pain produced by a second co-occurring painful stimulus at a distant body site. CPM was originally studied extensively in animals as the diffuse noxious inhibitory control (DNIC) paradigm (Le Bars, Dickenson, & Besson, 1979a, 1979b; Le Bars, Villanueva, Bouhassira, & Willer, 1992) but can also be measured psychophysically in the laboratory in human subjects (Figure 4), whereby Stimulus A (a test pain such as pressure pain) given together with Stimulus B (a conditioning pain such as cold pain) is perceived as less painful than when Stimulus A was given alone (Nir & Yarnitsky, 2015).

Figure 4 Conditioned pain modulation



Notes: Schematic diagram of conditioned pain modulation using an example of pressure pain threshold as test stimulus and cold pain as conditioning stimulus. Stimulus A (test-pain; pressure pain) when applied together with Stimulus B (conditioning pain; cold pain) on contralateral body sites is perceived as less painful (increased pressure pain threshold) than when it was applied alone.

2.2.3 Questionnaires

Questionnaires may also be used to provide necessary details about participants' self-reported experience of pain. The pain-related questionnaires used in this thesis are introduced and presented in the methods section of relevant chapters.

2.3 Assessment of inflammatory biomarkers implicated in sleep and pain

Protein or protein-like molecules that signal inflammatory pathways are termed cytokines. They serve as chemical messengers between cells and are involved in processes such as cell growth, tissue repair, and shaping inflammatory immune responses from blood cells (Wallace, 2006). Several inflammatory cytokines have been extensively studied in relation to sleep and pain. These cytokines play a role in both maintenance of pain and regulation of sleep homeostasis. Imbalance in activation and levels of these cytokines is implicated in transition from acute to chronic pain, and they often also play a pivotal role in central nervous system's sleep activation pathways (Imeri & Opp, 2009). Pain and inflammatory processes often co-occur, and inflammatory cytokines have been found not only to be present during the experience of acute pain but also inducing and facilitating the continued experience of chronic pain. Cytokines such as C-reactive protein, Interleukin 6, Interleukin-1 beta, and tumour necrosis factor-alpha are also known to be proinflammatory somnogenic cytokines implicated in the experience of pain, fatigue and sleep and are examined in this thesis.

2.3.1 Interleukin-6 (IL-6)

Interleukin-6 is often used as a marker for systemic activation of proinflammatory cytokines. Studies have also revealed that levels of IL-6 are elevated in normal populations as part of the normal aging process (Ershler & Keller, 2000; Klein & Flanagan, 2016; Wener, Daum, & McQuillan, 2000). IL-6 has both proinflammatory and anti-inflammatory properties, is consistently referred to in the pain and sleep literature and is linked with a host of sickness manifestations observed in chronic pain and sleep disturbances. In healthy adults, lack of sleep and poor sleep have been linked to elevation in the levels of IL-6. Increased circulation of IL-6 is often accompanied by daytime sleepiness and fatigue, whereas restorative sleep is related to decrease in IL-6 secretion and protection of bodily tissues from its proinflammatory damaging effect (Irwin, Wang, Campomayor, Collado-Hidalgo, & Cole, 2006; Vgontzas et al., 2003). For example, following sleep deprivation, an increase in circulating IL-6 was linked with increased pain ratings in response to sleep restriction not explained by tiredness and fatigue (Haack, Sanchez, & Mullington, 2007).

2.3.2 Interleukin-1beta (IL-1ß) and Tumour necrosis factor-alpha (TNF-α)

Interleukin-1ß directly affects the function of neurons in the hypothalamic and brainstem circuits responsible for the regulation of pain, sleep, and wakefulness. When activated, IL-1ß triggers many inflammatory cellular pathways involved in pain processing (Ren & Torres, 2009). In addition, IL-1ß enhances NREM sleep and EEG delta power during slow wave sleep and pharmacologically inhibiting IL-1b reduces the depth of NREM sleep and EEG delta power (Opp, 2005; Zielinski & Krueger, 2011). TNF-α is also a known marker of inflammation implicated in the regulation of sleep.

TNF-α levels and expression in the brain are enhanced during wakefulness and following sleep deprivation (Opp, 2005). In humans, TNF-α levels are also increased in certain medical conditions associated with altered sleep including sleep apnoea, fibromyalgia, and insomnia but it is not necessarily specific to these conditions (Zielinski & Krueger, 2011).

2.3.3 C-reactive protein (CRP)

CRP is a protein found in blood plasma, whose levels rise in response to inflammation. It is a key indicator of acute response and the formation of plasma proteins in response to an inflammatory stimulus (Pepys, 1981; Pepys & Hirschfield, 2003). In response to infection or tissue inflammation, CRP production is triggered by cytokines, particularly IL-6, IL-1ß, and TNF-alpha, hence the production of CRP is thought to reflect the activity of these cytokines, especially IL-6. Recent high sensitivity technology now permits detection of CRP levels as low as 0.007 mg/dl from the previous detectable limits of 3 to 5 mg/dl (Pepys & Hirschfield, 2003). High sensitivity C-reactive protein (hsCRP) has since been the extensively studied as a validated measure of vascular inflammation and predictor of risk of diseases such as arthritis, stroke, and cardiovascular diseases (Otterness, 1994; Pepys & Hirschfield, 2003). CRP can also serve as a marker of inflammatory processes activated by inadequate sleep. Elevated CRP has been associated with poor sleep quality in the general population (Liu et al., 2014), short sleep duration especially in women (Miller et al., 2009) and following short-term sleep deprivation in healthy individuals (Meier-Ewert et al., 2004).

2.4 Conclusion

This chapter explained the techniques that are used to assess sleep, pain and inflammation including: polysomnography, actigraphy, structured clinical interviews, sleep diaries, quantitative sensory testing, and inflammatory cytokines. This chapter aimed to set the scene for the methodological approach of this thesis, which is to use the range of sleep assessment options (PSG, actigraphy, sleep diaries etc.) to give an insight into both objective and self-reported sleep and associations with pain responses and related mechanisms. QST methodologies such as conditioned pain modulation provides a way to assess and quantify pain processing and central pain inhibitory mechanisms that have been implicated in poor sleep and perpetuating the progression of chronic pain. This also provides an opportunity to further examine the utility, reliability, and relevance of the CPM paradigm as a pain assessment tool. Finally, as another step to clarify both the physiological and psychological factors quantifying the association between sleep and pain processes, the thesis also considers the relevance of inflammation processes. Specifically, the focus was on the range of inflammatory markers heavily implicated in physiological sleep homeostasis, pain perception, and chronic pain maintenance.

3 Literature overview

3.1 Introduction

Researchers and clinicians have long been aware of the close link between pain and sleeplessness, with physical pain often regarded as one of the main causes of sleeplessness (Jones, 1913). Despite the large amount of research and literature investigating these phenomena separately, recent surge of interest in the interrelation between the two processes has stemmed from a lack of understanding of the fundamentals of the interaction between pain and sleep disturbances and how to tackle the problem when the two issues co-occur. Sleep and pain are known to have a reciprocal association, although a comprehensive review of literature has also suggested that sleep disturbances may have strong causal effects on the experience, maintenance and perception of chronic pain (Finan et al., 2013). Hence, possible mechanisms through which sleep disturbances impact on pain, functioning, and wellbeing are worth examining.

This chapter considers the interrelationship between sleep and pain and presents a brief overview of the body of evidence from experimental and observational longitudinal studies. Some of these studies have touched on the directionality of the sleep-pain relationship and suggested that the influence of sleep on pain may be stronger than the influence of pain on sleep. Furthermore, the chapter also visits some investigations into clinical correlates of the relationship. Specifically, the contributions of endogenous pain inhibition and inflammation in the regulation of

the relationship between sleep and pain and the implications of this on psychological functioning, overall pain experience, and clinical management.

3.2 Does pain disturb sleep?

Multiple nocturnal awakenings due to pain are commonly reported by individuals with chronic pain conditions. Lavigne et al. (2011) showed that females with chronic widespread pain reported significantly shorter sleep duration, lower sleep efficiency, twice the number of overnight awakenings, and had significantly less power in the EEG delta band in the first and second non-REM sleep cycle compared with pain-free controls. Drewes and Arendt-Nielsen (2001) argued that the level of pain is related to the severity of sleep disturbances, as reflected in disturbances in sleep at a microstructural level influencing arousability, disrupting sleep maintaining processes, and interrupting sleep depth and continuity. In spite of this, the CNS usually works to protect and preserve sleep continuity, and continues to filter nociceptive stimuli, facilitate descending inhibitory pathways, and regulate arousing ascending sensory information especially in the deeper stages of sleep (Doufas, 2017). However, it is also possible that this is very much dependent on individual's sensitivity to pain stimuli and differences in the capacity of the CNS to regulate the pain sensory information during sleep. In addition, the chronic engagement and dysregulation of this sensory filter during sleep may be perpetuated by the chronic presence of pain and this could alter the protective function of sleep.

3.3 Characteristics of sleep in chronic pain – evidence from observational and experimental studies

Chronic pain patients often report trouble initiating sleep, frequent awakenings overnight, decreased sleep duration, poor sleep quality, non-restorative sleep, daytime sleepiness, and fatigue which contributes to patients' experience of greater pain intensity and pain related disability and mood disturbances (Lunde, Pallesen, Krangnes, & Nordhus, 2010; Smith & Haythornthwaite, 2004). Observational PSG studies in mixed clinical pain populations have also corroborated that patients present with longer sleep latencies, reduced total sleep time, increased awakenings, and reduced sleep efficiency compared with healthy controls (Bjurstrom & Irwin, 2016; Diaz-Piedra, Di-Stasi, Baldwin, Buela-Casal, & Catena, 2015). Specifically, disturbances are observed in sleep architecture; sleep in chronic pain patients is often characterised by higher proportion of time spent in lighter stages of sleep and lower proportion of deep sleep and numerous sleep shift changes from deep to light sleep, respiratory disturbances, and movement disturbances (Bjurstrom & Irwin, 2016; Wu, Chang, Lee, Fang, & Tsai, 2017). Sleep in chronic pain patients is also characterised by microstructural disturbances and fragmentation of sleep continuity in form of microarousals and awakenings (Blägestad, Pallesen, Gronli, Tang, & Nordhus, 2016; Drewes & Arendt-Nielsen, 2001). Increased alpha EEG power and reduction in delta power in deep sleep and cyclic alternating patterns (CAP) are some measures assessed as markers of arousal instability and poor sleep quality in patients with chronic pain (Parrino, Ferri, Bruni, & Terzano, 2012; Rizzi et al., 2004). In addition, these microstructure abnormalities tend to be related to poorer self-reported sleep quality and severity of clinical pain symptoms (Blägestad et al., 2016).

While these markers are observable measures of sleep instability, it may be that they are not only a marker of fragmentation of sleep in chronic pain disorder but perhaps also a marker of a biological predisposition to emergence and maintenance of chronic pain. These sleep disturbances convey the brain's difficulty in maintaining and preserving sleep and it is thus reflective of sleep instability and internal and external sources of disturbances during sleep (Drewes et al., 1995; Roizenblatt, Moldofsky, Benedito-Silva, & Tufik, 2001). However, the phenomenon of microstructural disturbances requires further exploratory investigations to determine if this is indeed a defining quality of sleep disturbance in chronic pain and its relation to other physiological markers of pain. Studies have also not been consistent in reporting these manners of alterations in sleep and how it maps to pain experience across different pain conditions. Comparisons are needed to highlight the specific characteristics of sleep disturbance, pain, and functioning in different chronic pain conditions compared to healthy controls. Hence why this thesis will observe if there are possible differences between those with widespread pain (i.e. fibromyalgia) and individuals with a relatively focal regional pain condition such as chronic back pain. In addition, there will also be an initial exploration of how this may be related to pain perception and other aspects of the pain experience such as inflammation.

3.4 Prospective associations between sleep and experience of pain

Micro-longitudinal studies examining day-to-day sleep variations in individuals with chronic pain have shown that night-time sleep parameters more consistently

predict next-day pain compared to pain predicting subsequent sleep. Edwards et al. (2009) carried out two overnight polysomnography assessments in patients with temporomandibular disorder. The findings revealed that reductions in sleep efficiency and total sleep time were significantly associated with impaired conditioned pain modulation assessed the next day. Tang, Goodchild, Sanborn, et al. (2012) and Lewandowski, Palermo, De la Motte, and Fu (2010) have also shown that sleep quality is a significant and consistent predictor of next day pain. These micro-longitudinal studies have primarily examined the day-to-day within-person association between sleep and pain within homogeneous patient groups, but the balance of outcomes provide support for a temporal sequential relationship from sleep to pain among patients to whom pain is chronic and require specialist treatment.

The generalisability of these findings to the general population has been reinforced by macro-longitudinal (prospective) studies examining epidemiological prevalence and incidence of sleep disturbances and pain at the population level. These studies have found evidence that sleep tends to emerge as a primary factor determining longer-term risks of developing a pain condition and aggravation of pain responses (Drewes et al., 2000; Mork & Nilsen, 2012; Nitter et al., 2012). Even in those with no sleep problems, the presence of a chronic pain condition increases risk and predisposition to developing sleep disturbances (Jansson-Frojmark & Boersma, 2012; Tang, McBeth, et al., 2015).

Whilst sleep has been established as predictor of subsequent pain, next step forward for these investigations would be a thorough assessment of how the relationships between sleep and pain may evolve over time dependent on change in sleep status**.** Whilst it is understood that sleep patterns and quality fluctuate naturally over time, little is known about the association of these spontaneous sleep changes with pain and health outcomes over time in the general population. Studies evaluating changes in sleep can also examine the processes underpinning the interrelationship; sleep may render individuals more susceptible to the development and aggravation of pain over time by altering the physiological and psychological mechanisms underlying the interaction between sleep and pain. These studies could further highlight the role of sleep in the maintenance of chronic pain and perhaps illustrate that improving aspects of sleep may subsequently alleviate some of the short and long-term negative health outcomes associated with these conditions. Consequently, this thesis adopts an epidemiological perspective to explore the sleep and pain relationship over time in the general population. This incorporates a systematic review and analysis of the associations of changes in sleep problems over time with pain-related health outcomes.

3.5 Mechanisms underlying the interaction between sleep and pain

3.5.1 Endogenous pain inhibition

The literature has revealed that sleep quality seems to have a physiologically important role in the regulation of pain processing. Several experimental paradigms have been used to show the consequences of sleep disturbance on pain; these include

overnight total sleep deprivation, reducing total sleep duration (partial sleep restriction) or selectively interrupting sleep stages through the night (sleep fragmentation). Healthy populations that undergo these manipulations of sleep tend to report increased generalised pain sensitivity and decreased pain thresholds (Lautenbacher, Kundermann, & Krieg, 2006; Moldofsky, Scarisbrick, England, & Smythe, 1975). Even though these studies only simulate sleep disruption for a couple of nights and cannot accurately reflect the chronicity of the sleep disturbance in chronic pain populations, it is interesting that after sleep deprivation, healthy individuals are also seen to exhibit pain experience and behaviour similar to chronic pain conditions like fibromyalgia (Lautenbacher et al., 2006; Schuh-Hofer et al., 2013; Smith et al., 2007).

It is possible that sleep affects optimal endogenous inhibition of pain and this impairment in the body's ability to regulate its central pain inhibitory mechanism is then implicated in perpetuating the progression of chronic pain conditions. Conditioned pain modulation is a measure of pain inhibition in which a painful stimulus (conditioning stimulus) inhibits and subdues perception of pain produced by a second co-occurring painful stimulus (test stimulus) (van Wijk & Veldhuijzen, 2010). A systematic review of the evidence has also further suggested that CPM may be impaired in chronic pain conditions, as the application of a second noxious stimulus does not always show the expected decreased sensitivity or inhibitory response (Lewis, Rice, & McNair, 2012). Impairment in this central pain modulation and inhibitory system has been associated with maintaining the maladaptive persistent pain in chronic pain. Studies with healthy populations undergoing a partial sleep

restriction paradigm and insomniacs have also revealed greater pain sensitivity and impaired CPM response the next day (Haack et al., 2007; Haack et al., 2012; Smith et al., 2007). Another study showing the relationship between sleep disturbances and CPM responses in clinical pain population found that PSG measured higher sleep efficiency and longer total sleep time were positively correlated with better functioning CPM responses in their sample with temporomandibular joint disorder (Edwards et al., 2009).

Further studies are, however, needed to substantiate the associations between altered CPM and sleep disturbances across the range of chronic pain conditions. Considering that CPM reflects an interaction between physiological and psychological pain pathways, and is a phenomenon of growing interest, it may be an indicator of how poor sleep impacts the pain experience. Hence, it is also of consequence to consider its validity and applicability as a sensitive marker of endogenous pain inhibition. This thesis attempts to address this by exploring the validity and reliability of the pain stimuli and quantitative sensory testing protocols used to assess CPM response. As well as validating and refining the CPM testing paradigm, the thesis also delves into what distinguishes healthy individuals with normal CPM responses with those presenting with no CPM response, across pain and sleep parameters. This could be used to inform therapeutic pathways and to provide important phenotypic information to characterise pain perception in individuals susceptible to persistent pain conditions.

3.5.2 Inflammation

Sleep loss impairs inflammatory function and several inflammatory cytokines (IL-6, IL-1ß, and TNF-α) form part of the brain's neurobiological and neurochemical network regulating normal physiological sleep. How sleep alters inflammatory function is difficult to disentangle given the complexity and multiplicity of the actions and mechanisms of the immune system, but it is suggested that sleep disruption at least induces low- grade inflammation (Imeri & Opp, 2009; Opp & Krueger, 2017). It has also been suggested that boosting of immune system occurs during sleep (Moldofsky, 1995). Although most chronic pain conditions are not explicitly inflammatory diseases, the range of symptoms associated with them such as hyperalgesia, fatigue, sleep, pain sensitivity, anxiety, cognitive dysfunction are also stress and arousal-related and potentially influenced by cytokines (Wallace, 2006). Hence, we can acknowledge the potential role of physiological stress and inflammation as having an indirect influence on sleep and pain processes. It is possible that under the continual physiological and psychological stress resulting from chronic pain and sleep disturbances, cells of the immune system induce levels of chronic inflammation that foster chronic pain disorders and associated sleep disturbances (Bote, Garcia, Hinchado, & Ortega, 2012). Nevertheless, the co-occurrence of and interrelationship between sleep disturbances, pain, and inflammatory processes has not been extensively investigated in the context of chronic pain. The links between sleep disturbance and chronic pain, and inflammation remains puzzling, although several aspects underlying the puzzle have been considered.

Increased presence of proinflammatory cytokines and proteins (e.g. TNF-α, IL-1ß, IL-6 and CRP) has been linked to the molecular processes enhancing hyperalgesia in pain disorders and sleep disruption has also been associated with elevations of these inflammatory markers both in normal populations and in idiopathic chronic pain disorders (Drewes & Arendt-Nielsen, 2001; Haack et al., 2007; Vgontzas et al., 2003). A systematic review and meta-analysis by Irwin, Olmstead, and Carroll (2016) of 72 cohort and experimental studies assessed CRP and IL-6 levels in relation to sleep disturbances. Poor sleep quality especially in the long-term and more persistent sleep problems were associated with raised CRP, and to a lesser extent with raised IL-6. Shorter sleep duration was also associated with raised CRP and extreme long sleep duration with raised IL-6 and CRP. No associations were found for TNF-α and IL-1ß as not enough studies were found which investigated TNF-α and IL-1ß levels in relation to sleep. Associations between inflammatory makers and sleep were also not significant when pooled for experimental studies, which begs the question of whether sleep interacts with inflammatory process more cumulatively in the long-term rather than acutely. Research thus far has suggested that increase in inflammatory responses in the body may be linked with persistent sleep and pain disturbances, but this is yet to be assessed at length across both healthy and clinical population. Inflammation may play a role in the immediate and long-term association between pain and sleep, but further studies are needed to investigate the concurrent association of the triad of sleep, pain and inflammation. This thesis presents a quasi-experimental study considering the interrelationship between sleep, pain, and inflammation in the short term within the context of chronic pain. In addition, the thesis also considers within a systematic review the current evidence of how sleep problems may be associated with

pain-related physiological status and inflammation in the general population in the long-term.

3.5.3 Cognition and behaviour

Sleep and pain are processes relying on biological and physiological regulation. Yet, the perception, experience, and control of both sleep and pain is also heavily influenced by emotional and psychological characteristics. Chronic pain and sleep disturbances influence daily mental and physical functioning. Sleep may lead to greater daily pain and disability through sleep's influence on negative mood, subsequently affecting pain experience and perceived ability to cope with pain (Busch et al., 2012; Harrison, Wilson, Heron, Stannard, & Munafo, 2016; O'Brien et al., 2010, 2011). There are diverse ways in which sleep may be associated with pain and mood processing, increase emotional symptomology, and enhance the affective dimension of pain perception. People with chronic pain may develop depression due to the consequences of pain on their functioning and a lost sense of who they are (Tang, Goodchild, Hester, & Salkovskis, 2010). For example, when sleep is manipulated in those with rheumatoid arthritis compared with healthy controls, partial sleep deprivation led to increased self-reported fatigue, depression and anxiety symptoms and these were consequently associated with disease activity (Irwin et al., 2012). Furthermore, the neurological interrelation of emotional regulation, sleep, and pain in cortical areas such as the limbic area, anterior cingulate cortex, and amygdala also shed some light on the interrelationship (Boakye et al., 2016).

In addition, poor sleep has been consistently linked to the cognitive behavioural factors that perpetuate the unpleasantness of chronic pain condition and the maladaptive cognitive coping style found in this population (Smith & Haythornthwaite, 2004). For example, pain catastrophising is an exaggerated response to chronic pain, and hypervigilance to pain sensations and has been shown to impact individual perception of pain and daily functioning abilities (Crombez, Van Damme, & Eccleston, 2005; Sullivan, Bishop, & Pivik, 1995; Vlaeyen, Kole-Snijders, Boeren, & van Eek, 1995). Studies have addressed the role of sleep disturbance in mediating the effect of pain catastrophising in chronic pain and found that pain catastrophising is associated with greater sleep disturbance. A significant portion of variance in clinical pain severity and pain-related interference attributable to pain catastrophising was mediated by sleep disturbance in individuals with osteoarthritis (Campbell et al., 2015) and temporomandibular disorder (Buenaver et al., 2012). Psychological concepts such as pain catastrophising are generally of therapeutic importance in the non-pharmacological clinical management of chronic pain conditions in a clinical setting. Hence, this thesis aims to consider the influence of this psychological correlate of pain catastrophising when exploring the association between sleep and pain perception both in healthy and clinical chronic pain populations.

3.6 Clinical management of co-occurring sleep disturbance and chronic pain

Treating comorbid sleep and pain problems is a challenging task. The comorbid relationship between the two is a vicious cycle and forward-feeding interaction.

Getting rid of pain only may not necessarily lead to better sleep and address the cognitive-behavioural factors maintaining chronic sleeplessness. The current approach to clinical pain management is mostly focused on pharmacological treatments for pain – ranging from acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs) to opioids, and sometimes incorporating antidepressants, hypnotics and benzodiazepines, and anticonvulsants for widespread and neuropathic pain (Makris, Abrams, Gurland, & Reid, 2014). Notably, a lot of these medications also alter sleep; they may or may not bring about better self-reported sleep, but could also disrupt sleep continuity, suppress REM and slow wave sleep, as well as altering pain perception and improving functional outcomes. Goforth, Preud'homme, and Krystal (2014) and Park and Moon (2010) present more detailed overviews of influence of pharmacological treatment of sleep in chronic pain.

Despite the common co-occurrence, sleep is usually not routinely considered and highlighted as a therapeutic target for pain management (Tang, Goodchild, Hester, & Salkovskis, 2012). However, a growing body of evidence supports non-pharmacological treatments for sleep problems such as cognitive behavioural therapy for insomnia (CBT-I) for clinical pain management. Currently, there is already strong evidence for cognitive behavioural therapy for insomnia (CBT-I) as a pragmatic, and effective non-pharmacological intervention that provides clinically significant improvements in sleep for those with chronic insomnia. Trauer, Qian, Doyle, Rajaratnam, and Cunnington (2015) carried out a systematic review and meta-analysis analysing the effectiveness of CBT-I across 20 randomised controlled trials (RCTs) with total of 1162 participants with insomnia. Their findings reported that the treatment

led to significant improvements in time taken to fall asleep, overnight awakening, total sleep time and sleep efficiency in those with insomnia. Their analysis was however limited to studies on primary chronic insomnia and did not consider those with comorbid insomnia. More specifically for those with comorbid insomnia and chronic pain, RCTs have shown effectiveness of using CBT-I to treat insomnia associated with chronic pain across conditions such as musculoskeletal pain, fibromyalgia, chronic neck and back pain (Currie, Wilson, Pontefract, & deLaplante, 2000; Edinger, Wohlgemuth, Krystal, & Rice, 2005; Jungquist et al., 2010; Vitiello et al., 2009). Tang, Lereya, et al. (2015) also reported in their systematic review and meta-analysis of 11 RCTs with 1066 participants with malignant and non-malignant chronic pain that non-pharmacological treatment of insomnia in this population leads to better patient outcomes, not only in sleep quality but also in pain, fatigue, and depression up to a year after treatment.

Recent development is also underway to establish the efficacy of a hybrid cognitive behavioural therapy that aims to tackle pain and sleep problems simultaneously. Beyond just addressing sleep and pain problems alone or separately, the therapy places special attention to addressing patients' unhelpful beliefs about pain, sleep, and the interaction of the two. By addressing worries and anxiety concerning sleep and pain, tackling and altering sleep habits that impair sleep propensity and regulation, and reducing maladaptive pain coping cognitions such as pain catastrophising (Pigeon et al., 2012; Tang, 2009; Tang, Goodchild, & Salkovskis, 2012; Vitiello et al., 2014). The hybrid intervention is a worthwhile pursuit but for it to fulfil its efficacy potential, there is still a need to identify specific targets for

interventions and predictors of poor sleep and pain interference and individual differences in the physiological and psychological manifestation of pain and sleeplessness. An overarching aim of this thesis is to add to this body of evidence by considering the development of a clearer conceptualisation of the sleep and pain relationship and relevant bio-psychological mechanisms at play.

3.7 Conclusion

Sleep disturbance and chronic pain are complex intertwined biological and psychological processes. It can be argued that chronic pain provides the physiological and psychological stressor that invades sleep physiology and consequently sleep disturbances also works through several somatic mechanisms and psychological processes to foster the chronic pain process and the physiological and psychological pain experience. This chapter sought to present an overview of existing evidence on the biopsychosocial conceptualisations of the association between sleep and pain and potential directions for further experimental and epidemiological investigations. Consequently, the studies described in the subsequent chapters of this thesis considers the associations of objective and self-reported sleep with different aspect of the pain experience in healthy population and chronic pain conditions. The studies also explore physiological and psychological mechanisms underlying the sleep and pain relationship. The thesis further adopts a multi-methodological approach to allow for the investigations of these parameters within both an immediate experimental setting in healthy and clinical populations and the long-term consequences of the sleep and pain interrelationship within the general population.

4 Validity of the cold-pressor task and bag-holding task conditioning stimuli for eliciting conditioned pain modulation in healthy young adults: The influence of distraction, pain catastrophising, and self-reported sleep

4.1 Introduction

Conditioned pain modulation (CPM), as introduced in Chapter 2 (2.2.2) plays an important role in our understanding of not only how the brain perceives and inhibits acute pain but also the pathogenesis of chronic pain conditions. CPM is a normal, healthy response to a barrage of painful stimuli and is indicative of central pain inhibitory processes. Yet, dysfunction in this central modulation of nociceptive input may be indicative and predictive of development and aggravation of future chronic pain (Lewis et al., 2012; van Wijk & Veldhuijzen, 2010; Yarnitsky, 2015). Whilst CPM has been found to be impaired in a range of idiopathic chronic pain conditions such as fibromyalgia (FM) (Lautenbacher, Prager, & Rollman, 2007), irritable bowel syndrome (IBS) (Wilder-Smith, Schindler, Lovblad, Redmond, & Nirkko, 2004), migraine (Sandrini et al., 2006), temporomandibular joint disorder (TMD) (King et al., 2009). It is not as prominent in osteoarthritis (OA) (Kosek & Ordeberg, 2000), and chronic back pain (CBP) (Julien, Goffaux, Arsenault, & Marchand, 2005; Mlekusch et al., 2016). Impairment in CPM may be a wider characteristic of individual's pain profile and pain researchers have thus called for research into the utility of CPM for constructing profiles of pain modulation that can subsequently be used to predict important features of clinical pain and responses to treatment (Granovsky & Yarnitsky, 2013). However, before CPM can be used as a dependable biomarker of individual differences in pain perception and treatment response, the testing procedure involved and the mechanisms underlying the phenomenon still need standardisation

and clarification. As highlighted in a recent review, the reliability of the CPM response is often dependent on stimulation parameters and varying study methodology (Kennedy, Kemp, Ridout, Yarnitsky, & Rice, 2016). There is a clear need to establish practical, suitable and clinically relevant CPM protocols, the validity of CPM effect as a robust physiological phenomenon, and how CPM is being shaped by psychosocial aspects of pain experience such as pain catastrophising and sleep.

4.1.1 Validity and practicality of protocols assessing conditioned pain modulation

Theoretically, the CPM effect refers to the ability of a noxious conditioning stimulus to decrease the pain intensity of a noxious testing stimulus, and a dysfunction in this mechanism is taken to indicate a potential impairment in the body's endogenous pain modulatory ability. However, there is currently no defining characteristics to discern the intensity of noxiousness a conditioning stimulus must possess to elicit the CPM response. Based on current studies and protocols, it seems that the type, location, and intensity of a conditioning stimulus could affect the validity of the CPM response.

Oono, Nie, Matos, Wang, and Arendt-Nielsen (2011) assessed CPM effects using three different pain-inducing conditioning stimulus modalities (2-4^{0}C cold pain, ischemic tourniquet pain at 36kPa, tonic mechanical pressure pain) on pressure pain threshold and pressure pain tolerance test stimuli at different assessment body sites (masseter, forearm, leg). They found that a cold pain conditioning stimulus induced the greatest subjective pain intensity and the most powerful CPM effect on a pressure pain threshold test stimulus (i.e. resulted in the greatest increase in pressure pain

threshold) with the leg as the assessment site. This combination also had the greatest test-retest reliability and smallest intra and inter-individual variation compared with other body sites (masseter region and the forearm) and conditioning stimulus (tourniquet pain and mechanical pressure pain). They argued that CPM effect is usually greater with higher pain intensity of the conditioning stimulus. However, other studies have found that once the intensity of the conditioning stimuli reaches a certain level of moderate pain, any more increase in pain intensity is not related to the magnitude of the CPM effect (Granot et al., 2008; Nir, Granovsky, Yarnitsky, Sprecher, & Granot, 2011).

These variations in CPM response by conditioning stimuli could mean that different pain stimuli evoke endogenous inhibition through slightly different mechanisms. CPM effect could be more related to the type and intensity of the conditioning stimuli and the type of nociceptive or somatic nerve fibres it activates rather than the pain it induces (Lautenbacher, Roscher, & Strian, 2002; Le Bars et al., 1992). Consequently, it is worth exploring what underpins the different modalities of conditioning stimuli used to assess pain modulation capabilities. For example, a conditioning stimulus eliciting muscle pain originating from somatic tissue nociceptors may better represent certain clinical pain states such as in chronic back pain, where limited studies of CPM have been done (Weissman-Fogel, Sprecher, & Pud, 2008). Such a conditioning stimulus may optimise sensitivity and specificity of CPM to describe the clinical pain experience by activating pain of a nature that is relevant to the daily physical challenges faced by those with chronic back pain.

In addition, there has been an increased interest in individual variability in endogenous pain-inhibitory processes (Edwards, Dworkin, et al., 2016). However, research studies have not fully classified individual differences in response to CPM paradigms and the characteristics of 'normal' and 'abnormal' CPM response in healthy individuals. Few CPM studies have reported when healthy participants do not demonstrate the expected inhibitory response and instead show a facilitation of pain (Locke et al., 2014; Oono et al., 2011). Furthermore, the studies do not fully describe the characteristics of these non-responders compared with responders. Further evaluation of the proportion of participants that do not show the expected CPM effect would not only improve interpretation of the meaningfulness of CPM in healthy populations but also further contribute to understanding of the mechanisms underpinning and factors influencing impaired pain inhibition (Kennedy et al., 2016).

4.1.2 Conditioned pain modulation and cognitive distraction

Investigating the factors influencing CPM is also necessary to provide greater understanding of the physiological and psychological processes underlying the phenomenon. Cognitive processes such as attention and distraction have the potential to modify the way pain is perceived (Melzack & Wall, 1965). From a cognitive psychology view, the experience of pain is often reliant on attentional mechanisms dependent on the threat value of the stimuli and accompanying emotional arousal and expectations (Eccleston, 1995; Eccleston & Crombez, 1999; Wiech, 2016). The processing of both acute and chronic pain has been consistently shown to demand the central attentional resources. This is because multiple pain-related brain pathways send and receive projections from several cortical areas and thus can potentially

modulate pain through several cognitive and psychological mechanisms (Ossipov et al., 2010). As described in Chapter 2 (2.2.1) descending pain control pathways underlying CPM involve the PAG, RVM and DRt which are all connected to the forebrain and activates projections from areas such as the primary somatosensory cortex and insula to direct cognitive attention to painful stimuli (Bushnell et al., 2013; Tracey & Mantyh, 2007; Tracey et al., 2002). These pathways are receptive to cognitive manipulation as they can interact concurrently with both cognitive and affective pain processing regions in the brain.

These interactions explain why it has been suggested that the CPM phenomenon may in part be due to distraction. With the test and conditioning pain stimuli competing for limited cognitive resources for pain processing, a drawing of attention away from the perceived pain of the test stimulus to the greater pain of the conditioning stimulus may subsequently lead to lower pain being perceived from the test stimulus (Birnie, Chambers, & Spellman, 2017). However, the extent to which the CPM effect can be explained by distraction has not been fully quantified. Staud, Robinson, Vierck, and Price (2003) explored the effect of distraction during a CPM paradigm by prompting 11 fibromyalgia female patients, 22 healthy female controls, and 11 healthy male controls to focus their attention on either the conditioning stimulus of immersion of left hand in a hot water bath (distraction condition) or test stimulus which was repeated heat taps on the right hand (control condition 1), or given no prompts or explicit instructions as to where to focus their attention (control condition 2) whilst CPM was measured. Then, the participants were asked to rate the sensation felt at the non-attended site or the conditioning stimulus site (for the

control groups). Across both healthy and clinical groups, they found that the CPM effect was generally stronger in the distraction condition than the control conditions. This shows CPM as a physiological mechanism with some potential overlap with distraction and attentional processes. However, the researchers assessed distraction using attention manipulation and relied on whether or not the participants managed to shift their attention to or away from the pain stimuli based on self-report. Attention is often defined as selective intrinsic reaction to the presence of pain; pain interrupts attention and forces a new action and/or priority to escape (Eccleston & Crombez, 1999). A distraction from a painful stimuli requires the shifting of attention away from the pain sensation specifically via engagement in another affectively neutral competing task (Eccleston, 1995). Compared to this, the operationalisation of distraction in studies like Staud et al. (2003) deviates from the definition of distraction which ideally involves active engagement in a competing cognitive task.

Moont, Pud, Sprecher, Sharvit, and Yarnitsky (2010) presented a study that directly assessed the effect of cognitive distraction on CPM by including a non-painful distraction task that actively increased cognitive load. Their CPM paradigm consisted of intermittent heat pain pulse stimulation as test stimulus and tonic heat pain as a conditioning stimulus. They used a visual task with three levels of difficulties, which involved counting shapes appearing on a screen as a cognitive distracter task. Their testing conditions involved assessment of CPM using the conditioning stimuli, the distracter task, and a combination of the conditioning stimuli and distracter task. The results showed that CPM was most pronounced under the combined condition. This is expected and in line with theories of distraction and attention; under the combined

condition, the distraction task must have engaged extra cognitive processes that directed attention away from the test stimulus, thus enhancing CPM effect.

Moreover, their protocol also quantified CPM effect based on the self-reported pain ratings felt when the test stimulus was applied alone compared to when it was applied with the conditioning stimulus. From this rating, they did not provide a quantitative estimation of the effect of distraction. Psychophysical measures such as computerised pressure pain threshold assessments would be more reliable as a test stimulus as they would provide a clearer way to quantify the effect of distraction on pain inhibition (Kennedy et al., 2016; Oono et al., 2011). Noticeably, the similarity of their test and conditioning stimuli (both heat pain) could also have enhanced the distraction effect that they observed (Lautenbacher et al., 2007). Using a distracter stimulus that considers and mirrors the physical and sensory processes evoked by the conditioning stimuli may provide a better platform for comparing and quantifying the influence of distraction across the conditioning and distraction stimuli. For example, a distracter stimulus with perceptual similarity with a cold pressor task conditioning stimulus would incorporate a non-painful version of the task with an additional demanding cognitive task component. There is currently no study that has assessed the influence of distraction on CPM using these parameters.

4.1.3 Conditioned pain modulation and pain catastrophising

Pain catastrophising is described as a maladaptive heightened reaction to and interpretation of a painful stimulus (Quartana, Campbell, & Edwards, 2009). This could be an individual's tendency to engage and invoke certain affective and behavioural

responses towards pain, or a cognitive process that an individual engages in during a painful procedure (Sullivan et al., 1995). Studies have assessed situational pain catastrophising related to experimental pain procedures and general pain catastrophising which is a tendency to catastrophise about general daily pain experiences. The process of pain catastrophising may impact on pain experience via activation of cortical areas related to affective pain processing (Quartana et al., 2009). This may subsequently influence spinal gate control mechanisms, priming the descending pain modulation pathways towards facilitation of pain processing and, leading to a disrupted CPM response (Sullivan et al., 2001). Goodin et al. (2009) reported that situational pain catastrophising during the experimental CPM procedure was related to increased pain ratings and impaired CPM response.

On the other hand, studies assessing general pain catastrophising tendencies using the Pain Catastrophising Scale (PCS) by Sullivan et al. (1995) have found mixed results. Some studies have found that a greater tendency towards general pain catastrophising was related to impaired CPM response (Weissman-Fogel et al., 2008). Other studies have only found this association when eliciting CPM response using a specific conditioning stimuli such as the cold pressor task (Granot et al., 2008). A recent meta-analysis of 17 studies assessing pain catastrophising in relation to CPM response across a range of different protocols and modalities in healthy populations also revealed no significant correlation between pain catastrophising and CPM response (Nahman-Averbuch, Nir, Sprecher, & Yarnitsky, 2016). While the evidence supports situational catastrophising as a potential cognitive process of pain sensitisation during experimental procedures, less is known about trait

catastrophising and if a tendency and predisposition to engage in the pain catastrophising amplifies pain signals and distorts endogenous pain inhibitory mechanisms. Studies on the associations between catastrophising and CPM magnitude are needed to clarify if trait catastrophising is a psychological construct only present in those presenting with impaired CPM response or if CPM phenomenon is independent of this individual variability.

4.1.4 Conditioned pain modulation and sleep

The full clinical relevance of the interaction of sleep and physiological pain experience in managing and characterising clinical pain states is not fully understood. Assessment of sleep related factors may provide further predictive and defining information about individual pain processing profiles. Experimental manipulation of sleep, notably sleep restriction in healthy participants has been shown to alter sensitivity to different types of noxious stimuli. Increase in perception of muscle pain following sleep restrictions for example reflects greater pressure pain sensitivity and influence of sleep on descending pain inhibitory control systems (Lautenbacher et al., 2006). Smith et al. (2007) altered the sleep of 32 healthy adult females over 7 nights by randomising participants into either forced overnight awakenings, partial sleep restriction or control conditions where participants slept continuously for 8 hours. Polysomnographic measures of sleep revealed that the forced awakening paradigm that simulates overnight sleep continuity disturbance experienced by people with chronic pain led to impaired endogenous pain inhibition. Their CPM protocol involved using a pressure pain threshold test stimulus and cold pressor task conditioning stimuli. Using the same CPM protocol, a cross-sectional study by Edwards et al. (2009)

also reported that PSG measures of higher sleep efficiency and longer total sleep time were associated with better CPM response in those with temporomandibular joint disorder.

In other chronic pain patients, self-reported sleep efficiency was negatively associated with reduced CPM response in fibromyalgia patients (Paul-Savoie et al., 2012). In addition, CPM response was also poorer in those with rheumatoid arthritis compared to healthy controls and this interaction was mediated by greater self-reported sleep problems in those with arthritis (Lee et al., 2013). However, research in healthy population has yet to comprehensively explore associations between subjective sleep reports derived from standardised assessment methods such as daily sleep diaries and association of these with measures of pain inhibition derived from CPM. In addition, studies have yet to look specifically at the self-reported sleep profiles of healthy individuals presenting with impaired CPM response. Investigations of those in the general population with impaired CPM and any associated sleep problems would help isolate factors linked to the worsening or alleviation of pain experience.

4.1.5 Aim of the current studies

Two experiments are presented to assess the validity of the CPM paradigm elicited using two different conditioning stimuli and to evaluate if efficiency and magnitude of CPM response vary as a function of cognitive distraction, pain catastrophising, and self-reported sleep in a healthy population. The first experiment acts as a proof of concept study of a novel CPM testing paradigm using a conditioning

stimulus with potential clinical ecological validity (a bag-holding task to induce muscle pain) and comparing it in validity and reliability to the established cold pressor task conditioning stimuli. This experiment also aimed to explore the influence of pain catastrophising and sleep quality on CPM response. The second experiment serves to address some limitations of the first; a replication using a larger sample size and further test of the validity of the bag-holding task as a conditioning stimulus. In addition, the second experiment aimed to examine and quantify the role of distraction in CPM response.

4.2 Experiment 1 – Methods

4.2.1 Participants

The study sample included 57 healthy young adults (9 males and 48 females; mean age 19 years) recruited from within the university. Inclusion criteria were: aged between 18 and 65 years, healthy English-speakers and with the ability to understand and sign the consent form and complete all study procedures. Exclusion criteria were: i) acute pain due to injury, surgery etc., ii) malignant or non-malignant pain condition(s) present for at least 6 months or more, iii) any known organic sleep disorder(s) (e.g., sleep apnoea, restless leg syndrome/periodic limb movement disorder, narcolepsy) and iv) presence of Raynaud's disease, history of epilepsy, frostbite, cardiovascular disease, and any other medical problem(s) affecting participation in the cold pressor task. The cold pressor procedure closely followed a conservative guideline to ensure safety and comfort of the participants (von Baeyer, Piira, Chambers, Trapanotto, & Zeltzer, 2005). Of 57 participants, three participants did not complete the sleep diary data and full procedure at both visits and were

therefore excluded due to this non-compliance with study procedure and missing data. The final sample for analysis involved 54 participants. Those excluded from the final analysis did not differ from the final sample across the demographics, sleep, and pain variables.

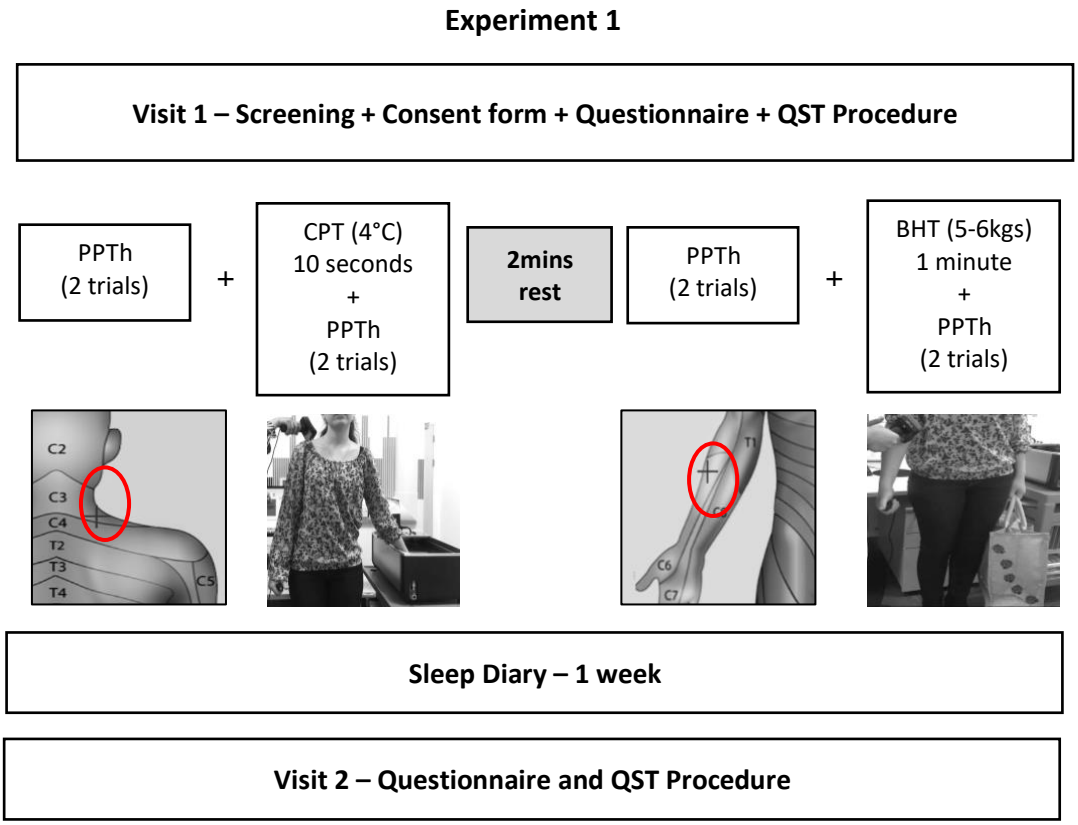
4.2.2 Design and Procedure

The study protocol was approved by the Department of Psychology Research Ethics Committee. After screening (Appendix 7) and reading the Participant Information Sheet (Appendix 2), participants gave signed informed consent (Appendix 1). The study used a repeated measures design; all participants completed 2 sessions of quantitative sensory test (QST) (2.2.2) – one week apart – to assess conditioned pain modulation response (CPM) and were also required to complete a daily sleep dairy for a week in between (see Figure 5 for study design). The two QST sessions were administered by the same experimenter who followed the same standardised experimental protocol. QST was done at the same time of the day for both visits to minimise any diurnal or circadian effects.

During Visit 1, the study was explained in detail to the participants, they provided demographic information, and were asked to complete self-report questionnaires (Appendix 8) to assess pain status, sleep quality, and pain catastrophising. After this, they were given a training and a practice trial opportunity to familiarise with the experimental procedure. This was essentially a short training session before beginning the experiment to familiarise participants with the sensation of the experimental stimuli, namely the pressure pain from algometer and cold-water

bath. Consequently, they underwent the actual test procedure as illustrated in Figure 5. Participants were also given detailed instructions and overview of a sleep diary to complete for the week. The sleep diary was used to tap into the participant's self-reported between the testing visits. Visit 2 took place exactly a week later, with the exception of one participant who completed Visit 2 a day later than planned. Participants returned their completed sleep diaries, and again at this session, completed a questionnaire to assess pain and underwent the same series of QST to assess CPM response. At the end of Visit 2, participants were debriefed (Appendix 3) about their participation, reimbursed with course credits, and given the opportunity to express concerns about the study and their participation.

Figure 5 CPM Experiment 1 Study design and QST protocol



Notes: Figure 5 presents the procedure for Experiment 1. At Visit 1 participants underwent screening and informed consent, completed questionnaires to assess pain status, sleep quality, and pain catastrophising. They also completed the QST procedure which involved a baseline assessment of pressure pain threshold the right upper shoulder (trapezius posterior) or right forearm (anterior brachoradialis) and then reassessment of pressure pain threshold after the application of the conditioning stimuli on the left side of the body (cold pressor task or bag holding task). The testing order of conditioning stimuli was randomly assigned for the first visit. The participants were given a sleep diary to complete during the week between the testing visits. Visit 2 took place exactly a week later at the same time of the day. At this visit, participants completed a questionnaire to assess pain status and completed the QST procedure in the same sequence as Visit 1.

QST (Quantitative sensory testing) **PPTh** (Pressure pain threshold) **CPT** (Cold pressor task) **BHT** (Bag holding task)

4.2.3 Measures

4.2.3.1 Pain measures

4.2.3.1.1 Conditioned Pain Modulation (CPM)

The QST protocol for assessing CPM was adapted from previous studies (Edwards et al., 2009; Martel, 2013; Smith et al., 2007). The CPM methodology assesses pain inhibition and involves the application of a test pain stimulus and a conditioning pain stimulus to two distant body sites.

Test stimulus

Pressure pain threshold (PPTh) was used as the test pain stimulus and was assessed using an Algomed Computerised Pressure Algometer by Medoc Ltd. It was recorded by pushing the tip of the algometer with gradually increasing pressure at approximately 30 KiloPascals on the right upper shoulder (trapezius posterior) or right forearm (anterior brachoradialis). Participants were instructed to press the response button when the 'pain threshold' is reached, which was defined in the current study as 'when the pressure stimulus had become just noticeably painful'. PPTh was assessed twice (once at each site) with a 5-second interval between trials and average of the two PPTh was taken and used for analysis. PPTh is reported in KPa (Kilopascals).

To measure CPM response, the test stimulus was combined with two conditioning stimuli [Cold pressor task (CPT) and Bag holding task (BHT)] that were applied to the contralateral (left) side of the body. This was done as per guidelines for assessing CPM recommending that conditioning stimuli are administered at a distant body site away from the test stimulus (Yarnitsky et al., 2015).

Conditioning stimuli

Cold pressor task

Pressure pain threshold was combined with the cold pressor task (CPT) as a conditioning stimulus in the current QST protocol. This combination is a consistently reliable way of eliciting CPM response (Kennedy et al., 2016; Oono et al., 2011). For this task, participants were asked to keep their left hand up to the wrist in a circulating water bath maintained at 4^{o}C whilst pressure pain threshold is reassessed at the baseline site (right upper shoulder) 10 seconds following hand immersion. 10-seconds was used in this experiment since prolonged immersion in other studies (e.g., 20 seconds or longer) is often deemed by participants as too painful and this often means they are unable to comply further and complete the full CPM procedure (Oono et al., 2011; Smith et al., 2007).

Bag-Holding Task

To measure CPM, the test stimulus was also combined with a bag holding task (BHT). This task was used as a novel conditioning stimuli to assess CPM response, in an attempt to generate musculoskeletal back pain to compare to the cold pressor task (Tang, Salkovskis, et al., 2007; Vlaeyen et al., 1995). Participants were asked to hold a weighted shopping bag (5kgs females/ 6kgs males) with their left hand, whilst pressure pain threshold is reassessed at the baseline site (right forearm) after 1 minute of bag-holding. The bag weight did not account for individual differences in physical strength, but all participants held it for the same standard time. One minute of bag-holding was trialled in this experiment to assess feasibility of the bag-task as a

conditioning stimulus to elicit to engage a CPM response, whilst minimising participant burden or boredom from holding the bag.

The order of applying the conditioning stimuli to assess CPM response was randomly assigned to each participant for the first testing visit and remained the same for the follow-up visit. During the CPM assessment, participants were standing, instructed to fixate their gaze on a spot on the wall to minimise distraction. They were especially reminded to focus on and pay attention to the pressure pain from the algometer and press the stop button immediately when *"the pressure stimulus had become just noticeably painful and not the conditioning stimulus".*

4.2.3.2 Sleep Measures and Questionnaires

Consensus Sleep Diary (CSD) (2.1.3) (Carney et al., 2012)

Participants were asked to fill in a daily sleep diary with the purpose of gathering information about participants' daily sleep pattern between testing visits. The CSD has items asking the participants to report bedtime ("What time did you get into bed?"; "What time did you try to go to sleep?") and risetime ("What time was your final awakening?"; "What time did you get out of bed for the day?"), to estimate sleep onset latency (SOL), ("How long did it take you to fall asleep?"), wake up after sleep onset (WASO) and WASO duration ("How many times did you wake up, not counting your final awakening?"; "In total, how long did these awakenings last?").

Demographic questionnaire

The demographic questionnaire provided details on participants' age, sex, ethnicity, and body mass index. Validated questionnaires described below were used to characterise participants based on sleep quality, pain rating, and pain catastrophising tendency.

Pittsburgh Sleep Quality Index (PSQI) (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989)

The PSQI assesses the overall sleep quality in the past month. It consists of 19 individual items computed into sub-components of subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. The score for each subscale ranges from 0 (no difficulty) to 3 (severe difficulty). A global PSQI score is then derived from the total of the seven component scores. The global PSQI score ranges from 0 to 21 and lower scores are indicative of better sleep quality; with a suggested a cut-off score of > 5 to indicate poor sleepers. The PSQI has shown good internal consistency in non-clinical groups, Cronbach's alpha 0.83 (Buysse et al., 1989). The scale also correlates with other objective and self-reported sleep measures and has shown strong reliability and stability as a subjective measure of sleep dissatisfaction across studies in non-clinical samples (Grandner, Kripke, Yoon, & Youngstedt, 2006; Mollayeva et al., 2016).

Pain Catastrophising Scale (PCS) (Sullivan, 2009; Sullivan et al., 1995)

The PCS is a 13-item scale to measure the tendency of pain catastrophising. The scale assesses thoughts and feelings that individuals may have experienced during past painful episodes. The scale requires the participants to think about these past

painful experiences and to rate the extent to which they experience the items on a 5-point scale of 0 (not at all) to 4 (all the time). The PCS has shown reliability and validity as a measure of catastrophic thoughts about pain, with high internal consistency (Cronbach alpha = 0.87) and test–retest reliability (r = 0.70–0.75) (Sullivan et al., 2001). The PCS total score ranges from 0 – 52 with higher scores indicating greater tendency to engage in catastrophic thinking about pain, with a suggested cut-off score of >30 to indicate clinically relevant levels of catastrophising (Sullivan, 2009).

Brief Pain Inventory (BPI) (Cleeland & Ryan, 1994)

The BPI is a measure that assesses pain severity and pain-related interference. For this study, only the 4 items assessing pain severity were used to confirm participants were not currently experiencing acute pain before starting the experimental procedure. These are numerical rating scales [0 (no pain at all) to 10 (pain as bad as you can imagine)] for assessing worst pain in the past week, least pain in the past week, pain on average, and pain right now.

4.2.4 Data Analysis

PPTh and CPM index were calculated separately for both visits and were also averaged across both testing visits. Consistent with previous studies and research recommendations (Edwards et al., 2009; Smith et al., 2007; Yarnitsky et al., 2010; Yarnitsky et al., 2015), CPM index was derived by calculating the percent change of PPTh during the conditioning stimulus to PPTh prior to conditioning stimulus ($\frac{Mean\ PPTh\ during\ CS}{Mean\ PPTh\ prior\ CS} \times 100$). CPT-CPM represents the index for the cold pressor task

conditioning stimulus and BHT-CPM represents the index for the bag holding stimulus. A CPM index greater than 100% indicates a positive CPM effect and an increased pain threshold during the CPM compared to baseline PPTh. A CPM index less than 100% reflects the reverse. The percent difference reflects the magnitude of the CPM effect (ΔCPM) which is the observed CPM index subtracted from a CPM index of 100% (no CPM effect).

As per previous studies (Biurrun Manresa et al., 2014; Lewis et al., 2012; Martel, 2013), intraclass correlation coefficients (ICCs) were calculated to examine the relative stability of CPM responses. This indicates the stability of interindividual differences in CPM responses across both testing visits. ICCs are established measures of relative stability. Coefficients ranging between 0.00 – 0.40, 0.41 – 0.60, 0.61 – 0.80, and 0.81 – 1.0 are interpreted as poor, moderate, good, and excellent reliability respectively (Shrout & Fleiss, 1979; Weir, 2005). ICC was calculated between visits 1 and 2, for PPTh and CPM index and for both conditioning stimuli (cold pressor and bag holding task). ICC analysis was carried out using a two-way mixed effect model with terms of absolute agreement and ICCs of average measurements are reported.

The sleep diary data was scored to extract and calculate a week average of subjective sleep parameters – sleep onset latency (SOL), wake after sleep onset (WASO) duration, sleep efficiency (SE), time in bed (TIB), and total sleep time (TST). SE was calculated using the formula: TST/TIB * 100. TST was estimated and derived based on the formula: TIB-(SOL+WASO duration) (Morin & Espie, 2004).

To examine the influence of sleep and pain catastrophising on CPM response, Pearson correlations were computed to examine simple bivariate relationships of sleep variables derived from the PSQI and sleep diary and pain catastrophising scores with PPTh and CPM index. Given the multiplicity of the correlations, a post-hoc Bonferroni correction was applied and all correlations were Bonferroni corrected to a $p < 0.001$.

Finally, participants were also split by CPM responders and non-responders. CPM responders and non-responders were defined as participants with a positive CPM effect (> 100%) and negative CPM effect (< 100%) respectively. To account for unequal sample sizes between the two groups, a non-parametric t-test was used to compare the two groups by pain catastrophising (PCS scores), sleep quality (PSQI scores), and sleep diary averages.

All statistical analyses were conducted using SPSS version 23 (IBM Corporation, 2013). Means are presented with standard deviations in parentheses, unless otherwise stated. The level of significance was set at $p < 0.05$ unless otherwise stated.

4.2.5 Results

4.2.5.1 Descriptive Statistics

Descriptive statistics for the participants' demographics, questionnaire variables, and sleep diary averages are presented in Table 1. The sample included 50.9% Caucasians, 35.2% Asians and 13.9% Black, other and mixed ethnicities.

Table 3 CPM Experiment 1 Participant Characteristics

N = 54	M (SD)
Age	19.4 (3.86)
BMI (*n* = 48; due to missing data)	22.01 (3.31)
Sex (Female %)	84.21%
Ethnic origins (Caucasian %)	50.9%
Pain catastrophising (PCS total score)	15.93 (10.52)
Sleep variables	
Sleep disturbance (PSQI total score)	5.91 (2.60)
Sleep diary – week average	
Sleep onset latency (mins)	19.30 (16.85)
WASO duration (mins)	10.99 (22.46)
Total sleep time (mins)	503.19 (73.91)
Sleep efficiency (%)	94.22 (5.52)

Notes: Means are presented with standard deviations in parentheses, unless otherwise stated. PCS (Pain Catastrophising Scale), PSQI (Pittsburgh Sleep Quality Index), Sleep onset latency (take taken to fall asleep), Wake after sleep onset (overnight awakenings), total sleep time (sleep duration), sleep efficiency (percentage of total time in bed spent asleep).

4.2.5.2 Reliability of CPM response across conditioning stimuli.

Table 4 shows the Mean PPTh (KPa) and CPM index measurement at Visit 1 and Visit 2, averages across both visits, and the ICC of scores between Visits 1 and 2. Pressure pain thresholds for both cold pressor and bag-holding stimuli conditioning stimuli showed good ICC scores across both sessions. CPM responses for cold pressor and bag-holding stimuli respectively showed poor and moderate ICC scores across both sessions.

Table 4 CPM Experiment 1 – PPTh (KPa), CPM index (%) and magnitude (Δ CPM) and interclass correlations

	Visit 1	Visit 2	Average	ΔCPM	ICC
CPT - PPTh	202.54 (29.34)	203.10 (35.54)	202.82 (28.41)		0.69[0.46 – 0.82] *** p = 0.000
CPT-CPM	107.10 (13.66)	108.28 (14.48)	107.69 (10.88)	7.69%	0.33[-0.16 – 0.61] p = 0.077
BHT - PPTh	203.06 (30.95)	208.06 (37.24)	205.56 (31.01)		0.78[0.62 – 0.87] *** p = 0.000
BHT-CPM	96.84 (8.97)	99.02 (13.27)	97.93 (9.60)	-2.07%	0.60[0.31 – 0.77] *** p = 0.000

Notes: *p < 0.05 ** p < 0.01 *** p < 0.001. ICC correlations are presented with 95% confidence intervals in square brackets. PPTh (Pressure pain threshold) CPT (Cold pressor task) BHT (Bag holding task) CPM (Conditioned pain modulation) ICC (Intraclass correlation) ΔCPM (percent magnitude of CPM effect)

4.2.5.3 Magnitude of CPM response across conditioning stimuli

To evaluate the magnitude of CPM index between the cold pressor and bag holding conditioning stimulus, the CPM effect and magnitude was calculated for both stimuli (Table 4). CPT stimulus elicited the strongest CPM response (7.69%) compared to the BHT stimulus (-2.07%) which on average produced a negative CPM response.

4.2.5.4 Associations between CPM response, pain catastrophising, and sleep

To explore the influence of sleep and pain catastrophising on the magnitude of CPM index, Pearson correlations were computed between PSQI scores, PCS scores, sleep diary variables, average PPTh, and CPM index (Table 5). These measures were not significantly associated with CPM scores after Bonferroni correction. Although,

sleep onset latency showed a small negative association with average pressure pain threshold (r = -0.3, [95%CI -0.539; -0.054] $p < 0.05$).

Table 5 CPM Experiment 1 – Associations between CPM response, pain catastrophising, and sleep

N = 54	PSQI	SOL	WASO	TST	SE	PCS	CPM	PPTh
PSQI	1	.237	.006	-.189	-.200	.259	.146	-.068
SOL		1	.027	.172	-.481	.079	.012	**-.317**
WASO			1	-.210	-.849	-.010	.102	.154
TST				1	.240	.131	-.071	-.175
SE					1	-.046	-.119	-.005
PCS						1	-.054	.109
CPM							1	-.203
PPTh								1

4.2.5.5 CPM responders and non-responders across pain catastrophising and sleep

Lastly, differences in pain catastrophising and sleep variables were examined for both CPM responders versus non-responders (Table 6). Only CPM response from the cold pressor task was used for this analysis as this was the conditioning stimulus that is already established and validated in other CPM protocols, whereas the validity and reliability of the bag-holding task was under evaluation in this experiment. There were a small number of CPM non-responders (n = 10) compared to responders (n = 44) and they reported higher PCS scores (M = 22.30, SD = 12.13) than responders (M = 14.60, SD = 9.73), U = 137.00, $z = -1.85$, $p < .05$. There were no other significant differences between the two groups.

Table 6 CPM Experiment 1 – CPM responders and non-responders

	CPM Non-responders N = 10	CPM Responders N = 44	Mann-Whitney U test
PSQI (Sleep quality)	6.20 (1.99)	5.79 (2.71)	U = 190.50, *z* = -0.663, *p* = 0.259
PCS (Pain catastrophising)	22.30 (12.13)	14.60 (9.73)	U = 137.00, *z* = -1.850, *p* = 0.032*
Sleep onset latency (SOL) (mins)	22.39 (16.34)	18.60 (17.06)	U = 176.50, *z* = -0.969, *p* = 0.170
WASO duration (mins)	9.29(15.72)	11.38 (23.87)	U = 186.00, *z* = -0.758, *p* = 0.229
Total sleep time (TST) (mins)	510.85(114.49)	501.44(63.03)	U = 175.50, *z* = -0.991, *p* = 0.164
Sleep efficiency (SE) (%)	94.24(4.12)	94.22(5.95)	U = 200.00, *z* = -0.445, *p* = 0.334

Notes: *Means are presented with standard deviations in parentheses*
****p < 0.001 **p < 0.01 *p < 0.05*

4.3 Summary of Experiment 1 findings and justification for Experiment 2

Experiment 1 aimed to evaluate the utility of using a novel conditioning stimulus to evoke the CPM response, however, there was no evidence that the bag holding task could reliably be used to elicit CPM. The CPM index was less than 100% suggesting that the task tend to show a reverse CPM effect, which is puzzling. Research has shown that the effect of CPM may be correlated with the intensity of the conditioning stimuli (Nir et al., 2011; Nir & Yarnitsky, 2015), hence perhaps having participants holding the weighted bag for just a minute was insufficient to elicit the pain necessary to evoke CPM. To clarify this, in Experiment 2, the length of bag-holding was increased to 2 minutes as an attempt to up the intensity of the pain. In addition, a pain rating was added to gauge how participants perceive the pain intensity from both conditioning stimuli. A body manikin (pain drawing tool) was also used to assess pain distribution after the application of the conditioning stimulus, to confirm the stimuli are perceived as painful and in the expected contralateral side of the body.

In Experiment 1, apart from CPM non-responders reporting greater pain catastrophising than responders, there was no other significant differences between the two groups across sleep variables. Given the small sample of non-responders in this experiment, we aimed to replicate the findings using a larger sample to characterise CPM responders and non-responders and to evaluate potential associations (or the lack thereof) with pain catastrophising and self-reported sleep. In addition, Experiment 2 aimed to further explore the validity of the CPM methodology as a measure of the body's endogenous pain-modulation system. Cognitive factors are known to play a part in affecting pain inhibition mechanisms, however, previous studies on the effect of distraction on CPM have only assessed the extent to which distraction affects participants' pain rating during the application of conditioning stimuli (Moont et al., 2010). Applying Experimental 1's CPM protocol of psychophysical pressure pain threshold as test stimulus and cold pressor task and hag holding task as conditioning stimulus, the aim of Experiment 2 was to quantify and compare the effect of modality-matching cognitive distraction tasks (as conditioning stimuli) on the magnitude of CPM index).

4.4 Experiment 2 – Methods

4.4.1 Participants

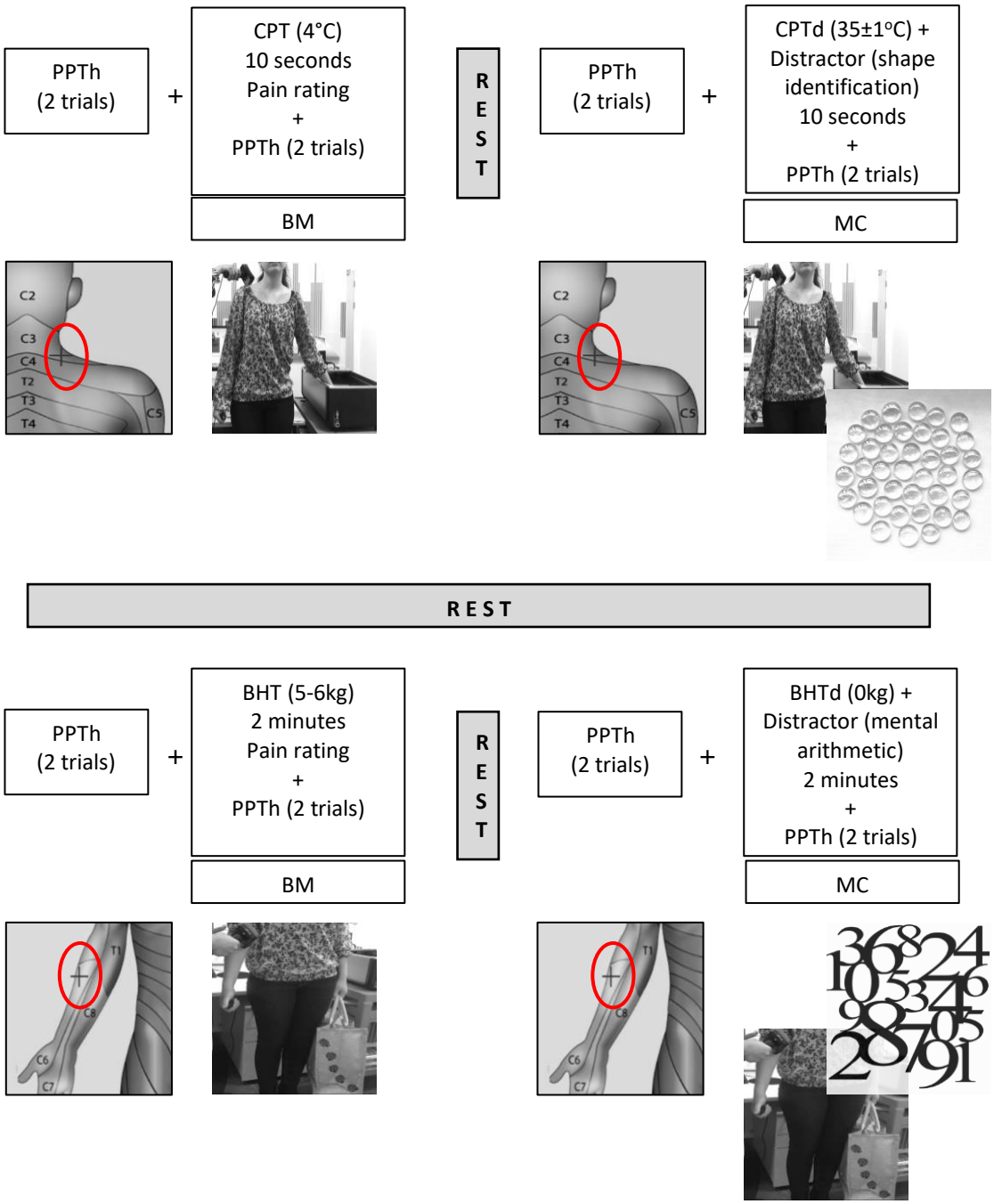
A separate sample of 124 healthy young adults from the university were recruited for this experiment and inclusion and exclusion criteria were the same as Experiment 1 (Appendix 7). Subjects gave signed informed consent (Appendix 4 – 6) and all procedures were approved by the Department of Psychology Research Ethics Committee. Of 124 participants, four participants were excluded due to the presence

of a non-malignant chronic pain condition (chronic back pain and migraines). In addition, two participants did not complete the sleep diary data and were excluded due to non-compliance with study procedure and missing data. The final sample for analysis was 118 participants; however, only 103 (87.29%) participants completed the full quantitative sensory testing protocol at both sessions. The overall study sample was consisted of 24 males and 94 females and included 61% Caucasians, 34% Asians and 5% Blacks, other, and mixed ethnicities. Those excluded from the final analysis did not differ from the final sample across most variables, although the four with chronic pain reported greater pain intensity.

4.4.2 Design and Procedure

The study used the same repeated measure design and order of procedure as described in Experiment 1 (4.2.2). Figure 6 details the different QST protocol used for Experiment 2. The order of conditioning stimuli and additional distracter tasks were randomly assigned for Visit 1 and remained the same for Visit 2.

Figure 6 CPM Experiment 2 – QST Protocol



Notes: Figure 6 presents the QST protocol for Experiment 2. QST procedure involved a baseline assessment of pressure pain threshold on the right upper shoulder (trapezius posterior) or right forearm (anterior brachoradialis) and then reassessment of pressure pain threshold after the application of the conditioning and distraction stimuli on the left side of the body.

QST (Quantitative Sensory Testing) PPTh (Pressure pain threshold) CPT (Cold pressor task) BHT (Bag holding task) CPTd (Cold pressor task distractor) BHTd (Bag holding task distractor) BM (Body Manikin) MC (Manipulation Check)

4.4.3 Measures

4.4.3.1 Pain measures

4.4.3.1.1 Conditioned pain modulation

The QST protocol to measure CPM response was similar to Experiment 1 (4.2.3). Pressure Pain Threshold was used as test stimulus and was combined with two conditioning stimuli – Cold Pressor Task and Bag Holding Task (with duration of bag holding increased to two minutes). Two additional distractor conditioning stimuli with perceptual similarity to the cold pressor and bag holding task were used to examine distraction effects.

Cold pressor task distraction stimulus

The cold pressor distraction stimuli (CPTd) aimed to be a pain-free task which mirrored the physical sensation of the standard cold pressor task (hand in water minus the cold pain sensation) whilst the participants were engaged in a distracting and attention demanding cognitive task adapted from Moont et al. (2010). Participants were asked to place their left hand in a water bath maintained at normal body temperature (35±1^{o}C) whilst identifying and remembering the figure of a set of 20 (26 during Visit 2) beads placed at the bottom of the water bath. The shape was standardised for every participant and they asked to describe the shape and recall the number of beads afterwards to ensure they had been counting. To avoid learning effects between the two visits, the shape was arranged differently for Visit 2 (trapezoid) than for Visit 1 (rhomboid).

Bag holding task distraction stimulus

The bag holding distraction stimuli (BHTd) was designed again as a pain-free version of the physical act of the bag holding task whilst the participants were engaged in a cognitively demanding distracting task. Participants were asked to hold up an empty shopping bag using the left hand and vocalise a mental arithmetic exercise adapted from Nilsen, Christiansen, Holmen, and Sand (2012). Participants were asked to subtract 3 (and 7 during visit 2) from 1000 successively. Evidently, subtracting 7 constitute a harder task than subtracting 3 but this was to avoid learning effect between the two visits and to ensure the task at Visit 2 was nevertheless still quite distracting.

4.4.3.2 Sleep measures and questionnaires

The same set of questionnaires was used as in Experiment 1 (4.2.3.2) (CSD, demographics questionnaire, PSQI, PCS, and BPI) (Appendix 8). Additional measures and questionnaires used in Experiment 2 are described below.

Pain rating

A VAS numerical rating scale [0 (no pain at all) to 10 (pain as bad as you can imagine)] was used to index pain intensity after application of the conditioning stimulus, immediately prior to PPTh reassessment. Participants were given additional training before the beginning of the experiments in the use of the pain rating scale.

Body Manikin (Lacey, Lewis, Jordan, Jinks, & Sim, 2005; Lacey, Lewis, & Sim, 2003; Margolis, Chibnall, & Tait, 1988)

A body manikin/ pain drawing was used to assess location and prevalence of pain after application of the conditioning stimulus. Participants were asked to shade their pain within the outlines of front and back views of a blank body manikin. This was visually inspected for the spread of the pain and the number of areas shaded was noted.

Manipulation check questionnaire

A manipulation check questionnaire was used at the end of the distraction task to assess participant's distraction levels and the extent to which the tasks were successful in drawing the participants' attention away from the test pain stimuli (Verhoeven et al., 2010). This was assessed using a numerical scale from 0 to 10 (0 = not at all; 10 = very much) to rate the perceived effect of the distraction task *("how much did this task distract you from the pressure pain"*).

4.4.4 Data analysis

Data analysis plan is the same as that reported for Experiment 1 (4.2.4) with some additional analyses. PPTh, CPM index, CPM magnitude and intraclass correlation coefficients (ICCs) were also calculated for the additional distraction stimuli and magnitude of the CPM effect was also compared across both conditioning and distraction stimuli. The pain ratings and drawings on the body manikin were examined visually to confirm that perception of pain after the application of the conditioning stimulus is present at the intended body areas. A t-test was used to compare the

perceived pain ratings during the cold pressor and bag holding stimuli and the perceived distraction effect during both distraction tasks.

4.4.5 Results

4.4.5.1 Descriptive statistics

Descriptive statistics for participants' demographics, questionnaire variables, and sleep diary averages are presented in Table 7.

Table 7 CPM Experiment 2 – Participant Characteristics

N = 118	M (SD)
Age	19.5 (2.09)
BMI (*n* = 113; due to missing data)	21.13 (3.84)
Sex (Female %)	79.66
Ethnic origins (Caucasian %)	61.01
Pain catastrophising (PCS total score)	17.83 (10.34)
Sleep variables	
Sleep disturbance (PSQI total score)	6.64 (1.28)
Sleep diary – week averages	
Sleep onset latency (mins)	21.64 (18.73)
WASO duration (mins)	9.75 (13.59)
Total sleep time (mins)	444.69 (72.23)
Sleep efficiency (%)	93.17 (6.28)

Notes: Means are presented with standard deviations in parentheses, unless otherwise stated.

4.4.5.2 Reliability of CPM response

Table 8 shows the Mean PPTh (KPa) and CPM index measurement at Visit 1 and Visit 2, the averages across both visits, CMP magnitude, and the ICC between Visit 1 and 2. In both experiments, the ICCs were mostly statistically significant. Pressure pain thresholds for all conditioning and distraction stimuli showed excellent ICC scores

across both sessions. CPM responses for cold pressor and bag holding stimuli respectively showed moderate and poor ICC scores across both sessions. CPM response for the bag holding and cold pressor distraction stimuli respectively showed moderate and poor ICC across both sessions.

4.4.5.3 Magnitude of CPM response across conditioning and distraction stimuli

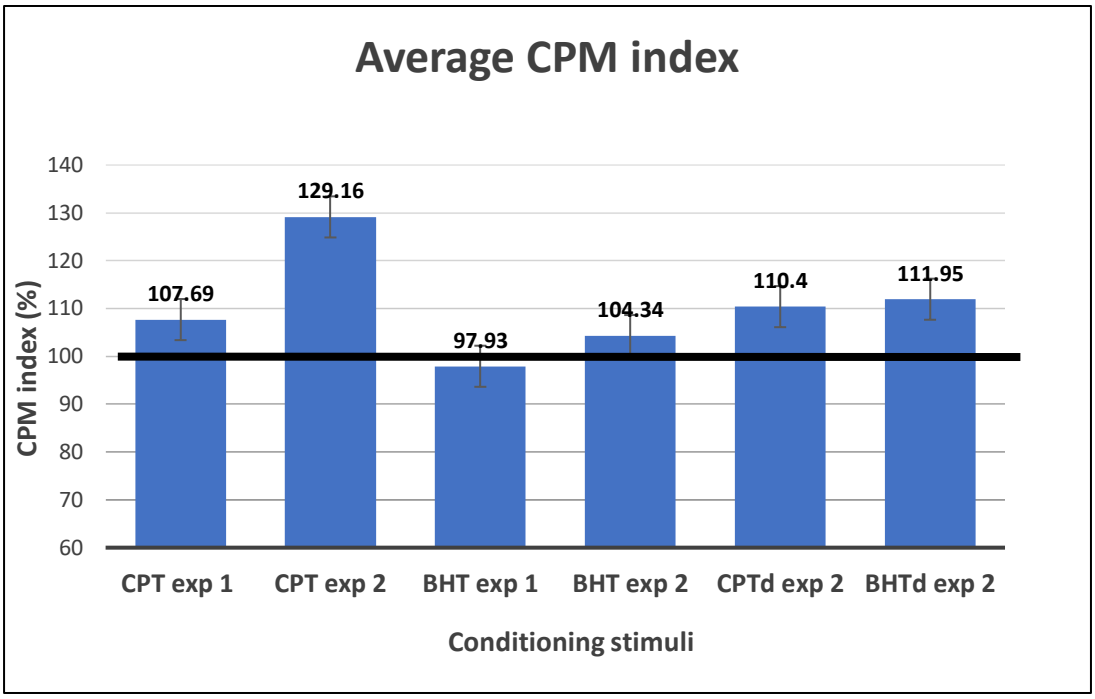
The magnitude of CPM effect was calculated across all conditioning stimuli used to elicit CPM response (Figure 7). All protocol showed CPM response; CPT stimulus elicited the strongest CPM response (29.16%) and the BHT showed a weak CPM response (4.34%). The distraction tasks also engaged the pain inhibition responses and elicited CPM response – cold pressor distraction tasks (10.40%) and bag holding distraction tasks (11.95%). The cold pressor task elicited stronger pain intensity than the bag holding tasks. Perceived pain rating during CPT (M = 5.8 SD = 1.95) was significantly higher than during BHT (M = 3.93, SD = 1.88), t (105) = 9.28, $p < .001$. The cold pressor distraction task (CPTd) had a lesser distraction effect than the bag holding distraction task (BHTd). Perceived distraction effect during CPTd (M = 3.46 SD 2.49) was significantly lower than during BHTd (M = 5.16 SD = 2.69) t (105) = -6.31, $p < .0001$.

Table 8 CPM Experiment 2 – PPTh (KPa), CPM index (%) and magnitude (∆CPM), intraclass correlations, pain and distraction (0-10) ratings

	Visit 1	Visit 2	Average	∆CPM	ICC
CPT – PPTh	178.74 (64.02)	166.77 (58.60)	172.76 (56.84)		0.83[0.74 – 0.86]*** p = 0.000
CPT – CPM index	129.88 (33.14)	128.44 (27.47)	129.16 (24.49)	**29.16%**	0.53[0.31 – 0.68]*** p = 0.000
CPT – pain rating	5.62 (2.17)	5.97 (2.05)	5.80 (1.93)		
BHT – PPTh	186.05 (52.67)	169.71 (56.52)	177.88 (50.39)		0.83[0.74 – 0.89]*** p = 0.000
BHT – CPM index	100.44 (19.71)	108.24 (23.25)	104.34 (16.96)	**4.34%**	0.29[-0.02 – 0.51] p = 0.033
BHT – pain rating	3.57 (1.97)	4.30 (2.17)	3.94 (1.85)		
CPTd – PPTh	185.37 (69.23)	164.83 (55.76)	175.10 (57.13)		0.77[0.62 – 0.85]*** p = 0.000
CPTd – CPM index	109.03 (22.57)	111.77 (23.94)	110.40 (15.95)	**10.40%**	-0.14[-0.67 – 0.23] p = 0.739
CPTd – distraction	3.40 (3.14)	3.53 (2.82)	3.47 (2.51)		
BHTd – PPTh	189.92 (60.66)	174.40 (55.88)	182.16 (53.67)		0.84[0.75 – 0.89]*** p = 0.000
BHTd – CPM index	111.44 (27.46)	112.45 (22.45)	111.95 (20.64)	**11.95%**	0.47[0.22 – 0.63]** p = 0.001
BHTd – distraction	4.63 (3.37)	5.71 (2.77)	5.17 (2.70)		

Notes: *p < 0.05 ** p < 0.01 *** p < 0.001. Number in [] are 95% confidence intervals. PPTh (Pressure pain threshold) CPT (Cold pressor task) BHT (Bag holding task) CPTd (Cold pressor task distractor) BHTd (Bag holding task distractor) CPM (Conditioned Pain Modulation) ∆CPM (percent magnitude of CPM effect), ICC (Intraclass correlation)

Figure 7 CPM Experiment 1 & 2 – CPM response across all conditioning and distraction stimuli



Notes: Average CPM index for cold pressor (CPT) and bag-holding (BHT) task conditioning stimuli and for the cold pressor (CPTd) and bag-holding distraction (BHTd) tasks across both Experiment 1 (exp 1) and Experiment 2 (exp2).

4.4.5.4 Association between CPM response, pain catastrophising, and sleep

To examine the association of sleep and pain catastrophising with the magnitude of CPM index, Pearson correlations were computed between PSQI scores, sleep diary variables, PCS scores, average PPTh, and CPM index (Table 9). These measures were not associated with CPM scores after Bonferroni correction. Although total sleep time showed a small positive correlation with CPM response (r = 0.2 [95%CI 0.023; 0.393], $p < 0.05$) and PPTh (r = 0.2 [95%CI 0.053; 0.418], $p < 0.05$).

Table 9 CPM Experiment 2 – Associations between pain catastrophising, sleep, and CPM response

N = 103	PSQI	SOL	WASO	TST	SE	PCS	CPM	PPTh
PSQI	1	.335	.127	-.187	-.329	.337	-.084	.032
SOL		1	.353	-.244	-.853	.075	.014	.027
WASO			1	-.269	-.644	.108	.106	-.080
TST				1	.470	.055	**.216**	**.244**
SE					1	-.110	.042	-.039
PCS						1	-.025	-.012
CPM							1	-.427
PPTh								1

4.4.5.5 CPM responders and non-responders across pain catastrophising and sleep

Table 10 reports sleep variables and pain catastrophising scores in CPM responders (n=91) compared with CPM non-responders (n = 12). CPM non-responders reported significantly less total sleep time. They also reported longer sleep onset latency and poorer sleep efficiency, but these were not statistically significantly after adjusting for the unequal sample sizes.

Table 10 CPM Experiment 2 – CPM non-responders and responders

	CPM Non-responders (n = 12)	CPM Responders (n = 91)	*Mann-Whitney U test*
PSQI (Sleep quality)	6.33 (2.77)	5.97(2.86)	U = 508.50, *z* = -0.389, *p* = 0.351
PCS (Pain catastrophising)	17.41(7.90)	17.78 (10.40)	U = 516.50, *z* = -0.303, *p* = 0.383
Sleep onset latency (SOL) (mins)	30.43 (28.86)	19.59 (16.41)	U = 422.50, *z* = -1.270, *p* = 0.104
WASO duration (mins)	9.11 (12.00)	6.56 (9.13)	U = 489.50, *z* = -0.581, *p* = 0.284
Total sleep time (TST) (mins)	404.28 (68.06)	453.39 (69.18)	U = 331.00, *z* = -2.210, *p* = 0.013**
Sleep efficiency (SE) (%)	90.64 (8.61)	94.03 (4.76)	U = 457.99, *z* = -0.915, *p* = 0.184

Notes: *Means are presented with standard deviations in parentheses ***p < 0.001 **p < 0.01 *p < 0.05*

4.5 Discussion

4.5.1 Summary of findings

In the present study, pressure pain threshold test stimulus with cold pressor task conditioning stimulus showed the strongest and most reliable CPM response, with bag holding stimulus showing a weak CPM response in this sample of healthy participants. CPM magnitude from this study (average 29%) is comparable to other studies using the same test and conditioning stimuli protocol in healthy participants; Oono et al. (2011) reported a CPM magnitude of 16.7% +/- 2.8 and Smith et al. (2007) reported 17% - 28%. Cognitive distraction had some effect on pain inhibition; the distraction tasks elicited CPM response, but the magnitude was only half as powerful compared to the cold pressor task conditioning stimulus. Compared to CPM responders, the few CPM non-responders showing impaired pain inhibitory responses reported greater pain catastrophising scores in Experiment 1. They also self-reported shorter sleep duration in Experiment 2.

4.5.2 Defining the characteristics of a conditioning stimulus to elicit CPM

Whilst it is generally thought that the test and conditioning stimuli to elicit CPM must be 'noxious', there is currently no standard approach and specification for determining this (Kennedy et al., 2016). Across these experiments, the findings show that the bag holding task either tended to show a reverse CPM response or a weak CPM response compared to the other conditioning stimulus used in the experiment. This could be because the pain elicited by the bag task was not enough to engage the descending pain inhibitory pathway. However, previous studies have found no relationship between self-reported pain rating of the conditioning stimulus and

magnitude of CPM effect (Granot et al., 2008; Nir et al., 2011). There was similarly no correlation here between participants' pain ratings for either cold pressor or bag holding task and extent of CPM response, although, pain ratings did show that the bag task was perceived as less painful than the cold pressor task.

Nir et al. (2011) had shown that increasing the intensity or perceived painfulness of the conditioning stimuli does not affect CPM response so long as the stimuli was initially perceived as painful. In their experiment, they used three different levels of exposure to the conditioning stimulus, hot water hand immersion at different temperature intensities (44.5^{o}C, 45.5 ^{o}C, and 46.5 ^{o}C) to induce mild, moderate, and intense pain levels. The findings showed that CPM was induced by the moderate and intense pain levels but there was no difference between the magnitudes of response between these two levels. This could also be due to the fact that the range of temperature assessed was not that wide. Furthermore, CPM was independent of perceived painfulness of the conditioning pain levels. In developing the bag holding task as a conditioning stimulus, it was important to bear in mind that the task was specifically developed as a behavioural task for chronic back pain patients and if the stimulus was too painful, it would not be tolerated by all participants. Moreover, if a conditioning stimulus is perceived as too painful by healthy participants, it will not have applicability within a chronic pain population. Indeed, other studies have used different modalities of conditioning stimuli to elicit CPM and these stimuli have often varied in intensity, exposure levels and in tolerability. The bag holding task may also have a different effect in a chronic pain population and thus should be tested within this population. The bag holding task was hoped to be a simple and accessible stimulus

to measure CPM and could still have utility to be used in a clinical setting to reduce participants burden associated with elaborate quantitative sensory testing procedures.

To ensure that both conditioning stimuli were tolerated and applied consistently for all participants and to ensure interpretability of the findings, the current experiment adopted a standard protocol and application of conditioning stimuli before reassessing the test pain, rather than until a specific numerical pain rating had been reached. Pain ratings were also assessed at both sessions to ensure that participants were pain free at both times. The application of both conditioning stimuli was also kept standard for all the participants, i.e. hand immersion in cold water for 10 seconds and bag holding for 2 minutes before reassessment of pressure pain threshold. Increasing time of bag-holding from 1 minute to 2 minutes in the Experiment 2 led to an increase CPM magnitude. Some participants may not have perceived the bag holding task as painful perhaps because of differences in muscle tone and physical strength which was not controlled for in the current study. Further amendment of the present experimental protocol may produce different results. For example, having a heavier bag to increase pain intensity and increasing the bag holding time could lead to an increase in the magnitude of CPM response. As a further consideration, the protocol could also be amended to involve continuous pain ratings whereby the duration of the bag-holding task for a participant would be determined by the level of pain achieved.

It is also possible that the musculoskeletal pain elicited by the bag-holding task is not a suitable conditioning stimulus to activate the necessary nerve fibres to engage the pain inhibitory pathway. Lautenbacher et al. (2002) explained that activation of the CPM response could be more dependent on the type and effect of nociceptive input produced by the conditioning stimulus, than the subjective painful sensation it elicits. Lewis et al. (2012) compared cold pressor task as a conditioning stimulus to ischemic pain (induced by tightening an inflatable cuff on the arm) and found that the cold pressor task was a more consistently reliable method of inducing CPM. They argued that compared to the direct focal pain from the cold pressor task, the diffuse effect of the ischemic pain may be the reason underlying why it did not consistently and reliably activate the descending inhibitory pathway. The same issue could be relevant here for the type of muscle pain evoked by the bag-holding task. Upon visual inspection of the body manikins, the spread of the pain induced by the bag holding task was generally more widespread (hand, wrist, forearm, shoulders, back, thighs, and legs). Whereas, spread of the cold pressor task pain was limited to the hand. Future studies can perhaps investigate and in a more quantitative manner how the spread of the pain produced by a conditioning stimulus could affect CPM response. Most of the conditioning stimuli used to assess CPM are usually quite direct and focal (cold, heat, or electrical pain). It may be interesting for future research to investigate the endogenous inhibitory pathways underlying cutaneous pain compared to more diffuse ischemic and muscle pain.

Physiological factors such as heart rate and blood pressure could also mediate the effect of a conditioning stimulus on CPM response. Shared brain structure

underlying pain modulation and cardiovascular regulatory systems include the anterior cingulate cortex, the amygdala and the functional connections between these cortical areas and descending pain pathways centres such as the periaqueductal grey are also implicated in autonomic cardiovascular activity (Bruehl & Chung, 2004). Chalaye, Devoize, Lafrenaye, Dallel, and Marchand (2013) found that increase in blood pressure induced by application of cold pressor task conditioning pain was positively correlated with magnitude of CPM response in a healthy population. Importantly, it could also be that conditioning stimuli inducing ischemic or muscular pain such as the bag holding task may not be engaging the cardiovascular reactivity necessary to drive a stronger pain inhibitory CPM response. It may be a worthwhile consideration for future studies to explore the mediating role of cardiovascular activity in CPM dysfunction and whether changes in blood pressure responses to different modalities of conditioning stimuli could be a cause or effect of CPM efficiency. Although, there are also additional challenges in getting reliable measure of blood pressure and heart rate; during the tasks, blood pressure and heart rate could also be affected by and interact with cognitive and psychological factors (e.g., attention, anxiety, and catastrophising).

4.5.3 The role of cognitive distraction in endogenous pain inhibition

Findings from this study revealed that a non-painful cognitively distracting conditioning stimulus can also induce CPM response. The magnitude of CPM effect across the distraction stimuli (10 – 11%) attests to the potency of the effect of cognitive distraction in driving a pain inhibitory effect however, the CPM magnitude was still lower than the cold pressor task conditioning stimulus (29%). The distraction

stimuli used in this experiment aimed to be comparable and easily interpreted alongside the conditioning stimuli. They were attention demanding, cognitively engaging, and involved the same perceptual modality as the cold pressor and bag holding task conditioning stimuli. Furthermore, in contrast to other studies evaluating effect of distraction on CPM (Moont et al., 2010), this study did not rely only on changes in pain ratings of the test stimuli to derive CPM response. Rather, a psychophysical criterion was used to determine difference in test stimulus (pressure pain threshold) prior to and after application of the conditioning stimulus. The distraction tasks were also consistently reliable across both testing visits, hence, expectation that the distraction tasks were not painful did not affect the pattern of results.

This study showed that the conditioned pain modulation phenomenon involves an act of directing attention towards the conditioning stimuli and thus the inhibitory effect elicited on the test stimuli. The findings show that the impact of a non-painful but cognitively distracting conditioning stimuli does not engage as much of an intensity to override and extend beyond the inhibitory effect expected from nociceptive sensations. These findings attest to the validity of the CPM as a measure of the central pain modulation but highlight that the process also comprises different functional physiological and psychological mechanisms. Distraction as a cognitive process is hypothesised to produce hypoalgesic effects by introducing stimuli to compete with noxious stimuli for attentional resources. The neural origin for this is perhaps from the decreased activation of pain-related activity in multiple cortical regions such as primary and secondary somatosensory cortices, anterior cingulate

cortex, insular cortex, regions of the frontal cortex, midbrain PAG (Bushnell et al., 1999; Frankenstein, Richter, McIntyre, & Remy, 2001; Petrovic, Petersson, Ghatan, Stone-Elander, & Ingvar, 2000; Tracey et al., 2002). In addition, the inhibition of incoming pain signals and behavioural pain reduction at the spinal cord level as proposed in the gate control theory of pain is perhaps also relevant (Sprenger et al., 2012). In relation to the CPM paradigm, distraction possibly causes hypoalgesia to the test stimuli, which in this case increases pressure pain threshold and drives a pain inhibitory response. Further work is needed to disentangle where the effects of distraction differs and separate from physiological CPM response. Studies should explore and specify the pain inhibitory mechanisms evoked by distraction hypoalgesia, how the sensory and affective components of pain perception and modulation work together and if this can be manipulated to control conditioned pain modulation response.

4.5.4 Associations between pain catastrophising and endogenous pain inhibition

In the present study, PCS scores was seen to be higher in CPM non-responders in Experiment 1 but not Experiment 2. This study assessed trait catastrophising whereas previous studies investigated the influence of pain catastrophising on CPM have asserted that situational catastrophising during the actual painful experimental procedure may be more related to increased pain ratings and impaired endogenous pain modulation (Goodin et al., 2009). In this study, PCS as a measure of trait pain catastrophising was not able to consistently discriminate between CPM responders and non-responders. Inconsistencies in the current finding may be explained by the relatively low level of pain catastrophising in this non-clinical healthy population.

There are perhaps more to consider about different aspects of cognitive, affective and behavioural factors underpinning pain catastrophising. Factors such as negative cognitive ruminations, misinterpretations of bodily sensations, exaggerated and inaccurate worries about pain, hypervigilance to pain stimuli may all have varying impact on different modalities and components of the quantitative sensory testing procedures to elicit CPM (Campbell et al., 2010; Quartana et al., 2009).

In an overview of studies that have assessed PCS score across different CPM protocols, only studies using electrical pain as test stimulus and cold pain as conditioning stimulus seem to show an effect for the influence of trait pain catastrophising (Nahman-Averbuch et al., 2016). However, the association was not in the expected direction, with higher pain catastrophising indicative of greater CPM response. Weissman-Fogel et al. (2008) on the other hand, demonstrated that higher trait PCS was related to diminished CPM response elicited by heat pain test stimulus and deep muscle pain conditioning stimuli. Inconsistencies across studies could be resulting from the fact that it is not clear which of the stimuli to elicit CPM is most affected by pain catastrophising. These authors further found that PCS scores were correlated with both the heat pain test stimulus and muscle pain conditioning stimulus but had no discriminative effect between test pain and conditioning pain. It could be that increased level of pain catastrophising in general leads to increased perception of the conditioning stimuli pain, away from the test stimuli and consequently resulting in a heightened CPM effect. Or it could be vice-versa, that pain catastrophising thoughts heighten perception of the test stimuli relative to the conditioning stimulus and attenuates CPM response. This again emphasises the need and importance of

standardising task instructions when telling participants where to focus their attention (on the test stimulus) during the procedure. In the current study, findings of higher PCS scores in non-responders may be related to increase perception of the pressure pain test stimulus but there was no means of determining this. Influence of pain catastrophising on CPM may be modality specific and have different effects on the test and conditioning stimulus. This underlines the need for future research to assess and consider the varying impact of different testing paradigms on specific underlying psychological factors.

4.5.5 Associations between self-reported sleep and endogenous pain inhibition

The current study provides some initial findings for disrupted self-reported sleep in those with impaired CPM response. Total sleep time seems to be correlated with CPM magnitude and lower in CPM non-responders than non-responders in Experiment 2. Other markers of sleep disturbance, namely sleep onset latency and wake after sleep onset duration were also higher in CPM non-responders in Experiment 2 but were not statistically significantly after adjusting for unequal sample sizes. These findings extend those other studies exploring the associations between sleep deprivation/restriction and pain perception and pain modulation. Schuh-Hofer et al. (2013) revealed the effect of one night of total sleep deprivation on objective pain measures in their 14 healthy participants in a cross-over design. They found lower cold, heat, and pressure pain threshold and mechanical pain sensitivity after the sleep deprivation condition compared to habitual sleep. Campbell et al. (2011) split healthy participants by self-reported sleep duration in past month and found that those reporting 6.5 hours or less reported subjective pain sensitivity and when subjected to

a 70-min application of heat and capsaicin nociceptive stimuli, they also showed physical signs of secondary hyperalgesia (higher pain sensitivity outside of the area the stimulus was applied to).

The mechanism underlying secondary hyperalgesia reflects descending pain inhibitory capability such as CPM and general disturbance of nociceptive modulation at the spinal cord level. Matre, Andersen, Knardahl, and Nilsen (2016) found similar results for hyperalgesia to heat pain used as a test stimulus in a CPM protocol. They used a cross-over design in which 22 healthy adults were assessed over 2 nights of habitual sleep, followed by 2 nights of 50% sleep restriction, based on the participant's reported habitual sleep length. The assessment was self-administered in the participant's home and involved an ambulatory EEG sleep assessment. A stronger CPM response was observed after the sleep restriction condition compared to habitual sleep. Notably, the test pain stimuli of heat pain threshold used in their study was perceived as significantly more painful after the sleep restriction condition compared to the habitual sleep condition. This finding suggests that it could be response to test pain that is dependent on the sleep duration effect, and indirectly influencing the overall CPM response.

Different types of sleep disturbance may also be implicated in central pain processing. Smith et al. (2007) found that it was an overnight forced-awakening sleep fragmentation protocol that led to attenuation of CPM response in their sample of healthy female participants. In their sleep restriction condition, similar to Matre et al. (2016) participants showed a tendency towards elevation of baseline test pain

pressure pain threshold and greater CPM response although this was not statistically significant. They explained that complex pain modulation processes such as CPM may be reflective of slow wave sleep loss as observed in the sleep fragmentation condition compared to the sleep restriction condition where there was no significant loss of slow wave sleep. Slow wave sleep usually responds weakly to sleep restriction protocols possibly due to increased sleep pressure (Akerstedt, Kecklund, Ingre, Lekander, & Axelsson, 2009). These preliminary findings reveal that those with pain regulation dysfunction also seem to show mild sleep disturbance and provide some support for the idea that sleep disturbance and disrupted sleep processes may be risk factors for greater pain disability.

4.5.6 Limitations of the experiments

The two experiments presented have some limitations that should be considered. First, participants were young healthy individuals undergoing laboratory based QST procedures and this may limit generalisability to general and clinical population. CPM procedures have been shown to be relevant across clinical chronic pain populations (Edwards, Dolman, et al., 2016; Valencia, Kindler, Fillingim, & George, 2013) and it would be important to further investigate the relevance of the bag-holding task in eliciting pain of certain focus and threshold that would trigger CPM responses. Second, gender differences and ethnicity were not examined due to the fairly homogenous sample. Males are thought to have more pronounced CPM effect and although this predominantly female sample still showed significant CPM response, the skewness in gender may affect findings. Furthermore, other potential confounding factors in females such as menstrual cycle was not controlled for

(Popescu, LeResche, Truelove, & Drangsholt, 2010; Wilson, Carvalho, Granot, & Landau, 2013).

Third, the experiments relied on self-reported natural sleep patterns and sleep disturbances and so causal interpretations cannot be drawn from these findings. However, there was the advantage of ecological validity from getting an aggregate of sleep report across the week using a standardised sleep diary to yield information about relevant sleep measures (SOL, WASO, TST and SE). Sleep parameters from standard self-reported sleep measures such sleep diaries remain an accurate assessment of sleep quality, even comparable to objective assessments (Carney et al., 2012; Lockley et al., 1999). Nevertheless, future experiments should endeavour to investigate and replicate findings of associations of sleep in CPM non-responders with a combination of both self-reported and objective measures of sleep using PSG and actigraphy. This would offer deeper insights into the multi-dimensionality of the sleep experience.

Lastly, there was a risk of inflated Type 1 errors given the large number of comparisons involved in both studies reported in this chapter. To correct for this, a Bonferroni correction (Bland & Altman, 1995) was applied and all correlations were adjusted to a $p < 0.001$. Correlations were observed between sleep onset latency and pressure pain threshold in Experiment 1 and between total sleep time and pressure pain threshold and conditioned pain modulation in Experiment 2. However these were non-significant once a blanket Bonferroni correction was applied to all analyses. It has been argued that the Bonferroni itself is quite a conservative test and with greater

number of tests and corrections, alpha levels may become set so small that sets up an eventuality for Type 2 errors and this may mean that important findings may be deemed as non-significant (Fiedler, Kutzner, & Krueger, 2012; Savitz & Olshan, 1995). Calculating confidence intervals for correlations provide another way to interpret effects based on magnitude of the correlation and likely size of the population effect. These recommendations were followed when reporting the results in this chapter, however, ideally, to keep the risk of Type 1 and 2 errors minimal, an increase in sample size would be needed to combat multiplicity corrections (Bender & Lange, 2001; Savitz & Olshan, 1995).

4.6 Conclusion

Conditioned pain modulation (CPM) has been found to be impaired in a range of chronic pain conditions and is commonly thought to be a key clinical marker of central pain inhibitory processes. Importantly, CPM reflects an interaction between physiological pathways and psychological cognitive processes. This study aimed to assess the validity of the CPM paradigm elicited using two different conditioning stimuli and to evaluate if efficiency and magnitude of CPM response vary as a function of cognitive distraction, pain catastrophising, and self-reported sleep in a healthy population. Findings reveal that different modalities of conditioning stimulus could be a key factor underlying CPM efficiency. Cognitive distraction also had some effect on pain inhibition; the distraction tasks elicited CPM response, but less magnitude compared to the cold pressor task. This provides further support for CPM as a robust physiological marker of central pain processing and inhibition. Evidence on the influence of pain catastrophising on CPM remains inconclusive but has highlighted the

possible varying impact of different CPM testing paradigms on specific underlying psychological factors.

The findings also provide insight that less efficient CPM response may be associated with self-reported daily sleep disruptions. This association is further tested in the next chapter and could have implications for understanding of sleep disturbance and pain processing in healthy individuals and clinical populations with chronic pain. In all, these experiments extend our understandings of the descending pain modulatory pathway and the neurobiological and cognitive influences on CPM response. Consequently, this enhances CPM's value as a predictive clinical marker of pain perception in both healthy and chronic pain conditions.

5 Objective and self-reported sleep, psychological functioning, pain responses, and inflammation in fibromyalgia and chronic back pain compared with healthy controls

5.1 Introduction

As explained in Chapter 1 (1.1), sleep is a dynamic form of restfulness that serves as a restorative process permitting the reorganisation of cortical neural activities and maintenance of various homeostatic processes. Complaints of sleep being "non-restorative" is common among people with chronic pain disorders, particularly in those with fibromyalgia. However, it is unclear why this is the case and what the underpinning mechanisms of non-restorative sleep are. This chapter presents a study that attempted to examine polysomnographic and self-reported sleep, physiological, and psychological characteristics of patients with fibromyalgia and chronic back pain, compared with pain-free controls.

5.1.1 Sleep architecture and spectral analysis in chronic pain conditions

As described in Chapter 2 (2.1), sleep electroencephalography (EEG) provides an electrophysiological analogue of the brain processes and neuronal activity during sleep and gives insight into features of the sleep process (Bjurstrom & Irwin, 2016). This understanding has helped to improve the knowledge of disrupted objective sleep in response to pain and in the pathophysiology of chronic pain conditions. PSG studies in those with chronic pain (notably fibromyalgia and arthritis) compared with healthy controls usually report disruption of sleep continuity as the most common alteration of sleep architecture. A comprehensive review of observational PSG studies in chronic

pain patients by Bjurstrom and Irwin (2016), revealed that individuals with a range of long term pain conditions (including fibromyalgia, chronic widespread pain, rheumatoid and osteoarthritis, ankylosing spondylitis, migraines, temporomandibular disorders, and other mixed chronic pain conditions) tend to report poor sleep. This included decreased sleep efficiency (SE), increased sleep onset latency (SOL), increased wake after sleep onset (WASO) and decreased total sleep time (TST) (Drewes et al., 1995; Lavigne et al., 2011; Rizzi et al., 2004; Roehrs et al., 2013; Sergi et al., 1999). Some alterations have also been noted in sleep architecture such as an increase of N1, some equivocal results for both an increase and decrease in percentage of N2 and reduction in deep sleep and REM sleep but this evidence was limited and not consistent across studies (Landis, Lentz, Tsuji, Buchwald, & Shaver, 2004; Rizzi et al., 2004; Sergi et al., 1999).

The emergence of new analytic techniques in sleep assessment further allows the use of spectral analysis to provide a quantitative measurement of the frequency analysis of different power bands of sleep EEG (2.1.1.2). For example, high frequency beta and alpha waves reflect arousal processes and are associated with higher cognitive activities during sleep and low frequency delta bands reflect deep slow wave sleep and the normal homeostatic processes maintaining sleep (Achermann, 2009; Campbell, 2009). Sigma waves reflect the sleep spindles observed in stage 2 sleep represent regulatory activities of the thalamic neurons for information relay from the arousal centres to the cortex. They are sometimes associated with unresponsiveness during sleep and perception of greater sleep depth by the sleeper (Feige et al., 2013; Halasz, Terzano, Parrino, & Bodizs, 2004). Moldofsky et al. (1975) were one of the first

to assess sleep microarchitecture in patients with fibromyalgia symptoms by visually inspecting and noticing increased alpha EEG in all NREM stages even in slow wave sleep, a stage that normally would be dominated by delta waves. This increase in alpha waves was consequently associated with greater reports of pain and fatigue. They also found that selective disruption of slow wave sleep in healthy subjects produced the same effect of increased alpha activities during the sleep period and subsequent reports of pain and fatigue the next day. Other studies reporting manually scored EEG alpha and delta waves in fibromyalgia patients have also reported increased alpha power in stages N2 and N3 and reduced delta power in these sleep stages (Drewes et al., 1995; Roizenblatt et al., 2001).

It is thought that this alpha-EEG anomaly is a marker for non-restorative sleep as it indicates central internal arousal mechanisms interfering with normal restful sleep and subsequently leading to subjective complaints of unrefreshed sleep (Drewes, 1999). In healthy individuals, when muscle and joint pain was experimentally invoked during sleep, this led to increased power in beta and alpha bands and reduced power in delta and sigma bands (Drewes et al., 1997). In insomniacs and those undergoing SWS deprivation, increased power for beta and sigma bands during sleep have also been noted (Spiegelhalder et al., 2012). Perlis, Giles, Bootzin, et al. (1997) also noted that in those with fibromyalgia, this alpha-EEG dysfunction reflects increased vigilance and arousability during sleep. This translates into a heightened state of perceptual sensitivity and increased awareness of environment and self, rather than the usual unconsciousness associated with sleep. However, the phenomenon is not distinct to fibromyalgia and it may not play a direct etiological role

in producing pain responses (Rains & Penzien, 2003). It has also been observed in other pain disorders such as rheumatic diseases (Drewes & Arendt-Nielsen, 2001) and by one study in chronic back pain patients (Staedt et al., 1993).

In spite of this accumulating evidence, alterations in sleep microstructure still need to be characterised to determine their clinical significance in chronic pain conditions. The majority of older studies have focused on manually scored analysis of alpha waves in sleep EEG and not utilised the recent technologies that allows for analysis of the other power bands. Furthermore, the focus of analyses has been specifically in alpha and delta bands. This has limited further comprehensive insights into the relevance of other power bands as markers of disruptions in sleep-maintaining processes. A study by Blägestad et al. (2012) assessed polysomnography sleep variables in 24 older adults with mixed chronic pain conditions (chronic back pain, rheumatoid arthritis, osteoarthritis, and fibromyalgia), compared with age- and sex- matched 19 healthy controls. They found differences in sleep variables investigated in this study, namely poorer sleep in the chronic pain group compared to the control group. Specifically, longer sleep onset latency and longer latency to N2, poorer sleep efficiency, longer wake time after sleep onset, and increased number of awakenings. Furthermore, spectral analysis revealed that the chronic pain groups showed lower delta power throughout the whole night, especially in the initial hours of sleep, indicating lower intensity of deep restorative sleep.

A doctoral thesis (Yeung, 2015) also compared polysomnography sleep characteristics in patients with fibromyalgia and osteoarthritis with healthy controls.

This was carried out with the aim to assess and evaluate the role of sleep microstructure especially the alpha-delta sleep anomaly as either a possible contributor to or consequence of pain experience. The study did not find differences in power bands except across sigma bands. The patterns of sleep microstructure were statistically similar in both chronic pain groups. Only psychological measures (trait anxiety and depression) better discriminated the chronic pain group from the healthy controls rather than sleep variables. Nevertheless, the study gives some insights into the association of the levels of cortical arousal reflected by these spectral power bands and sleep microstructure with dysregulation of sleep processes. However, the study only compared those with fibromyalgia and osteoarthritis and did not include other musculoskeletal conditions such as chronic back pain. Other similar studies with a focus on sleep microstructure abnormalities in pain conditions have mostly either been in mixed pain groups or exclusively in those with fibromyalgia.

Fibromyalgia is often readily investigated in relation to sleep especially since sleep problems accompany the somatic symptoms that characterises a diagnosis of fibromyalgia (1.3.1) (Clauw, 2014). However, to fully understand the nature of sleep across the full extent of pain conditions and a reliable view of the sleep-pain dynamic, it remains to be determined if association of sleep and pain varies across conditions and the extent to which sleep disturbances differentially affects pain experiences across different pain diagnosis. The pain that accompanies conditions like fibromyalgia and other rheumatic conditions are usually multi-factorial involving varying levels of central pain modulations processes. The interaction between sleep and pain may then differ with respect to the sensory, physiological, and behavioural aspects of a

condition such as chronic back pain (Drewes, 1999). Hence, further comparative investigations across different types of pain conditions would further corroborate extant findings and elucidate if there are differential occurrences of these sleep processes across different pain conditions and associations with pain experience.

5.1.2 Sleep and conditioned pain modulation in chronic pain conditions

Chapter 4 (4.5.1) of this thesis reported initial findings to suggest a relationship between disruptions in self-reported sleep (notably reduced sleep quantity) and impaired conditioned pain modulation (CPM) response. The current study aimed to combine self-reported sleep assessment with objective PSG sleep parameters to explore the extent of the association of patterns of sleep disturbances with measures of pain threshold and pain inhibition, specifically in those with chronic pain. Disinhibition of descending inhibitory pain pathways represents a significant pathophysiological alteration prominent in pain conditions and is implicated as a mechanism of hyperalgesia and central sensitisation in chronic pain conditions (Lewis et al., 2012). This impairment in pain inhibition may also be one of the key mechanisms linking the co-occurrence and interrelationship between sleep and pain. A study in patients with chronic temporomandibular joint disorder showed that impaired CPM may be associated with disrupted PSG measured sleep (Edwards et al., 2009). In these patients, a positive correlation was observed between polysomnography-verified total sleep time, sleep efficiency, and pain inhibitory CPM, assessed with pressure pain threshold as the test stimuli and with 4 °C cold water as conditioning stimuli. However, the study did not involve the use of a comparative healthy pain-free control group, hence the associations may be different for healthy controls and even those with a

different pain condition. Good sleep may be key to maintaining the function of endogenous pain modulatory systems and disruptions in optimal sleep processes may be a marker for an impaired pain inhibition response, but the differential effects of these associations across different pain conditions and compared to healthy controls require further examination.

5.1.3 Sleep and inflammatory processes in chronic pain conditions

Upregulation of peripheral proinflammatory cytokines (2.3) has been suggested as one of the most important factors linked to pain processing and subsequently also contributing to the development of chronic pain (Marchand, Perretti, & McMahon, 2005). Raised levels of inflammatory cytokines interleukin-6 (IL-6) and tumour necrosis factor alpha (TNF-α) are also typically elevated in sleep disorders that result in daytime fatigue and sleepiness, such as chronic insomnia, sleep apnoea and narcolepsy (Vgontzas et al., 1999; Vgontzas et al., 2002). In healthy adults, these cytokines are usually elevated after acute sleep deprivation and may mediate sleep propensity and fatigue the next day (Vgontzas et al., 1999; Vgontzas et al., 2004; Vgontzas et al., 2003). Haack et al. (2007) have also found that small peripheral changes of IL-6 levels even as little as 1pg/ml may be involved in the onset and facilitation of pain experienced following a prolonged phase of insufficient sleep. Their study used a sleep restriction protocol of 8 hours to 4 hours per night for 10 days in healthy participants sleeping from 23:00 to 03:00, compared to people in the control group who were not subjected to sleep restriction. Levels of C-reactive protein (CRP) serum levels were also elevated but not significantly different. Levels of other markers; plasma soluble tumour necrosis factor receptor p55 (sTNF-R p55), urinary

levels of prostaglandin (PG) metabolites D2 and E2, remained the same. Importantly, the study reported that self-reported bodily discomfort, tiredness, and fatigue also increased in the sleep restriction group and that the increased IL-6 levels were associated with these increased self-reported ratings. Meier-Ewert et al. (2004) also reported a similar pattern of findings with increased concentrations of CRP following total (88 hours) and partial sleep deprivation condition where sleep was decreased from 8.2 to 4.2 hours for 10 consecutive days and compared to normal sleeping control groups. These inflammatory markers were also correlated with self-reported levels of pain and discomfort.

In those with chronic pain, Heffner, France, Trost, Mei-Ng, and Pigeon (2011) assessed 25 patients with chronic back pain present for 6 months or longer compared with 25 age-matched and sex-matched healthy controls without chronic pain. Sleep was assessed using the PSQI and they found the pain group reported more sleep disturbances, greater daytime dysfunction, and lower habitual sleep efficiency compared with controls. In this group as well, lower sleep quality was associated with raised IL-6 levels. IL-6 was further related to affective ratings of pain as 'tiring' and 'exhausting', and this association was mediated by sleep quality. Poor sleep quality (PSQI global scores) has also been shown to be associated with greater pro-inflammatory cytokine levels: IL-1β, IL-6, and TNF-α in a study of 60 women with chronic fatigue syndrome and/or myalgic encephalomyelitis (Milrad et al., 2017).

Regarding the other inflammatory cytokines linked with sleep, a systematic review and meta-analysis by Irwin et al. (2016) did not find a relationship between

sleep disturbances or sleep duration with TNF-alpha. The review also did not consider the cytokine IL-1β since not enough studies were done to confirm its associations with sleep disturbances. Overall, the consistency of which cytokines are most implicated in sleep disturbances reported in chronic pain is still debated. Few studies have specifically explored the concurrent associations between sleep, pain, and inflammation levels by simultaneously assessing a range of relevant inflammatory cytokines, pain inhibition impairment, and sleep disturbances in pain conditions compared with healthy controls. A first step would be observing how levels of these markers of inflammation differ across chronic pain groups. This could be another step clarifying if there are indeed associations between chronic pain, elevated inflammatory markers, sleep disruptions, and the pain experience.

5.1.4 Aims of the current study

This current study therefore intended to use a range of self-reported and quantitative measures to observe and assess the associations between sleep and pain parameters across two different chronic pain populations (fibromyalgia and chronic back pain) compared with healthy controls. As an attempt at unravelling the mechanisms underlying the interrelationship between sleep and pain, the study also considered the association between sleep and pain inhibition pathways, and compared levels of inflammatory cytokines across the groups.

It was hypothesised that the chronic pain group (fibromyalgia and chronic back pain) would show greater sleep and functioning disturbances compared with healthy controls. However, the specific direction of the associations between sleep, pain, and

inflammation level were exploratory since studies have not considered the associations between all these variables in these specific chronic pain groups compared with healthy controls.

5.2 Methods

5.2.1 Design

The current study is quasi-experimental comparative study comparing three groups – fibromyalgia patients, chronic back pain patients and age-matched healthy controls free of chronic pain. Ethical approval for the study was granted by the University of Warwick Biomedical & Scientific Research Ethics Committee (BSREC) and NHS Research Ethics Service Committee East Midlands – Leicester (REC reference: 14/EM/1138) (Appendix 9).

5.2.2 Participants and recruitment

Participants in the study included 26 adults and aimed to be age and sex-matched. This included nine fibromyalgia patients (M = 45.44, SD = 8.17, females = 7), eight chronic back pain patients (M = 49.50, SD = 12.35, females = 7) and nine participants in the healthy control group (M = 49.75 SD = 10.07, females = 3). The groups were age-matched (within 5 years) at the group level rather than individual level based on mean and counts observed during the recruitment process. The chronic pain group were recruited first and consequently the healthy controls were recruited to reflect a similar age distribution observed in the chronic pain group. The inclusion and exclusion criteria are presented below.

Inclusion criteria for chronic pain patients (fibromyalgia and chronic back pain) were as follows:

- Adults 18 – 65 years of age
- English-speaker with ability to understand and sign the consent form and complete the study.
- Medical diagnosis of fibromyalgia OR chronic back pain present for more than 6 months.
- No other malignant (e.g., cancer pain) or non-malignant co-morbid chronic pain condition (e.g., arthritis, migraines etc.)
- Non – smoker

An additional inclusion criterion for pain-free healthy controls was the:

- Absence of diagnosis of any malignant (e.g., cancer pain) or non-malignant chronic pain condition present for more than 6 months (e.g., arthritis, chronic back pain, fibromyalgia etc.)

Exclusion criteria for all groups were as follows:

- Presence of acute pain due to injury, surgery etc.
- Presence of any debilitating or life threatening medical condition (e.g., cancer, HIV, dementia etc.) or diagnosis of learning disability or recurrent history of psychiatric disorder that would impede the ability to give consent and full participation in the study
- Pregnant or breastfeeding females
- Shift worker with irregular sleep pattern
- Diagnosed with an organic sleep disorder (e.g., sleep apnoea, periodic limb movement disorder, narcolepsy) or periodic leg movements during sleep (PLMS)

arousal index per total sleep time outside of the “mild” range (5-25 per hour) or a sleep apnoea hypopnea (AHI) index per total sleep time of greater than the “mild” range (5-14) per hour as per AASM criteria and as determined on adaptation and screening PSG on Night 1 of the lab session (Berry et al., 2017).

- Currently receiving psychological treatments for pain/insomnia or enrolled in drug trials

Exclusion criteria specifically for the quantitative sensory testing and CPM procedure as additional precaution for participants’ safety and wellbeing and based on von Baeyer et al. (2005) guideline as used in the study described in Chapter 4 (4.2.1):

- History of cardiovascular disorder/heart disease
- History of fainting or seizure
- History of frostbite
- History of Reynaud’s phenomenon (hands gets white then blue on exposure to cold, then red on warming)
- Open cut, sore or fracture on arm or hand

5.2.3 Procedure

Figure 8 details the recruitment procedures for the study. As an avenue for recruitment for the chronic pain groups, patients were approached and recruited from the pain management and rheumatology clinic of the local hospital (UHCW). Recruitment posters were distributed in the waiting rooms of the clinic and the researcher was also present at the clinic with permission to approach interested patients after their outpatient appointment. Eligible participants screened using inclusion and exclusion criteria checklist were provided with further information for

participating and enrolling in the study. The researcher also collaborated with consultants from both clinics to accept referrals of potentially suitable patients with fibromyalgia or chronic back pain.

The healthy controls and some of the chronic pain participants were drawn and recruited from the local community through distribution of recruitment posters, the local chronic pain support groups and word of mouth. The laboratory also had an online database where individuals with or without chronic pain interested in participating in a study can submit interest by providing their contact details. Individuals from this database were contacted with an invitation email and sent further information about the study if they were eligible. For individuals with chronic pain recruited through the database and from the community, with their consent their GP was contacted to confirm their diagnosis of fibromyalgia or chronic back pain.

If a participant responded and met the inclusion and exclusion criteria for the study as confirmed either face to face or telephone screening using the screening checklist (Appendix 13), they were provided with further information about the study and sent a copy of the Participant Information Sheet (Appendix 11) by email. The researcher was contactable to answer any questions and address any concerns and each participant was given at least a 24-hour period after being given study information to consider taking part in the research. Once they were happy to take part, they were invited for the baseline and assessment visit. At this visit, the experimental procedures involved in the study was explained again in detail to the participant and written informed consent (Appendix 10) was taken.

Figure 8 Sleep and chronic pain – Recruitment flowchart

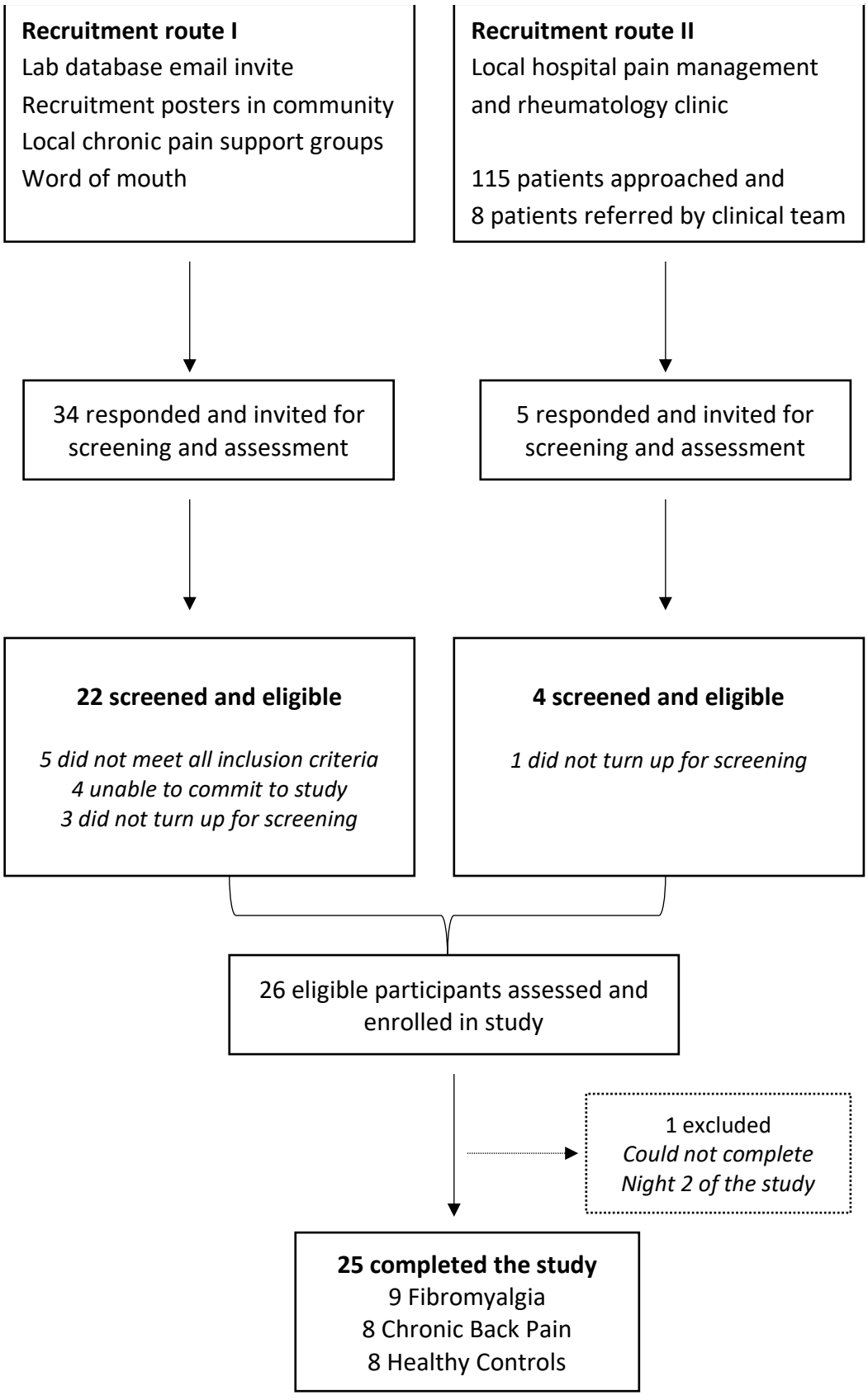


Figure 9 Sleep and chronic pain – Study schedule

Assessment Visit **and** **Informed Consent**	Screening – Duke Structured Interview for Sleep Disorders Questionnaires – Demographics, pain history, BPI, PCS, PVAQ, PSWQ, BDI, STAI, POMS, SSS, PSQI, PSAS, DBAS-16, APSQ, MQS Overview and practice of lab session procedures Instruction for actigraphy and diaries
Baseline Week	Complete Consensus Sleep Diary (CSD), pain and mood rating Actigraphy monitoring

Lab Session Night 1	Arrives at lab Actigraphy check Pain rating	Adaptation and screening PSG Actigraphy monitoring	
Lab Session Day 1	**Morning questionnaire** CSD **30 mins after wake** • QST – CPM	**Cognitive Tasks** PVT	**Day Leave** No strenuous exercise No naps No caffeine No alcohol

Lab Session Night 2	Return to lab Actigraphy check Pain rating	PSG assessment Actigraphy monitoring	
Lab Session Day 2	**Morning questionnaire** CSD **30 mins after wake** • Blood Sampling • QST – CPM	**Cognitive Tasks** PVT	End of study and debrief

Notes: Figure 9 presents screening, assessment, and lab session schedule. CSD – Consensus Sleep Diary, PSQI – Pittsburgh Sleep Quality Index, DBAS-16 – Dysfunctional Beliefs & Attitudes about Sleep, APSQ – Anxiety & Preoccupation about Sleep Questionnaire, PSAS – Pre-Sleep Arousal Scale, SSS – Stanford Sleepiness Scale. MQS– Medication Quantification Scale, BPI – Brief Pain Inventory, PCS – Pain Catastrophising Scale, PVAQ – Pain Vigilance & Awareness Questionnaire. PSWQ – Penn State Worry Questionnaire, STAI – State Trait Anxiety Inventory, BDI – Beck Depression Index, POMS – Profile of Mood States. PVT – Psychomotor Vigilance Task, QST – Quantitative Sensory Testing, CPM – Conditioned Pain Modulation, PSG – Polysomnography.

5.2.4 Study schedule

5.2.4.1 Baseline assessment

At the assessment visit, a further screening interview was carried out using a version of the Duke Structured Interview for Sleep Disorders Schedule (Edinger et al., 2009) adapted by the lab team for Diagnosis and Statistical Manual of Mental Disorders 5th Edition (DSM-V) and International Classification of Sleep Disorders 2nd Edition (ICSD-3) (2.1.3). This was used to establish that individuals have no other medical illnesses, psychiatric conditions, organic sleep disorders (e.g., sleep apnoea, narcolepsy, restless leg syndrome/periodic limb movement syndrome), or strong dependency on medication and substances that could be contributing to any reported or unknown sleep disturbance asides from insomnia. After this interview, eligible participants were also asked to complete a questionnaire pack (Appendix 14).

The schedule of the laboratory session was then explained to participants and they were given instructions and overview of the procedures that they will be performing during the study. Specifically, for the quantitative sensory testing (QST), they were given a practice trial opportunity to adjust to the experimental procedure. This was essentially a short training session to minimise noise due to unfamiliarity and other confounding as it would familiarise participants with the sensation of the experimental stimuli, namely the pressure pain from algometer and cold-water bath, and to explain the concept of QST and terms such as ‘pain threshold’ as described in Chapter 4 (4.2.3.1).

At this visit, participants were also trained in how to complete a week of sleep diary and pain diary prior to the laboratory session and given instructions for the actigraphy monitoring. They were to complete the sleep diary upon waking and the pain diary in the evening before sleeping. They were also to wear the actigraphy device on the wrist of their non-dominant arm continually, only to be taken off in instances such as bathing or swimming as the device was not water-proof. They were instructed to press the device marker upon light out (start of the sleep period) and getting up (end of the sleep period). The sleep and pain diary were used to gain a record of an individual's baseline sleeping and waking times and related information about their sleep, daily mood, pain and medication use. The actigraphy also provided objective sleep data and served as a further screening measure and to rule out any unreported irregular sleep patterns (caused by shift-work, jetlag or any other cause of unusually early/late bedtime and wake time). In order to observe a true reflection of the participants' habitual sleep, participants were asked not to change their usual medication or sleep-wake pattern prior to the laboratory session. The use of stimulants and substances that may influence sleep were not directly restricted during the baseline week as again the aim was to capture an unfiltered and unadulterated typical week for the participants, but there were more specific restrictions given during the lab sessions.

5.2.4.2 Laboratory session

The laboratory session was carried out in the sleep and pain laboratory within the university. Participants stayed in the laboratory for two consecutive nights and

mornings and underwent two overnight polysomnography procedures, quantitative sensory pain testing and other physiological, cognitive and psychological assessments as detailed in the study schedule (Figure 9). The first night of the laboratory session consisted of a PSG screening to detect the presence of sleep disorder such as parasomnias, sleep apnoea, and periodic limb movement syndrome. During the second day (Lab Session Day 1), after the quantitative sensory testing session, participants could leave the lab for the day and were advised to refrain from strenuous exercise, naps and consumption of caffeine and alcohol that could affect their sleep. They returned to complete the second night of PSG monitoring and subsequent procedures the next morning. After the end of study (Lab Session Day 2), participants were reimbursed with gift vouchers and travel expenses directly incurred by participation in the study. Participants were provided with an oral and written debrief (Appendix 12) of the rationale, purpose, design, and implications of the study. After data analysis, participants were also sent a brief description and summary of their sleep pattern overnight and a result summary of the study in lay terminology.

5.2.5 Measures

5.2.5.1 Pain measures

Conditioned pain modulation (CPM)

The QST protocol for assessing CPM was exactly as described in Experiment 1 in Chapter 4 (4.2.3.1). CPM methodology assesses pain inhibition and involves the application of the test pain stimulus (pressure pain threshold) gradually increasing pressure (approx. 30 KPa/s) on right forearm (anterior brachoradialis) and combined with two conditioning pain stimuli applied to the contralateral (left) side of the body:

Cold pressor task (CPT) and Bag holding task (BHT). The order of applying the conditioning stimuli to assess CPM response was randomly assigned for the Lab Session Day 1 and remained the same for Lab Session Day 2.

Pain and mood diary

Record of daily level of average and current pain intensity and mood on a 0 (not at all) to 10 (pain as bad as you can imagine) rating and filled in the evening before sleep.

Demographics and Pain Characteristics

This included general questions to capture demographics and pain history (pain location, pain duration, history of any pain-relieving interventions).

Pain Catastrophising Scale (PCS) (Sullivan, 2009; Sullivan et al., 1995) – as in Chapter 4 (4.2.3.2)

Medication Quantification Scale version 3 (MQS-III) (Harden et al., 2005)

This is a record of the name and dosage of all the medications the participant is currently using. It is used to quantify and monitor the variety of medications used to treat a variety of chronic pain conditions. In this study, it was used to quantify and compare the current medication regimen of the chronic pain participants. It provides a score based on three aspects of medication regimen; the drug class, dosage level and detriment weighting. Detriment weight refers to the potential risk of the drug class to produce acute or chronic adverse effects in those with chronic pain (e.g.,

system toxicity, abuse potential, tolerance and dependence, sleep problems). A detriment weight is given for each drug class and these were determined by a survey of physician members of the American Pain Society. The measure consists of 22 drug classes used in the chronic pain management (e.g., nonsteroidal anti-inflammatory drugs [NSAIDs], antidepressants, benzodiazepines, opiates). An MQS score is calculated for each medication by multiplying value for the detrimental weight by score given for dosage scores based on current prescribing recommendation obtained from the British National Formulary (Joint Formulary Committee, 2017). Scores for each medication are then summed to give a total overall score and a single numeric value to describe a participant's medication profile. Higher values reflect increased medication use and the 'relevant risk' of their current medication regime.

Brief Pain Inventory (BPI) (Cleeland & Ryan, 1994)

The BPI is a self-report questionnaire administered to assess the severity of pain and a measure of pain-related interference. Of the 4 items assessing pain severity, the numerical rating scale of current pain rating [0 (no pain at all) and 10 (pain as bad as you can imagine)] was utilised to index present pain intensity in the current study. The interference sub-scale assesses the extent to which pain interferes with 1) general activity; 2) mood; 3) walking ability; 4) work both inside and outside the home; 5) relations with people; 6) sleep; and 7) enjoyment of life. Participants were asked to rate the 7 items between 0 (does not interfere) and 10 (interferes completely) during the past week. A total pain interference score is calculated as the average of the 7 items. The interference subscale for sleep was also examined separately for the current study. A higher average interference subscale score

indicates greater interference in daily life due to pain. The BPI has been shown to have good internal consistency (Cronbach's α = .88), and high sensitivity to the effect of treatment

Pain Vigilance and Awareness Questionnaire (PVAQ) (McCracken, 1997)

The PVAQ is a 16-item measure of pain-related awareness and vigilance and assesses preoccupation with or attention to pain. Participants are asked to rate on a scale of 0 (never) to 5 (always) how items such as "I focus on sensations of pain" is reflective of them and their behaviours. Total score for the PVAQ ranges from 0 – 80, with a higher score indicating a greater preoccupation to attention to pain sensations. The scale has shown reliability and validity in chronic pain populations with high internal consistency (Cronbach alpha = 0.83 – 0.86) and test–retest reliability over two weeks (r = 0.80) and correlations with similar constructs such as the pain catastrophising scale , pain anxiety symptoms scale, and Tampa scale of kinesiophobia (Roelofs, Peters, McCracken, & Vlaeyen, 2003).

5.2.5.2 Sleep measures

Actigraphy as described in Chapter 2 (2.1.2)

Polysomnography as described in Chapter 2 (2.1.1)

During the recording, participants were monitored continuously for duration of time similar to their normal sleep schedule. This was determined based on the average of habitual bedtime and wake time recorded using the actigraphy and sleep diary data collected during the baseline screening week.

Sleep Scoring as described in Chapter 2 (2.1.1.1)

Spectral Analysis as described in Chapter 2 (2.1.1.2)

Consensus Sleep Diary (CSD) (Carney et al., 2012) – as in Chapter 4 (4.2.3.2)

Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989) – as in Chapter 4 (4.2.3.2)

Dysfunctional Beliefs and Attitudes about Sleep (DBAS-16) (Morin, Vallières, & Ivers, 2007)

The brief version of the DBAS contains 16 items for the assessment of general negative beliefs and attitudes about sleeplessness, perceived consequences of insomnia, and control of sleep habits such as (e.g., "I need 8 hours of sleep to feel refreshed and function well during the day"). DBAS-16 was used because it has proven to be as reliable and valid as the original 30-item version, but shorter and briefer thus less burdensome to complete. Participants were asked to rate their level of agreement with each statement between 0 'strongly disagree' and 10 'strongly agree'. Scores are summed and averaged across the 16-items to reflect possible score of between 0 - 10 and a higher average score is indicative of more strongly held negative beliefs about sleep. The DBAS-16 has demonstrated acceptable internal consistency (Cronbach's $\alpha \geq .77$), temporal stability ($r = .83$) over a 2-week interval and concurrent validity (correlation with Insomnia Severity Index: $r = .45$).

Anxiety & Preoccupation about Sleep Questionnaire (APSQ) (Tang & Harvey, 2004)

Sleep-related anxiety was assessed using the 10-item APSQ which includes scale items such as "I worry about my loss of control over sleep". Participants were asked to reference the previous month and rate their agreement to each item between 1 (not true) and 10 (very true). The total calculated score is between 10 and

100; higher total scores indicate greater sleep related anxiety. The APSQ has shown good internal consistency (Cronbach's α = .92) and concurrent validity with both measure of sleep disturbances (Pittsburgh Sleep Quality Index: r = .44) and anxiety (Beck Anxiety Inventory: r = .37).

Pre-Sleep Arousal Scale (PSAS) (Nicassio, Mendlowitz, Fussell, & Petras, 1985)

This is a 16-item self-report questionnaire to measure the state of cognitive (e.g. worrying and racing mind) and somatic (e.g., heart racing and muscle tension) manifestations of arousal prior to falling asleep. The scale is scored on a 5-point scale (1 = not at all – 5 = extremely) to reflect how strongly an individual experience each symptom as they try to fall sleep. The scale is computed to provide a total and summary score for each subscale (cognitive and somatic). Scores for each subscale range from 8 – 40, higher score reflecting increased presleep arousal. The scale has shown good internal consistency in normal sleepers and insomniacs for both cognitive and somatic subscales (Cronbach's α ranging from 0.67 – 0.76 and 0.81 – 0.84). Test-retest reliability over three weeks were also r = 0.72 for cognitive and r = 0.76 for somatic subscales. It has shown good correlation with sleep indices of sleep onset latency, overnight awakenings, and self-reported measures of sleep disturbances.

Stanford Sleepiness Scale (SSS) (Hoddes, Zarcone, Smythe, Phillips, & Dement, 1973)

The SSS is 8-point Likert scale to quantify self-reported changes sleepiness for any time period. It consists of 7 statements denoting increasing degrees of sleepiness ranging from "feeling active, vital alert, or wide awake" (score = 1) to "no longer fighting sleep, sleep onset soon and having dream-like thoughts" (score = 7). The

measure has shown test-retest reliability over the period of day (r = 0.88) and correlation with vigilance tests and other standard measures of performance and is indicative of the effect of acute sleep loss.

5.2.5.3 Blood sampling

Blood samples were taken from 18 participants, the remaining participants either had poor veins (n = 3), felt faint during the blood sampling procedure (n =2) or did not consent to have blood samples taken (n = 3). Blood samples were taken during the second morning of the lab session. The samples were all taken in the morning between 06:00am – 09:00am to minimise the influence of circadian and diurnal variations in circulating levels of inflammatory markers (Keller et al., 2009; Meier-Ewert et al., 2001; Zhou, Fragala, McElhaney, & Kuchel, 2010). Participants were in a sitting position with arms elevated and blood samples were obtained through venepuncture using a Vacutainer (plastic hub, a hypodermic needle and a vacuum tube) into two 5mls blood collection tube. The researcher completed training in venepuncture and the procedure was carried out according to the relevant University's Health and Safety and Human Tissue Authority guidelines and NHS ethical approvals and clinical practice guidelines (Appendix 9). The collected blood samples were transferred by fast courier within 1-2 hours to the biochemistry laboratory at University Hospital Coventry & Warwickshire (UHCW).

At the lab, the samples were allowed to clot at room temperature for up to 2 hours until centrifuged and plasma was extracted into aliquots and frozen and stored at −80 °C until assayed for expression of intracellular inflammatory cytokines (IL-6,

hsCRP, TNFα, IL-1β) at the end of the study. Analysis of hsCRP was carried out on the main automated Roche/Hitachi cobas c system used in the UHCW biochemistry lab according to manufacturer's instructions. The levels of cytokines were assessed in the University of Warwick CSRI Medical School unit within UHCW, with high sensitivity ELISA MSD technology Proinflammatroy Panel 1 (humans) assay kit. Samples were assayed in duplicate and according to the manufacturer's (Meso Scale Discovery) instructions. Appendix 15 further details the inter- and intra assay coefficients of variability to test the precision and sensitivity of the immunoassay test results.

5.2.5.4 Cognitive task

Psychomotor Vigilance Task (PVT) (Dinges & Powell, 1985)

This is a sustained-attention reaction timed task used to assess vigilance levels. It is widely used, methodologically reliable and versatile assessment of vigilance as it is brief and devoid of practice and learning effects (Loh, Lamond, Dorrian, Roach, & Dawson, 2004). For the task, participants were asked to sit in front of a Lenovo ThinkVision LT2934z 29-inch display computer monitor with a 2560 x 1080 resolution and the PVT task was administered from The Psychology Experiment Building Language (PEBL) test battery computer software (Mueller, 2014; Mueller & Piper, 2014). Duration of the task was set to 5 minutes and the participants were asked to press the spacebar button when the stimulus (a red dot) appears. The circle stimulus appeared for each trial randomly at delays between 2 and 12 seconds, and participants were told to press the spacebar as quickly as possible. Derived variables from the task were reaction time (RT) (in milliseconds) and lapses of attention (% number of times relative to number of trials where reaction time was > 500 ms).

5.2.5.5 Psychological characteristics

Penn State Worry Questionnaire (PSWQ) (Meyer, Miller, Metzger, & Borkovec, 1990)

The PSWQ is a trait measure of worry. Its 16-items rate how typical sentences such as "Once I start worrying I cannot stop" on a scale of 1 (not typical of me) to 5 (very typical of me) and gives a total score ranging from 16 – 80. Higher scores reflect a greater tendency to worry. The scale has shown reliability and validity with high internal consistency (Cronbach's α >0 .9) and test–retest reliability over 8-10 weeks (r = 0.92) and is correlated with other psychological measures on heightened anxiety levels and depression.

Profile of Mood States - Short (POMS – Short) (Curran, Andrykowski, & Studts, 1995; McNair, Lorr, & Droppleman, 1971)

The POMS-Short is a 36-items rating scale to assess transient and fluctuating affective mood states. The POMS assesses both positive and negative affective states. The POMS items can be computed into subscales – Anger-Hostility, Confusion-Bewilderment, Depression-Dejection, Fatigue-Inertia, Tension-Anxiety, and Vigour-Activity. The scale has shown excellent internal consistency of subscales (Cronbach's α 0.76 – 0.95) in both healthy and clinical populations and has shown correlations with other measures of mood and affective states. In the present study, the global indices of negative affect (NA) (Anger-Hostility + Confusion-Bewilderment + Depression-Dejection + Fatigue-Inertia + Tension-Anxiety) and sub-index of Fatigue-Inertia were calculated for analysis.

State-Trait Anxiety Inventory (STAI-Form Y) (Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983)

The STAI is a self-report measure of anxiety, with twenty items assessing trait anxiety (e.g., I am tense) and 20 items assessing state anxiety (e.g., I worry too much over something that really doesn't matter. These items are assessed on a four-point scale from 1(not at all/almost never) – 4 (very much so/almost always). Score for each trait and state subscales ranges from 20 – 80 with higher scores suggesting greater levels of anxiety. The scale has shown reliability and validity with high internal consistency (Cronbach's α 0.86 – 0.95) and test–retest reliability over 2 months (r = 0.65 – 0.75).

Beck Depression Inventory (BDI-II) (Beck, Steer, & Brown, 1996)

The BDI-II is a widely used 21-item self-report inventory used for measuring the severity of depression and assessment of symptoms. It contains items related to depressive symptoms such hopelessness, feelings and thoughts of guilt and physical symptoms such as weight loss and fatigue. Response for each item ranges from 0 – 3 to reflect increasing intensity of symptoms. Total score ranges from 0 – 63, higher scores indicative of more severe depressive symptoms. The following cut-offs have been suggested for the BDI-II: 0–13: minimal depression; 14–19: mild depression; 20–28: moderate depression; and 29–63: severe depression. The scale has shown reliability and validity with high internal consistency (Cronbach's α = 0.91) and test–retest reliability over one week (r = 0.93).

5.2.6 Data analysis

5.2.6.1 Power calculation

A sample size calculation was performed using G Power – a statistical software specifically designed for doing power and sample size calculations (Faul, Erdfelder, Lang, & Buchner, 2007). No other study has specifically considered differences across sleep in the three specific groups proposed for this study using all the objective PSG sleep parameters. Hence, the theoretical rationale for sample size calculation was based on the sleep parameter of sleep efficiency. This is a consistently reliable indicator of sleep quality, has been assessed routinely in PSG studies comparing sleep in chronic pain groups with healthy controls (Bjurstrom & Irwin, 2016) and has shown significant differences when chronic pain populations are compared with healthy controls. Therefore, it was considered a good parameter to use as a basis to distinguish group differences in sleep disturbance. Sleep efficiency scores range from 0% to 100%. As per previous studies (Blägestad et al., 2012; Wu et al., 2017), a mean difference of at least 9-10% was hypothesised between the chronic pain groups and healthy controls. This would be sufficiently large enough to indicate a clinically significant change. Specifically, Blägestad et al. (2012) 's difference of 8.03 ($p < 0.01$) between a chronic pain group and healthy control formed the basis of the rationale of an expected effect size of $f = 0.4$ ($d = 1.0$). Furthermore, since an ANOVA can only indicate if at least one group is different from the others, post hoc testing with t-tests would have to be done to determine which groups differ, hence the sample size calculation was based on a comparison of 2 group means (a chronic pain group vs. healthy controls) so that the t-tests during post-hoc testing will not be underpowered. The sample required based on this calculation then informed the size of each of the three

equally sized groups to be tested. Subsequently, with alpha set to 0.05 level, results expected to have 80% power and an effect size f = 0.4 (d=1.0), a sample size of 17 per group (51 in total) was deduced from G Power calculations (Figure 10). However, the sample size was not achieved due to difficulties with recruitment.

Figure 10 Sleep and chronic pain power calculation

[10] -- Monday, June 30, 2014 -- 19:11:29
t tests - Means: Difference between two independent means (two groups)

Analysis:	A priori: Compute required sample size		
Input:	Tail(s)	=	Two
	Effect size d	=	1
	α err prob	=	0.05
	Power (1-β err prob)	=	0.8
	Allocation ratio N2/N1	=	1
Output:	Noncentrality parameter δ	=	2.9154759
	Critical t	=	2.0369333
	Df	=	32
	Sample size group 1	=	17
	Sample size group 2	=	17
	Total sample size	=	34
	Actual power	=	0.8070367

Notes: 1-β refers to the required power/ the population effect size to be detected with probability (Cohen's d), **α err prob** refers to the pre-specified level of significance. In 'output', **Noncentrality parameter δ** refers to the noncentral distribution of the t statistics results if the alternative hypothesis is true, **critical t** refers to the number of standard deviations from the null mean where an observation becomes statistically significant, and **df** refers to number of degrees of freedom.

5.2.6.2 Analysis

A series of one-way ANOVAs were carried out to determine group differences (fibromyalgia x chronic back pain x healthy control) on all sleep, pain, inflammation, and psychological measures. $\chi 2$ for chi square tests are reported for between-samples differences for categorical data. F values for one-way ANOVAs are reported for between sample-differences for continuous data categories. Bonferroni post-hoc tests were reported for significant results of the ANOVA, except when the assumption

of homogeneity was not assumed, Dunnett T3 post hoc tests are reported (Field, 2013). As a post-hoc consideration since the chronic pain groups differed significantly from the healthy controls in terms of MQS scores, these results were further adjusted for MQS scores as a co-variate and these adjusted ANCOVAs are also reported. Non-parametric Kruskal-Wallis H test was used to explore inferential differences between the groups across EEG spectral powerbands. The adjustment for MQS scores was only feasible and appropriate for linear outcomes and hence this was not reported for the non-parametric Kruskal-Wallis H test analysis.

PPTh and CPM index were calculated for both lab days and also averaged across both days CPM index calculations are as described in Chapter 4 (4.2.4), derived by calculating the percent change of PPTh during the conditioning stimulus to PPTh prior to conditioning stimulus ($\frac{Mean\ PPTh\ during\ CS}{Mean\ PPTh\ prior\ CS} \times 100$).

Pearson correlations were computed to examine simple bivariate relationships between sleep variables derived from PSG and self-reported sleep parameters with pain catastrophising scores, PPTh, CPM index on Lab day 2 and separately for each group. Given the multiplicity of the correlations, a post-hoc Bonferroni correction was applied and all correlations were Bonferroni corrected to a $p < 0.001$. Means are presented with standard deviations in parentheses, unless otherwise stated. Different sample sizes are due to cases with missing data excluded from the analysis on a test-by-test basis. For all results (unless otherwise stated): *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

5.3 Results

5.3.1 Descriptive statistics

Table 11 presents a general overview of the three participants groups by demographic characteristics. The groups were age-matched to within 5 years and there were no significant differences between the groups in terms of age, BMI, ethnicity, relationship status, employment status, and highest education level attained. The groups were not sex-matched due to difficulties with recruitment, and thus resulted in a larger percentage of females in the patient group compared to the healthy controls. The majority of the participants were of Caucasian ethnicity. In addition, the majority of those in the fibromyalgia group had degree level education or above as opposed to the chronic back pain group.

Table 11 Sleep and chronic pain – Demographics and lifestyle

Demographics	Fibromyalgia N = 9	Chronic Back Pain N = 8	Healthy Controls N = 8	Test Statistics	p value	Between-Samples Differences
Age	45.44 (8.17)	49.50 (12.35)	49.75 (10.07)	Unadjusted F (2,24) = 0.480 Adjusted F (2,20) = 0.334	p = 0.625 p = 0.720	n/a
Gender (Female %)	77.8%	87.5%	37.5%	$\chi 2$ (2, n = 25) = 5.213	p = 0.074	n/a
BMI	27.37 (5.30)	26.31 (2.03)	25.16 (2.43)	Unadjusted F (2,24) = 0.776 Adjusted F (2,20) = 0.206	p = 0.472 p = 0.816	n/a

Ethnicity (Caucasian %)	88.9%	87.5%	100%	χ2 (2, n = 25) = 3.986	p = 0.408	n/a
Relationship (Marriage %)	55.6%	75.0%	37.5%	χ2 (2, n = 25) = 4.380	p = 0.821	n/a
Employment (Paid work %)	55.6%	50.0%	62.5%	χ2 (2, n = 25) = 6.878	p = 0.866	n/a
Education (Degree or above %)	66.7%	37.5%	50.0%	χ2 (2, n = 25) = 6.546	p = 0.365	n/a

5.3.2 Pain characteristics

Table 12 presents pain characteristics of the fibromyalgia, chronic back pain, and healthy control participants. Overall, the pain measures suggest that the chronic pain groups were similar in terms of pain intensity, pain interference, pain duration, and medication use. They were both significantly different to the pain-free healthy control group who reported negligible medication use. After adjustment for medication use scores, the three groups did not show significant differences in most pain characteristics.

Table 12 Sleep and chronic pain – Pain characteristics

Baseline Subjective Pain	**Fibromyalgia N = 9**	**Chronic Back Pain N = 8**	**Healthy Controls N = 8**	**Test Statistics**	**p value**	**Between-Samples Differences**
Baseline – BPI average pain	4.55 (2.19)	4.00 (2.00)	0.88 (1.81)	Unadjusted F (2,24) = 8.013**	p = 0.002	FM – HC CBP – HC
				Adjusted F (2, 20) = 2.672	p = 0.092	n/a
Week – average pain	5.27 (1.82)	5.32 (2.36)	1.72 (2.32)	Unadjusted F (2,24) = 7.401**	p = 0.003	FM – HC CBP – HC

				Adjusted F (2, 20) = 3.457	p = 0.05	n/a
Lab session – average pain	4.22 (3.15)	4.75 (3.15)	0.50 (1.07)	Unadjusted F (2,24) = 8.934***	p = 0.001	FM – HC CBP – HC
				Adjusted F (2, 20) = 3.462	p = 0.05	n/a
Baseline – BPI sleep interference	7.22 (2.77)	6.50 (2.67)	-	Unadjusted F (2,24) = 25.626***	p = 0.000	FM – HC CBP – HC
				Adjusted F (2, 20) = 14.370***	p = 0.000	FM – HC CBP – HC
Baseline – BPI average interference	5.02 (2.21)	4.99 (1.90)	1.30 (2.18)	Unadjusted F (2,24) = 8.403**	p = 0.002	FM – HC CBP – HC
				Adjusted F (2,20) = 3.428	p = 0.051	n/a
PCS	16.00 (11.68)	19.36 (12.97)	14.86 (9.57)	Unadjusted F (2,24) = 0.334	p = 0.720	n/a
				Adjusted F (2,20) = 0.204	p = 0.817	n/a
PVAQ	35.78 (16.83)	52.50 (9.90)	29.75 (7.07)	Unadjusted F (2,24) = 4.278*	p = 0.027	CBP – HC
				Adjusted F (2,20) = 2.744	p = 0.087	n/a
Pain duration (months)	110.22 (79.77)	114.00 (92.90)	-	Unadjusted F (2,24) = 6.748**	p = 0.005	FM – HC CBP – HC
				Adjusted F (2,20) = 2.419	p = 0.113	n/a
MQS score	10.90 (7.88)	11.04 (10.04)	0.75 (2.12)	Unadjusted F (2,24) = 5.062*	p = 0.016	FM – HC CBP – HC

5.3.3 Quantitative sensory testing

Table 13 presents pressure pain threshold and conditioned pain modulation measures for all three groups. After adjustments for MQS scores, there were no significant differences noted for pressure pain threshold measurements and CPM response. In addition, across the three groups, CPT stimulus elicited the strongest CPM response compared to the BHT stimulus which on average did not produce a CPM response. In this study, CPM index for the cold pressor task ranged from 15% - 19% compared to 7% - 29% in Chapter 4. For the bag task, a pattern of negative CPM index emerges -12% to -8% compared to -2% - 4% in Chapter 4 (4.4.5.3).

Table 13 Sleep and chronic pain – Quantitative sensory testing

QST Average across lab session and Day 2	Fibromyalgia N = 8	Chronic Back Pain N = 7	Healthy Controls N = 8	Test Statistics	p value	Between-Samples Differences
PPTh (KPas) – lab average	177.47 (52.07)	203.54 (32.91)	232.25 (43.03)	Unadjusted F (2,22) = 3.125*	p = 0.056	FM – HC
				Adjusted F (2,20) = 1.584	p = 0.231	n/a
PPTh (KPas) – day 2 average	172.44 (53.11)	195.50 (38.27)	236.86 (52.80)	Unadjusted F (2,22) = 3.539*	p = 0.048	FM – HC
				Adjusted F (2,20) = 1.656	p = 0.217	n/a
CPM % (CPT) – lab average	115.74 (24.60)	113.33 (10.82)	119.75 (16.35)	Unadjusted F (2,22) = 0.234	p = 0.794	n/a
				Adjusted F (2,20) = 0.747	p = 0.487	n/a

CPM % (CPT) – day 2 average	111.32 (11.76)	113.64 (13.92)	118.73 (22.77)	Unadjusted F (2,22) = 0.397	p = 0.678	n/a
				Adjusted F (2,20) = 0.711	p = 0.504	n/a
CPM % (BHT) – lab average	88.20 (19.94)	92.11 (12.37)	92.80 (15.84)	Unadjusted F (2,22) = 0.757	p = 0.482	n/a
				Adjusted F (2,20) = 1.283	p = 0.300	n/a
CPM % (BHT) – day 2 average	94.31 (20.71)	94.57 (10.06)	94.56 (15.54)	Unadjusted F (2,22) = 0.001	p = 0.999	n/a
				Adjusted F (2,20) = 0.311	p = 0.736	n/a

5.3.4 Psychological characteristics

Table 14 presents baseline psychological characteristics to compare psychosocial status between the fibromyalgia, back pain, and healthy controls groups. After adjustment for MQS scores, there were mostly no significant differences for measures of mood, worry, depression and anxiety traits. Based on the BDI-II cut-off scores, the fibromyalgia group reported levels of mild depression symptoms, chronic back pain group reported levels of moderate symptoms, and healthy controls reported minimal depression symptoms.

Table 14 Sleep and chronic pain – Psychological characteristics

Baseline psychological characteristics	Fibromyalgia N = 9	Chronic Back Pain N = 8	Healthy Controls N = 8	Test Statistics	p value	Between-Samples Differences
PSWQ	49.78 (16.05)	53.88 (14.07)	47.13 (10.52)	Unadjusted F (2,24) = 0.483	p = 0.623	n/a

				Adjusted F (2,20) = 0.571	p = 0.573	
BDI	18.00 (14.76)	20.00 (10.09)	11.13 (11.80)	Unadjusted F (2,24) = 1.121	p = 0.344	n/a
				Adjusted F (2,20) = 0.184	p = 0.833	
STAI-state	38.44 (14.57)	41.38 (16.22)	33.00 (14.02)	Unadjusted F (2,24) = 0.648	p = 0.533	n/a
				Adjusted F (2,20) = 0.560	p = 0.579	
STAI-trait	43.89 (12.92)	43.63 (12.81)	39.13 (12.47)	Unadjusted F (2,24) = 0.362	p = 0.701	n/a
				Adjusted F (2,20) = 0.070	p = 0.932	
POMS-fatigue	13.22 (5.21)	10.25 (7.70)	5.00 (6.23)	Unadjusted F (2,24) = 3.533*	p = 0.047	FM – HC
				Adjusted F (2,20) = 1.148	p = 0.337	n/a
POMS-negative	26.44 (12.08)	26.75 (21.92)	14.13 (22.15)	Unadjusted F (2,24) = 1.168	p = 0.330	n/a
				Adjusted F (2,20) = 0.460	p = 0.637	n/a
Mood – week average	6.19 (1.39)	7.55 (1.11)	7.84 (1.30)	Unadjusted F (2,24) = 4.101*	p = 0.031	FM – HC
				Adjusted F (2,20) = 2.969	p = 0.073	n/a

5.3.5 Cognitive task

Table 15 presents PVT scores during the lab sessions. The fibromyalgia and chronic back pain groups showed the slowest reaction time (RT) and greater percentage of lapses but there were no significant group differences noted after adjustments for MQS scores.

Table 15 Sleep and chronic pain – Cognitive task

PVT functioning (lab day 2)	Fibromyalgia N = 9	Chronic Back Pain N = 8	Healthy Controls N = 8	Test Statistics	p value	Between-Samples Differences
PVT – lapse %	23.75 (22.65)	34.09 (27.67)	6.44 (3.38)	Unadjusted F (2,24) = 3.605*	p = 0.044	CBP – HC
				Adjusted F (2,20) = 1.549	p = 0.236	n/a
PVT – RT	432.83 (62.96)	450.06 (62.20)	386.69 (25.62)	Unadjusted F (2,24) = 2.997	p = 0.071	n/a
				Adjusted F (2,20) = 1.206	p = 0.319	

5.3.6 Sleep characteristics during the baseline week

Table 16 compares self-reported sleep variables across all three participant groups including fibromyalgia, chronic back pain, and healthy control groups. After adjustments for MQS scores, the chronic pain groups did not differ from one another but show significantly worse PSQI scores than healthy controls. Their PSQI scores were 12.48 and 14.00 respectively and greater than the suggested clinical cut-off for poor sleep quality (> 5). The chronic pain groups also reported greater somatic arousal and anxiety about sleep than healthy controls. There were no group differences noted for sleepiness, cognitive arousal, and maladaptive beliefs about sleep as measured by

DBAS-16. For self-reported sleep diary parameters, fibromyalgia and chronic back pain groups had longer sleep onset latency and worse sleep efficiency (respectively) than healthy controls. The chronic pain groups reported sleep efficiency lower than the 85% cut-off for good sleep efficiency. However, there were no significant group differences noted for overnight awakenings and total sleep time. There was also no group difference noted for week baseline actigraphy derived sleep variables.

Table 16 Sleep and chronic pain – Baseline sleep assessment

Baseline Sleep	Fibromyalgia N = 9	Chronic Back Pain N = 8	Healthy Controls N = 8	Test Statistics	p value	Between-Samples Differences
SSS	2.89 (1.27)	2.75 (1.58)	2.00 (0.93)	Unadjusted F (2,24) = 1.140	p = 0.338	n/a
				Adjusted F (2,20) = 0.053	p = 0.948	n/a
PSQI	12.78 (3.40)	14.00 (3.29)	3.25 (1.58)	Unadjusted F (2,24) = 28.725***	p = 0.000	FM – HC CBP – HC
				Adjusted F (2,20) = 15.799***	p = 0.000	FM – HC CBP – HC
PSAS	38.44 (14.93)	41.88 (13.35)	21.50 (4.50)	Unadjusted F (2,24) = 6.668**	p = 0.005	FM – HC CBP – HC
				Adjusted F (2,20) = 6.163**	p = 0.008	FM – HC CBP – HC
PSAS somatic	17.56 (6.56)	16.63 (6.21)	8.75 (0.71)	Unadjusted F (2,24) = 6.849**	p = 0.005	FM – HC CBP – HC
				Adjusted F (2,20) = 6.216**	p = 0.008	FM – HC CBP– HC
PSAS cognitive	20.89 (9.97)	25.25 (8.61)	12.75 (4.50)	Unadjusted F (2,24) = 4.870*	p = 0.018	CBP – HC

				Adjusted F (2,20) = 4.541*	p = 0.023	n/a
DBAS-16	5.53 (1.95)	5.83 (2.06)	4.31 (2.09)	Unadjusted F (2,24) = 1.172	p = 0.328	n/a
				Adjusted F (2,20) = 0.295	p = 0.748	n/a
APSQ	56.78 (24.44)	70.25 (24.88)	28.25 (16.66)	Unadjusted F (2,24) = 7.347**	p = 0.004	FM – HC CBP – HC
				Adjusted F (2,20) = 4.516*	p = 0.023	CBP – HC

Sleep diary (week average)	**Fibromyalgia N = 9**	**Chronic Back Pain N = 8**	**Healthy Controls N = 8**	**Test Statistics**	**p value**	**Between-Samples Differences**
SOL	35.16 (21.71)	32.68 (11.81)	9.29 (3.54)	Unadjusted F (2,24) = 7.615**	p = 0.003	FM – HC CBP – HC
				Adjusted F (2,20) = 3.836*	p = 0.038	FM – HC
WASO duration	41.13 (39.21)	48.98 (22.97)	4.22 (5.51)	Unadjusted F (2,24) = 6.265**	p = 0.007	FM – HC CBP – HC
				Adjusted F (2,20) = 2.847	p = 0.081	n/a
TST	402.71 (62.09)	376.81 (78.31)	430.18 (56.22)	Unadjusted F (2,24) = 1.303	p = 0.292	n/a
				Adjusted F (2,20) = 0.889	p = 0.426	n/a
Sleep efficiency %	84.33 (9.55)	81.53 (7.43)	96.91 (1.24)	Unadjusted F (2,24) = 10.568***	p = 0.001	FM – HC CBP – HC
				Adjusted F (2,20) = 5.069*	p = 0.016	CBP – HC

Actigraphy (week average)	Fibromyalgia N = 9	Chronic Back Pain N = 7	Healthy Controls N = 8	Test Statistics	p value	Between-Samples Differences
Actigraphy SOL	12.77 (7.59)	11.79 (10.68)	4.85 (4.19)	Unadjusted F (2,23) = 2.501	p = 0.106	n/a
				Adjusted F (2,19) = 0.569	p = 0.575	n/a
Actigraphy 'wake times'	71.29 (50.10)	56.94 (27.40)	48.45 (15.79)	Unadjusted F (2,23) = 0.907	p = 0.419	n/a
				Adjusted F (2,19) = 0.431	p = 0.656	n/a
Actigraphy TST	424.05 (44.34)	448.98 (55.68)	403.91 (35.32)	Unadjusted F (2,23) = 1.850	p = 0.182	n/a
				Adjusted F (2,19) = 0.915	p = 0.417	n/a
Actigraphy SE	83.41 (6.65)	86.79 (3.94)	87.91 (3.96)	Unadjusted F (2,23) = 1.765	p = 0.196	n/a
				Adjusted F (2,19) = 1.135	p = 0.341	

5.3.7 Sleep during the lab session

Table 17 presents self-reported sleep from sleep diary, actigraphy and polysomnography during the lab sessions, only data from the second night of sleep monitoring were analysed for comparison. Night 1 sleep was used for screening sleep disorders only and no participant was excluded because of PSG abnormalities. There was no significant group difference noted across all sleep variables. During the lab session, compared to the baseline week, self-reported sleep efficiency remained poor for chronic pain group (less than 85%) compared to healthy controls. However, for

objective sleep efficiency derived from actigraphy and PSG, all groups had fairly similar patterns of poor sleep efficiency (85% or lower).

Table 17 Sleep and chronic pain – Lab session sleep assessment

Sleep diary (Lab night 2)	Fibromyalgia N = 9	Chronic Back Pain N = 8	Healthy Controls N = 8	Test Statistics	p value	Between-Samples Differences
Night 2 SOL	31.67 (17.68)	25.00 (19.09)	31.88 (16.24)	Unadjusted F (2,24) = 0.397	p = 0.677	n/a
				Adjusted F (2,20) = 0.817	p = 0.455	n/a
Night 2 WASO duration	55.00 (44.44)	53.75 (47.87)	15.00 (20.87)	Unadjusted F (2,24) = 2.666	p = 0.092	n/a
				Adjusted F (2, 20) = 0.893	p = 0.424	n/a
Night 2 TST	385.00 (90.59)	404.13 (69.43)	450.25 969.43)	Unadjusted F (2,24) = 1.190	p = 0.323	n/a
				Adjusted F (2,20) = 0.448	p = 0.645	n/a
Night 2 SE	80.81 (14.26)	82.88 (16.64)	90.85 (5.55)	Unadjusted F (2,24) = 1.355	p = 0.279	n/a
				Adjusted F (2,20) = 0.333	p = 0.721	n/a
Actigraphy (Lab night 2)						
Night 2 Actigraphy SOL	16.11 (9.18)	28.86 (39.92)	22.63 (21.69)	Unadjusted F (2,24) = 0.503	p = 0.612	n/a
				Adjusted F (2,20) = 1.264	p = 0.303	n/a

Night 2 Actigraphy 'wake times'	71.00 (28.30)	52.37 (18.94)	51.25 (35.23)	Unadjusted F (2,24) = 1.328	p = 0.285	n/a
				Adjusted F (2,20) = 1.317	p = 0.289	n/a
Night 2 Actigraphy TST	410.89 (60.93)	439.37 (67.88)	435.75 (64.19)	Unadjusted F (2,24) = 0.456	p = 0.640	n/a
				Adjusted F (2,20) = 0.579	p = 0.569	n/a
Night 2 Actigraphy SE	80.98 (8.35)	84.79 (6.61)	85.75 (9.07)	Unadjusted F (2,24) = 0.839	p = 0.445	n/a
				Adjusted F (2,20) = 0.524	p = 0.600	n/a
Polysomnography (Lab night 2)						
Night 2 PSG SOL	22.78 (18.06)	10.84 (10.25)	19.85 (19.53)	Unadjusted F (2,24) = 1.177	p = 0.327	n/a
				Adjusted F (2,20) = 1.171	p = 0.330	n/a
Night 2 PSG WASO duration	91.19 (39.53)	89.83 (58.33)	96.63 (72.87)	Unadjusted F (2,24) = 0.031	p = 0.969	n/a
				Adjusted F (2,20) = 0.017	p = 0.983	n/a
Night 2 PSG TST	377.83 (67.64)	405.81 (82.28)	388.44 (80.46)	Unadjusted F (2,24) = 0.278	p = 0.760	n/a
				Adjusted F (2,20) = 0.261	p = 0.772	n/a
Night 2 PSG SE	76.43 (9.54)	79.94 (13.41)	78.71 (14.01)	Unadjusted F (2,24) = 0.177	p = 0.839	n/a
				Adjusted	p = 0.849	n/a

				F (2,20) = 0.164		
Night 2 PSG awakening index	7.02 (3.62)	4.34 (1.41)	5.90 (2.76)	Unadjusted F (2,24) = 1.963	p = 0.164	n/a
				Adjusted F (2,20) = 1.867	p = 0.179	n/a
Night 2 PSG arousal index	8.75 (10.72)	11.88 (9.49)	6.21 (4.83)	Unadjusted F (2,24) = 0.831	p = 0.422	n/a
				Adjusted F (2,20) = 0.698	p = 0.509	n/a
Stage N1 %	26.27 (12.71)	23.20 (9.38)	24.74 (13.91)	Unadjusted F (2,24) = 0.134	p = 0.875	n/a
				Adjusted F (2,20) = 0.172	p = 0.843	n/a
Stage N2%	42.40 (15.05)	37.10 (12.22)	38.56 (11.86)	Unadjusted F (2,24) = 0.369	p = 0.696	n/a
				Adjusted F (2,20) = 0.599	p = 0.558	n/a
Stage N3%	16.79 (8.67)	19.74 (7.73)	18.85 (7.25)	Unadjusted F (2,24) = 0.354	p = 0.706	n/a
				Adjusted F (2,20) = 0.826	p = 0.452	n/a
Stage REM%	14.54 (6.78)	19.96 (7.43)	17.89 (5.44)	Unadjusted F (2,24) = 1.462	p = 0.253	n/a
				Adjusted F (2,20) = 1.410	p = 0.266	n/a

5.3.8 Spectral analysis

The aim of spectral analysis of the EEG data from the three groups was to investigate the microstructure of sleep for the whole night. Across all the power bands, there were no significant group differences observed across all NREM, Stage 2, Stage 3, and REM sleep stages.

Table 18 Sleep and chronic pain – Spectral analysis

Logarithmic Log (10) transformed means and standard deviation of power of EEG frequency (Hz) in all frequency bands [Delta-1 (0.1-1Hz), Delta-2 (1-3.5Hz), Theta (3.5-8Hz), Alpha (8-12Hz), Sigma-1 (12- 16Hz), Beta-1 (16-24Hz), Beta-2 (24-32Hz) and Gamma (32-48Hz)] in the sleep EEG for sleep stages NREM merged, N2, N3 and REM. Group differences assessed with Kruskal-Wallis test.

Sleep stage	Group (n)	Delta-1	Delta-2	Theta	Alpha	Sigma	Beta-1	Beta-2	Gamma
NREM (1 – 3)	FM (9)	7.34 (0.45)	7.79 (0.19)	8.39 (0.15)	8.74 (0.22)	9.03 (0.18)	9.19 (0.16)	9.37 (0.26)	9.19 (0.31)
	CBP (8)	7.16 (1.03)	7.60 (0.79)	8.18 (0.74)	8.54 (0.76)	8.75 (0.78)	8.95 (0.87)	9.21 (0.92)	9.11 (0.98)
	HC (8)	7.46 (0.50)	7.83 (0.25)	8.38 (0.17)	8.74 (0.25)	9.03 (0.33)	9.23 (0.45)	9.48 (0.56)	9.33(0.68)
	X^2 (p value)	0.375 (0.829)	0.339 (0.844)	0.352 (0.839)	0.088 (0.957)	0.572 (0.751)	1.242 (0.538)	2.098 (0.350)	1.656 (0.437)
N2	FM (9)	7.50 (0.58)	7.87 (0.20)	8.41 (0.13)	8.74 (0.21)	9.02 (0.18)	9.18 (0.17)	9.42 (0.31)	9.25 (0.40)
	CBP (8)	7.47 (0.48)	7.90 (0.17)	8.43 (0.11)	8.79 (0.17)	8.99 (0.22)	9.22 (0.19)	9.49 (0.29)	9.39 (0.38)
	HC (8)	7.58 (0.58)	7.91 (0.26)	8.41 (0.13)	8.76 (0.18)	9.07 (0.28)	9.39 (0.17)	9.70 (0.21)	9.64 (0.24)
	X^2 (p value)	0.534 (0.766)	0.616 (0.735)	0.538 (0.764)	0.180 (0.914)	0.489 (0.783)	4.210 (0.122)	3.424 (0.180)	4.635 (0.099)
N3	FM (9)	7.23 (0.34)	7.54 (0.24)	8.27 (0.22)	8.66 (0.39)	9.12 (0.22)	9.33 (0.23)	9.58 (0.31)	9.48 (0.38)
	CBP (8)	7.52 (0.12)	7.66 (0.19)	8.34 (0.14)	8.82 (0.17)	9.11 (0.16)	9.38 (0.19)	9.64 (0.36)	9.59 (0.48)
	HC (8)	7.27 (0.39)	7.58 (0.22)	8.32 (0.10)	8.86 (0.12)	9.21 (0.21)	9.52 (0.22)	9.80 (0.24)	9.71 (0.32)
	X^2 (p value)	3.750 (0.153)	0.958 (0.619)	0.583 (0.747)	1.848 (0.397)	0.512 (0.774)	4.920 (0.085)	2.035 (0.361)	1.500 (0.472)
REM	FM (9)	7.74 (0.74)	8.19 (0.60)	8.58 (0.36)	8.89 (0.27)	9.19 (0.21)	9.11 (0.21)	9.36 (0.40)	9.32 (0.62)
	CBP (8)	7.84 (0.41)	8.39 (0.21)	8.75 (0.81)	9.05 (0.13)	9.29 (0.19)	9.20 (0.24)	9.51 (0.33)	9.42 (0.41)
	HC (8)	7.65 (0.61)	8.28 (0.46)	8.68 (0.18)	8.99 (0.16)	9.34 (0.21)	9.26 (0.24)	9.49 (0.30)	9.44 (0.45)
	X^2 (p value)	0.897 (0.639)	0.093 (0.955)	1.308 (0.520)	2.394 (0.302)	1.925 (0.382)	2.263 (0.323)	0.825 (0.662)	0.371 (0.831)

5.3.9 Inflammatory biomarkers

Across groups there were no significant differences noted across levels of inflammatory biomarkers. The chronic pain groups often had slightly elevated levels of hsCRP and TNF-alpha that are out of normative reference range (Table 19) compared with healthy controls and healthy controls with slightly lower levels of Il-1beta and within range levels of other cytokines (Figure 11).

Figure 11 Sleep and chronic pain – Inflammatory marker levels

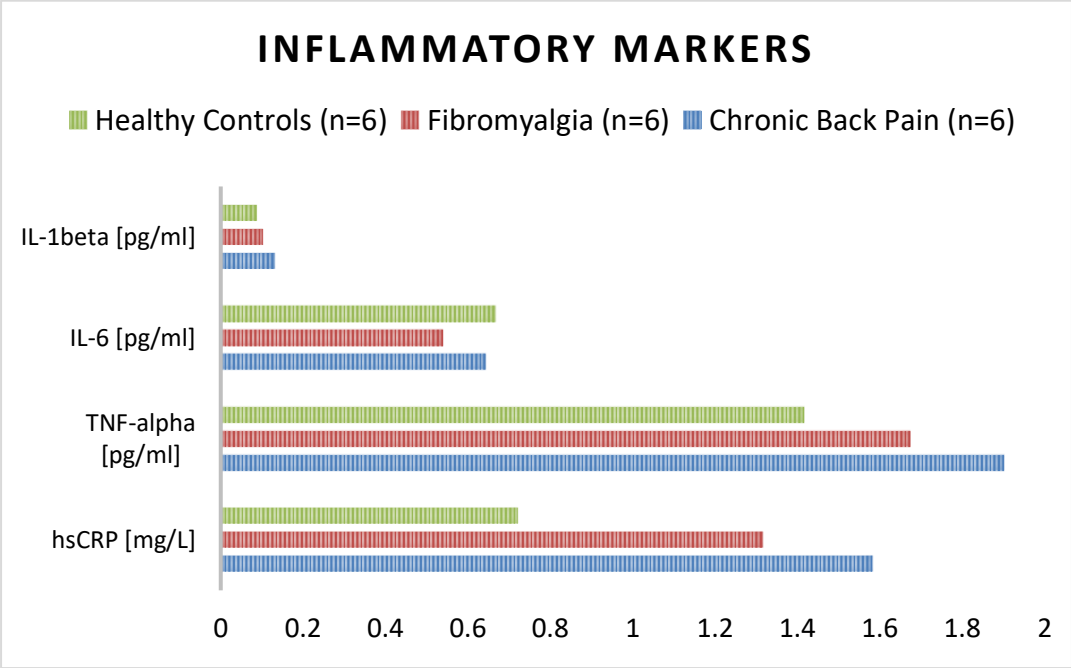


Table 19 Sleep and chronic pain – Inflammatory marker levels

(Out of range values are shown in red)

hsCRP (mg/L)	Fibromyalgia N = 6	Chronic Back Pain N = 6	Healthy Controls N = 6	Test Statistics	Between-Samples Differences
Reference for disease risk <1 = No/low risk 1-3 = Average risk >3 = High risk	0.43 1.08 0.43 2.66 0.53 2.77	2.73 0.73 2.42 0.75 1.51 1.36	0.63 0.31 0.62 0.97 1.32 0.48		
Mean value	**↑1.32**	**↑1.58**	**0.72**	Unadjusted F (2, 17) = 1.697 p = 0.217 Adjusted F (2,13) = 0.250 p = 0.782	n/a n/a

TNF-alpha (pg/ml)	Fibromyalgia N = 6	Chronic Back Pain N = 6	Healthy Controls N = 6	Test Statistics	Between-Samples Differences
Reference range 0.10 - 1.75	1.70 1.20 1.46 1.20 2.23 2.26	1.64 1.89 2.71 1.16 2.45 1.56	1.08 1.42 1.34 1.7 1.53 1.44		
Mean value	**↑ 1.68**	**↑ 1.90**	**1.42**	Unadjusted F (2, 17) = 1.725 p = 0.212 Adjusted F (2,13) = 0.573 p = 0.576	n/a n/a

Sleep and chronic pain – Inflammatory marker levels

(Out of range values are shown in red)

IL-1beta (pg/ml)	Fibromyalgia N = 6	Chronic Back Pain N = 6	Healthy Controls N = 6	Test Statistics	Between-Samples Differences
Reference range	0.09	0.10	0.07		
0.11 - 24.3	0.19	0.18	0.12		
	0.08	0.11	0.03		
	0.05	0.11	0.06		
	0.15	0.17	0.06		
	0.06	0.12	0.19		
Mean value	↓ **0.10**	**0.13**	↓ **0.09**	Unadjusted F (2, 17) = 1.156 p = 0.341	n/a
				Adjusted F (2,13) = 1.685 p = 0.221	n/a

IL-6 (pg/ml)	Fibromyalgia N = 6	Chronic Back Pain N = 6	Healthy Controls N = 6	Test Statistics	Between-Samples Differences
Reference range	0.10	0.89	0.28		
0.16 - 27.2	0.22	0.18	0.51		
	0.23	0.87	0.15		
	0.79	0.31	2.43		
	1.13	0.86	0.59		
	0.77	0.75	0.05		
Mean value	**0.54**	**0.64**	**0.67**	Unadjusted F (2, 17) = 0.079 p = 0.925	n/a
				Adjusted F (2,13) = 0.090 p = 0.914	n/a

5.3.10 Associations between PSG sleep, pain catastrophising, and pain response

To examine the association of objective PSG sleep in the lab with pain responses, Pearson correlations were computed between Night 2 PSG sleep variables, PCS scores, average day 2 PPTh and CPM indices (Table 20). For the healthy controls, a correlation was not observed between the PSG sleep measures, pain catastrophising, and PPTh and CPM indices, unlike Chapter 4 (4.2.5.4) where correlations between total sleep time and sleep onset latency with PPTh and CPM were observed in the healthy population sample.

For the chronic pain groups, after Bonferroni corrections was applied, there were no significant correlations observed between the PSG sleep measures, pain catastrophising, and PPTh and CPM indices. Prior to adjustment, for the fibromyalgia group, arousal index showed a negative correlation with pressure pain threshold ($r = -0.7$ [95% CI -0.941; -0.009], $p < 0.05$) and CPM response ($r = -0.8$, [95% CI -0.962; -0.218] $p < 0.01$). In addition, sleep onset latency showed a negative correlation with CPM response ($r = -0.8$, [95% CI -0.962; -0.218] $p < 0.01$). For the chronic back pain groups, total sleep time showed a positive correlation with CPM response ($r = 0.8$ [95% CI -0.969; -0.118], $p < 0.05$) and arousal index showed a negative correlation (unadjusted) with pressure pain threshold ($r = -0.8$, [95% CI -0.969; -0.118] $p < 0.01$).

Table 20 Sleep and chronic pain – Associations between pain catastrophising, sleep, and CPM response

Correlations between PSG sleep parameters, pain catastrophising, PPTh, and CPM Fibromyalgia (N=8)

	PSQI	PSG SOL	PSG WASO	PSG TST	PSG SE	Arousal	PCS	CPM	PPTh
PSQI	1	-.193	.444	-.263	-.337	-.020	.410	.401	-.383
PSG SOL		1	-.298	-.031	-.144	.859	.169	**-.849**	-.595
PSG WASO			1	-.752	-.863	-.377	-.286	.594	.074
PSG TST				1	.927	.256	.564	-.265	-.101
PSG SE					1	.096	.379	-.226	.078
Arousal						1	.492	**-.835**	**-.740**
PCS							1	-.223	-.551
CPM								1	.298
PPTh									1

Correlations between PSG sleep parameters, pain catastrophising, PPTh, and CPM Chronic Back Pain (N=7)

	PSQI	PSG SOL	PSG WASO	PSG TST	PSG SE	Arousal	PCS	CPM	PPTh
PSQI	1	.508	.309	-.007	-.360	-.032	.549	.032	-.031
PSG SOL		1	.075	.492	-.077	.573	.066	.218	-.727
PSG WASO			1	-.776	-.994	.101	.788	-.577	.081
PSG TST				1	.799	.309	-.607	**.777**	-.612
PSG SE					1	-.043	-.813	.619	-.149
Arousal						1	-.010	-.037	**-.884**
PCS							1	-.559	.194
CPM								1	-.393
PPTh									1

Correlations between PSG sleep parameters, pain catastrophising, PPTh, and CPM Healthy Controls (N= 8)

	PSQI	PSG SOL	PSG WASO	PSG TST	PSG SE	Arousal	PCS	CPM	PPTh
PSQI	1	.074	.516	-.032	-.462	-.575	.474	.662	-.240
PSG SOL		1	.785	-.757	-.788	.136	.235	.074	.566
PSG WASO			1	-.752	-.995	-.299	.546	.557	.154
PSG TST				1	.805	.300	-.135	-.395	-.389
PSG SE					1	.304	-.472	-.556	-.191
Arousal						1	-.145	-.334	.038
PCS							1	.260	-.119
CPM								1	-.216
PPTh									1

5.4 Discussion

5.4.1 Summary of findings

This study aimed to gain insight into what characterises and differentiates those with fibromyalgia, chronic back pain, and pain-free healthy controls. As hypothesised, the chronic pain groups mostly showed greater self-reported sleep disturbances compared with healthy controls and also showed signs of slightly elevated inflammatory marker levels, but this was not significantly different from healthy controls. In addition, objective sleep in the chronic pain groups was not significantly correlated with physiological pain response and pain inhibition.

5.4.2 Sleep characteristics

When the three groups were compared across sleep characteristics, it was observed that only on self-reported sleep characteristics did the chronic pain groups significantly differ from the healthy controls. On baseline sleep questionnaires and from the sleep diary over the week, both the chronic back pain and fibromyalgia reported poorer sleep quality, longer sleep onset latency, more overnight sleep awakenings, and lower sleep efficiency. Unlike the present study, a few studies and systematic reviews have been able to show that there are objective differences in actigraphy sleep parameters, sleep microarchitecture and macro architecture in polysomnography measured sleep between those with chronic pain, especially between fibromyalgia and healthy controls (Bjurstrom & Irwin, 2016; Diaz-Piedra et al., 2015; Lunde et al., 2010; O'Donoghue, Fox, Heneghan, & Hurley, 2009; Roth, Bhadra-Brown, Pitman, Roehrs, & Resnick, 2016).

Nevertheless, the observation in the current study was in the right direction towards greater physiological abnormalities of sleep in chronic pain groups and stronger self-reported sleep disturbance. Moreover, a meta-analysis of case-control studies found that sleep difficulties in fibromyalgia were of greater severity when self-reported than when assessed objectively. The pooled effect sizes across studies of the differences in sleep disturbance measured using the PSQI was larger than that measured using PSG (Wu et al., 2017). This is consistent with the idea that insomnia is still inherently a subjective experience, and this is apparent in the current findings in these groups of pain patients. Furthermore, thinking about the interaction between pain and sleep is said to be an integral part of chronic pain patients' insomnia experience (Afolalu, Moore, Ramlee, Goodchild, & Tang, 2016; Ramlee, Afolalu, & Tang, 2016; Smith, Perlis, Smith, Giles, & Carmody, 2000; Tang, Wright, et al., 2007) and excessive cognitive arousal has been highlighted as a key feature of both primary and pain-related insomnia (Byers, Lichstein, & Thorn, 2016; Dillon, Thomas, & Lichstein, 2011).

It has further been suggested and demonstrated in a pilot intervention of hybrid cognitive behavioural therapy that aims to tackle pain and sleep simultaneously and is focused on helping patients understand the pain-sleep interaction and addressing the cognitive-behavioural factors perpetuating their insomnia may be a fruitful intervention (Tang, Goodchild, & Salkovskis, 2012). Further studies are still needed to determine the efficacy of these treatments and elaborate the cognitive and behavioural concepts underlying and perpetuating sleep disturbances within the

context of chronic pain so as to improve the efficacy of such interventions in sustaining better quality of life in spite of ever-present chronic pain

5.4.3 PSG sleep parameters, pain response and inflammation

As a further extension of Chapter 4 (4.5.5), this study also aimed to explore the association between objective pain measures and sleep but this time using polysomnography sleep measures and within a chronic pain population. The groups did not differ on conditioned pain modulation (CPM) response, a marker of pain inhibitory processes. The chronic pain group did show slightly lower pressure pain threshold and CPM response and inflammatory markers that were slightly out of range but this was not significantly different from healthy controls.

Furthermore, there was no association between the pain measures and sleep in healthy controls. Prior to Bonferroni corrections, for the group with chronic back pain, less total sleep time was associated with lower CPM response and greater arousal index associated with lower pressure pain threshold assessed the next morning. Similar pattern was observed in the fibromyalgia group where a greater arousal index was related to lower pressure pain thresholds and CPM, and longer sleep onset latency with lower CPM. It is important to emphasise that these were the unadjusted simple correlations and associations within very small sample sizes, which limits any causal interpretations and generalisability. The actual study sample was below the recruitment target derived from the power calculation, and this compromised study power. Furthermore, this limited sample did not permit for a

meaningful comparison and discrimination of the characteristics of CPM responders and non-responders within these groups as was done in Chapter 4 (4.4.5.5). This would have provided additional benefit of deciphering the significance of the associations between overnight sleep parameters and next day pain, CPM, and inflammatory responses.

Chapter 4 (4.5.5) discussed the relevance of an association between disrupted sleep, especially in those with impaired CPM response. Previous studies have emphasised that chronic pain patients with self-reported sleep quality, poor sleep efficiency and reports of non-restorative sleep were associated with attenuated CPM response (Edwards et al., 2009; Lee et al., 2013; Paul-Savoie et al., 2012). There is also the possibility of an association between CPM response and increased disruption in objective markers of sleep quantity and arousal index, reflecting both greater sleep insufficiency and sleep instability overnight. Conditioned pain modulation is generally impaired in populations with chronic pain (Lewis et al., 2012), but studies have also found impaired endogenous pain inhibitory systems exclusively in fibromyalgia but not chronic back pain when the two patient groups were compared (Julien et al., 2005). Other findings have demonstrated that perhaps CPM response may have low sensitivity and specificity within chronic pain groups. Potvin and Marchand (2016) proposed that deficient endogenous pain inhibition may not be a definitive feature of FM but rather a contributing mechanism, a cause or consequence of prolonged pain in a subgroup of patients with FM. This needs to be better characterised to sufficiently characterise pain patients and their sleep disturbances based on their pain inhibition

profiles. Further studies are required to expand these findings in larger chronic pain groups. Knowledge of influences of sleep on a patients' pain perception may subsequently open up further areas for possible interventions and treatments within pain management.

5.4.4 Pain and psychological characteristics

Surprisingly, the three groups did not show differences in their scores on the questionnaires measuring cognitive pain processes (e.g., pain catastrophising). The chronic back pain group seemed to report greater scores on pain vigilance and attention and those with fibromyalgia reported greater fatigue levels compared to healthy pain-free controls. Pain vigilance and attention to pain have been shown to be positively associated with reports of pain, distress, disability, and health care utilisation in those with chronic musculoskeletal problems (McCracken, 1997). The fear-avoidance model is a behavioural and cognitive model of pain-related fear which posits those that are fearful of their pain will tend to attend to possible signs of pain and threats (Leeuw et al., 2007; Vlaeyen et al., 1995; Vlaeyen & Linton, 2000). This hypervigilance restricts ability to shift attention away from pain-related information or potentially pain-inducing problems and consequently impacts negatively on active coping with daily lives, mood, greater distress and disability and disuse resulting from limited engagement in activities (Crombez, Eccleston, Baeyens, van Houdenhove, & van den Broeck, 1999; Crombez et al., 2005). In the current study, this was more pronounced in those with chronic back pain, although the fear-avoidance model does not suggest that pain related fear of movement is only exclusive in sustaining chronic

pain disability in chronic back pain. Fibromyalgia patients in this study still reported heightened pain related vigilance relative to healthy controls, as already shown in previous studies (Crombez et al., 2005; Peters, Vlaeyen, & van Drunen, 2000).

Although fibromyalgia is marked by chronic widespread pain, fatigue remains one of the condition's most troublesome and common problems. This was also observed in the current findings. Fatigue in those with fibromyalgia is often more widely reported than with other rheumatic or chronic pain conditions. Daily clinical fatigue levels with as high prevalence as 76% have been reported in fibromyalgia patients and it prevents ability to effectively carry out daily tasks and activities (Overman, Kool, Da Silva, & Geenen, 2016; Wolfe, Hawley, & Wilson, 1996). However, there remains a general lack of understanding concerning the aetiology of fatigue, its relationship with sleep problems in those with long-term pain, and the most effective management approach for tackling the issue. Nicassio, Moxham, Schuman, and Gevirtz (2002) investigated the role of depression, sleep and pain status in determining fatigue levels in fibromyalgia patients. In the cross-sectional phase of their study, in a sample of 105 fibromyalgia patients, greater depression scores and lower sleep quality were concurrently associated with higher fatigue. When a subset of 63 patients were monitored for over a week to assess the daily relationship between their pain, sleep quality, and fatigue, average daily scores revealed that previous day's pain and sleep quality predicted next day's fatigue. Importantly, daily poor sleep quality mediated the positive relationship between pain and fatigue. This is suggestive that non-restorative sleep may be a key factor contributing to fatigue in

this population. Self-reported sleep may have more of a contributing factor in the resulting pain-related psychological, behavioural, and fatigue problems. Further empirical assessments of the dynamic daily patterns between sleep, mood, pain, and fatigue in FM and other chronic pain condition are needed to carefully discriminate the potential temporal role of both objective and subjective sleep in precipitating fatigue episodes and shaping psychological and behavioural pain responses.

5.4.5 Limitations

It is important to note that the study is limited by an overall small sample size and the sample was also not sex-matched. The final sample size differed from the kind of sample size needed to detect a sizeable and significant difference between groups (n = 17 in each group as per the power calculation). Recruitment was complicated by low participant uptake from the pain clinic recruitment avenue and also due to practical difficulties of recruitment within the time frame of the doctoral project. Subtle differences between the groups could have been undetected due to statistical power limitations and increased risk of Type 2 errors. Extant PSG studies do not often have large sample sizes and a lot of studies in this field are underpowered. Larger sample sizes and further systematic reviews and meta-analyses are required for PSG studies in chronic pain patient to drive optimal statistical power, especially to detect differences in sleep microstructure using spectral analysis. On the other hand, the study reported in this chapter also contained a large number of multiple and simultaneous testing. This could also pave way for Type 1 errors and greater chance of observing at least some significant results even if all of the tests are not actually

significant. The study is also subject to the same limitations concerning adjustments for Type 1 errors as discussed in Chapter 4 (4.5.6).

Notably, even though the healthy controls reported good sleep patterns during screening and from self-reported sleep assessments, their objective actigraphy and PSG derived sleep was relatively poor and not markedly different from the chronic pain groups. It is possible that these group of participants may have not been as good a sleeper as they characterised themselves to be. This could also contribute to lack of observable differences in microstructure and power spectral analysis where differences have been observed between groups with chronic pain and those without in other studies (Blägestad et al., 2012; Drewes et al., 1995). Participants also underwent only 2 nights of polysomnography assessment and this may have limited the specificity and sensitivity of the sleep assessment. While there is a possible first night effect that could affect sleep in the lab, reverse first night effect may also come into play cancelling the first night differences out. This phenomenon has been observed in insomniac participants who usually sleep better than normal for the first night, but even more poorly than normal on the second night (Hauri & Olmstead, 1989; Riedel, Winfield, & Lichstein, 2001). Hence, it is now recommended that more than two nights of PSG recording be obtained in order to reflect more realistic variability of sleep in participants (Bjurstrom & Irwin, 2016).

This study deliberately did not exclude patients based on medication use. Some of the medications used by participants in this study included ibuprofen (NSAID),

paracetamol (acetaminophen), tramadol, amitriptyline (tricyclic anti-depressant), opioids such as fentanyl patch, codeine, and morphine and less rarely benzodiazepines such as diazepam. These analgesics, hypnotics, antidepressants, and other pharmacotherapy measures in pain management are known to disturb sleep (Onen, Onen, Courpron, & Dubray, 2005). Yet despite patients being on these medications for a long time, they continue to report problems with sleep. For ethical reasons and to gain a naturalistic observation of the sleep characteristics within these groups of patients and a wider perspective of the pain and sleep experience, it was necessary to allow the use of these medications as commonly prescribed. Nevertheless, the study did quantify medication use with the Medication Quantification Scale (Harden et al., 2005) and the two chronic pain groups were on average fairly matched and similar concerning the relevant clinical risk weighting of their current medication regime. The analysis was also adjusted for differences in MQS scores between the chronic pain groups and healthy controls, although given the small sample size, the effect of the adjustment was fairly negligible. Nevertheless, future case-controlled experimental studies may want to eliminate the confounding effect of medications and gain a clearer picture of sleep processes in pain conditions and to establish further causal inferences from the interrelationship between sleep and pain problems. To maintain ecological validity, it may also be useful to match or stratify pain groups appropriately and draw comparisons between chronic pain patients who do not use such medications or who do not experience sleep problems. Whilst at the same time, statistically controlling for other confounding variables (such as age,

gender, ethnic group, educational level, marital status, body mass index, physical activity, health status etc.).

5.5 Conclusion

This study aimed to observe and characterise sleep and pain characteristics in two chronic pain groups compared with healthy controls. Notably, findings revealed that those with fibromyalgia did not greatly differ from patients with chronic back pain across a range of sleep, pain, physiological and psychological characteristics. Although limited by a small sample size, this study suggests further need for comparative knowledge regarding the sleep disturbances in individuals with chronic pain. For those with chronic pain conditions such as fibromyalgia and chronic back pain, it may still be worthwhile in clinical settings to consider how their sleep infers on aspects of their pain experience. This can range from self-reported mood, fatigue, pain catastrophising to other physiological markers such as pain inhibitory processes and inflammation. There is potential benefit to investigate how the interaction between sleep and these factors can inform and affect chronic pain management.

6 Sleep changes and pain-related health outcomes in the general population: A systematic review of longitudinal studies with exploratory meta-analysis

6.1 Introduction

There is increasing epidemiological evidence highlighting sleep deficits and disturbances as risk factors of poor physical health (Cappuccio et al., 2011; Leng et al., 2015) and mental well-being (Bernert et al., 2014; Riemann & Voderholzer, 2003). Sleep problems have been specifically linked to the development of chronic pain, which refers to pain that persists beyond the expected time of healing from injury, illness or tissue damage (3-6 months) (Merskey & Bogduk, 1994; Treede et al., 2015). Unlike acute pain that serves the important function of signalling harm to the body's integrity, chronic pain is in itself a disease with poor prognosis, featuring peripheral and central sensitisation to pain signals in the absence of clear underlying pathology (Siddall & Cousins, 2004; Tracey & Bushnell, 2009). Despite its invisible nature, chronic pain - like insomnia - can considerably limit one's day-to-day functioning; from concentrating on a task, to walking, sleeping, maintaining social relationships, and holding down a job for independent living (Breivik et al., 2006). In primary care, chronic pain is ranked the top cause of quality-adjusted life-year loss, surpassing cardiovascular disease, high blood pressure, mood and anxiety disorders, diabetes, and common respiratory conditions (Fernandez et al., 2010). Considering the high prevalence of both insomnia symptoms (10 – 30%; (LeBlanc et al., 2009; Ohayon, 2002; Roth, 2007)) and chronic pain (10 – 20%; (Breivik et al., 2006; Goldberg & McGee, 2011)) in the general population and their potency to impair well-being, the

frequent co-occurrence of sleep and pain presents a serious public health challenge to our aging society (Gureje, Von Korff, Simon, & Gater, 1998; Simon & Von Korff, 1997; Tang, Afolalu, & Ramlee, in press).

6.1.1 Evidence for the effect of sleep problems on pain from micro-longitudinal studies

Conventionally, sleep disturbance is thought to be a symptom secondary to pain and the two conditions are assumed to be broadly bi-directionally linked. However, recent research has been able to show that sleep problems may have a stronger contributory effect on pain than the effect of pain on sleep, shifting the research emphasis onto the temporal association from sleep to pain (Finan et al., 2013; Smith & Haythornthwaite, 2004). Much of the evidence on the temporal impact of sleep on subsequent pain has come from longitudinal studies. Micro-longitudinal studies as described by Affleck, Zautra, Tennen, and Armeli (1999) use 'time-series' designs to examine day-to-day sleep and pain variations in individuals over a period of one to two weeks. These studies have shown that night-time sleep parameters more consistently predict next-day pain compared to pain predicting subsequent sleep. Edwards, Almeida, Klick, Haythornthwaite, and Smith (2008) found evidence to support a close link between sleep and pain on a day-to-day basis. In their sample of 971 healthy adults assessed over the telephone for a week, self-reported sleep duration the previous night was a significant predictor of pain symptoms frequency the next day. Whilst pain symptoms did in turn predict subsequent sleep duration, the magnitude of the effect was only half as strong as the influence of sleep duration predicting pain.

Tang, Goodchild, Sanborn, et al. (2012) monitored sleep and pain reports over a week in a sample of 119 mixed chronic pain patients in their natural living and sleeping environments, using actigraphy and electronic daily diaries to assess sleep, pain, and mood reports at three time points over the course of the day. Results from multilevel modelling indicated that sleep quality was a significant and consistent predictor of next day pain at all assessment points. In contrast, whilst presleep pain was a predictor of poorer sleep efficiency calculated based on sleep diary entries, it was not a significant predictor of subsequent sleep efficiency as estimated by actigraphy. Compared to pain, presleep cognitive arousal and mood were better predictors of subsequent sleep.

6.1.2 Evidence for the effect of sleep problems on pain from macro-longitudinal studies

There are some macro-longitudinal (prospective) studies with less frequent assessments but longer timeframes that have examined the incidence of insomnia and chronic pain at the population level. These studies have found evidence that poor sleep is a primary factor predicting aggravation of pain responses and determining longer-term risks of developing a pain condition. Mork and Nilsen (2012) demonstrated in a sample of 12,350 healthy women that incidence of self-reported sleep problems tripled the risk of reporting physician-diagnosed fibromyalgia 11 years later. The analyses were adjusted for age, general physical health status, and psychological wellbeing, with the resultant risk increasing depending on the frequency and severity of sleep problems. Gupta et al. (2007) and McBeth et al. (2014) also

reported that poor self-reported sleep quality strongly predicted the onset of widespread pain symptoms up to 3 years later, even when other psychological, lifestyle, and health factors were all controlled for. Similarly, Nitter et al. (2012) found that self-reported disrupted and non-restorative sleep were significant predictors of chronic pain onset in pain-free individuals over the course of 17 years. The same sleep predictors also increased the risk of pain persistence and worsening among those who already had chronic pain at baseline. Despite not having intensive repeated assessments of sleep, findings from these prospective studies have shed light on the potential long-term impact of sleep on pain.

6.1.3 Focusing on the long-term impact of *changes* in sleep on pain outcomes

That said, the causality of the relationship between sleep and pain needs finer characterisation. Whilst it is understood that sleep patterns and sleep quality fluctuate over time, little is known about the effect of these sleep *changes* on pain and other health variables in the long run. This is in part due to the fact that many macro-longitudinal studies examined sleep statically at a certain time point rather than studying the dynamic changes in sleep across multiple assessment points. Further research using repeated measurements of sleep disturbances would help establish whether greater or lesser exposure to sleep problems over time leads to remission of pain and related symptoms (Bradford-Hill, 1965; Ferrie, Kumari, Salo, Singh-Manoux, & Kivimaki, 2011).

Macro-longitudinal studies also often do not have suitable designs and assessment technologies to explore the processes underpinning sleep changes. In experimental studies, acute sleep restriction in healthy pain-free participants in the form of 88-hour total sleep deprivation (Haack, Lee, Cohen, & Mullington, 2009) and partial sleep deprivation of 6 hours a night over a week (Vgontzas et al., 2004) or 4 hours a night over 10 days (Haack et al., 2007) were associated with impaired immunity, elevated inflammatory response and raised cytokines levels, namely, interleukin-6(IL-6), C-Reactive Protein (CRP), cortisol, prostaglandin E2 (PGE2), and tumour necrosis factor alpha (TNF-α). These biomarkers are also believed to be related to greater self-reported pain, exaggerated pain sensitivity, fatigue, and consequent decline in self-reported health status (Irwin, 2011). However, the use of measures that assess these biomarkers is sporadic in longitudinal studies and as such their roles in influencing the impact of sleep changes on long-term pain outcomes require confirmation. Finally, it should be mentioned that, of the few studies that examined change in sleep, the focus of analysis is primarily on the effects of negative rather than positive changes. It would be important to verify whether improvement in sleep – outside of clinical trials – is also associated with improvement in pain-related health outcomes.

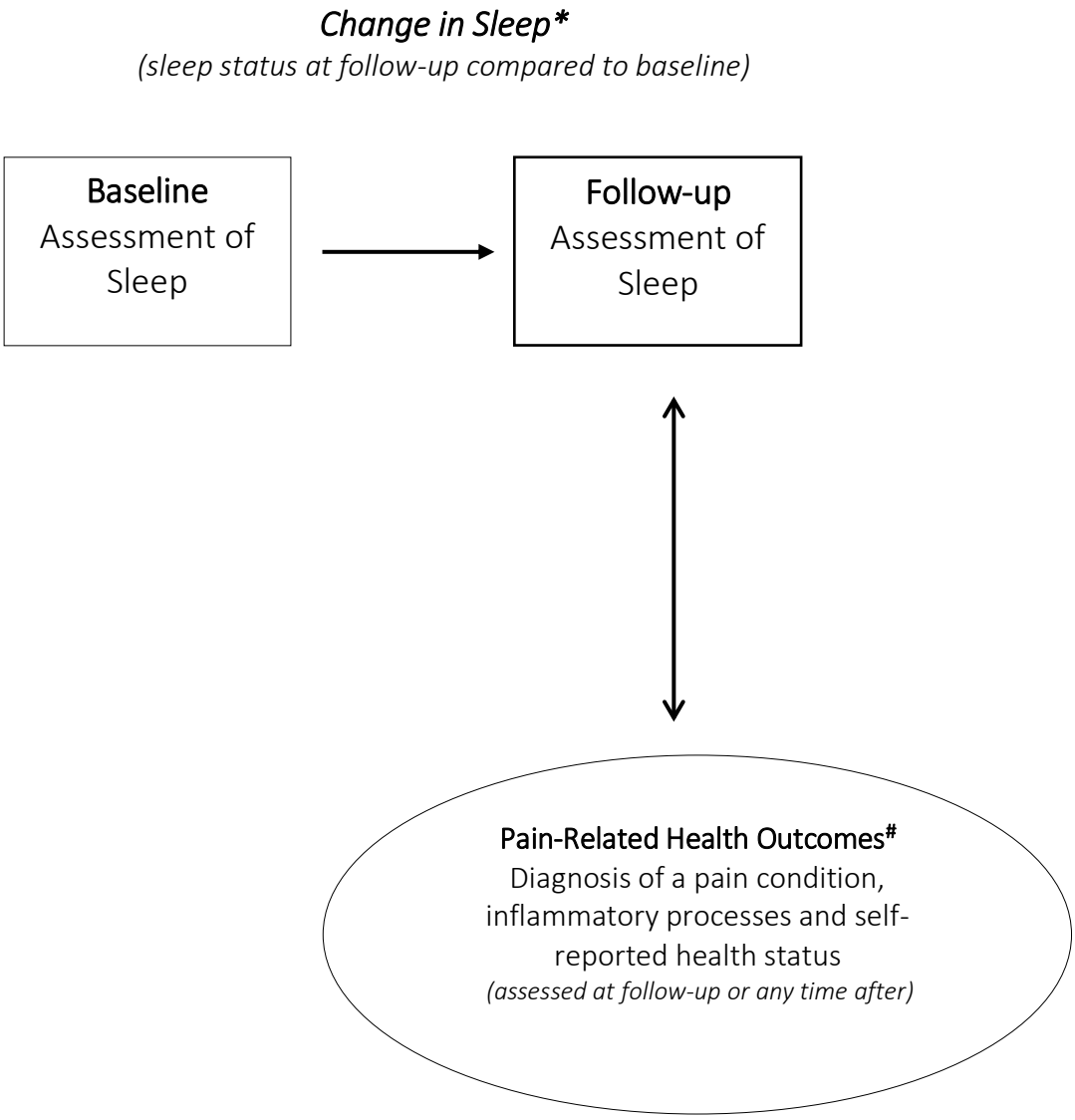
6.1.4 Aim of the current systematic review

Given the above considerations, the present review examined prospective (macro-longitudinal) studies that have assessed improvement and deterioration in sleep over time and the association of these changes with pain-related outcomes. The

aims of this review were thus to: (i) systematically summarise the state of the research, (ii) critically assess the methodological quality of and consistency in findings across existing studies, and (iii) carry out an exploratory meta-analysis to quantify the effect of changes in sleep on self-reported health outcome over time.

The predicting/exposure variable was defined as changes in sleep parameters (e.g., insomnia symptoms, sleep quantity, and sleep quality). To gain a clearer idea of how different sleep measures influence pain, findings were separated by different pain-related health outcomes. These outcomes were not only limited to diagnosis of the pain condition itself, but also included pain-related physiological status such as inflammation/immune functions and self-reported health status (Refer to Figure 12 for a schematic figure summarising this approach, and the methodologies of included studies). Factors such as anxiety and depression may play an important role in changes in sleep and subsequent health outcomes. However, since they were not the focus of this review, the reader is referred to Alvaro, Roberts, and Harris (2013) and Lustberg and Reynolds (2000) for comprehensive reviews on these topics and the long-term effect on sleep status.

Figure 12 Systematic review – Summary of framework and methodology of included studies



Notes: Summary of the framework underlying this systematic review and methodological design on the included studies. Based on the experimental and epidemiological evidence, the figure illustrates the potential prospective relationship between changes in sleep and chronic pain experience. Changes in sleep from baseline to follow-up represents the variable associated with subsequent chronic pain experience. ***Change in sleep**** refers to change in (i) sleep duration, (ii) sleep quality, and/ or (iii) insomnia symptoms. ***Pain-related health outcomes#*** represents the factors that make up overall pain experience, namely, the risk of developing a pain condition, changes in physiological inflammatory and immune processes and changes in subjective reports of pain-related health and functioning status.

6.2 Methods

6.2.1 Data source and search strategy

The data source for this systematic review was studies that have evaluated the associations of prospective changes in sleep with pain-related health outcomes. Relevant articles were identified through electronic searches performed using PubMed MEDLINE, Ovid EMBASE, and Proquest PsycINFO. Reference lists of included studies and relevant reviews were also hand-searched to ensure comprehensive coverage. The protocol of this systematic review was reviewed and registered with PROSPERO, an international prospective register of systematic reviews. The Prospero Registration Number is 2015:CRD42015023943.

The initial search was carried out by the researcher (EA) in June 2015 and repeated just before the final analysis (April 2017) to provide an update. Searches were carried out on each database using both study subject (sleep* OR insomnia) AND study methodology (longitudinal OR prospective) search terms in the Title and Abstract fields. There was no restriction on publication year, but filters were set limiting the search to human studies and in the English language. Given that a broad array of measures can be used to index pain-related health outcomes, no restriction was set to limit the search by outcomes reported. This approach returned a large volume of potentially eligible articles. Whilst the screening process was laborious, it was considered a more comprehensive and inclusive method to capture all relevant studies.

6.2.2 Screening

Due to the large volume of hits returned, the first round of screening was a "title" screen carried out by the author to screen for unrelated articles, animal studies, studies in children populations and in critically ill/hospitalised patients. This resulted in a number of irrelevant articles being eliminated. The next step was an eligibility assessment of both titles and abstracts and involved four researchers (FR, SA, NK, and PC - a doctoral student and three undergraduate students), all of whom had been given training and detailed guidance on the screening procedure. They did the screening collaboratively using an eligibility checklist to identify relevant studies. The screening checklist included six questions requiring a 'yes' or 'no' response. Each question reflects each of the inclusion criteria (see Table 21). Only studies with a 'yes' response to questions 1, 2, 4, 5, and 6 and a 'no' response to question 3 were included for full-text screening. The title and abstract screen was cross-checked by the author, and differences in opinion among the reviewers were resolved through team discussion. The discussion erred on the side of caution to include studies for further full-text screening even if there were doubts on study eligibility based on response to the six questions. A total of 14 studies required further extensive discussion on eligibility. Interrater agreement rate (Cohen's Kappa) between reviewers and the author was 0.77, a value considered 'good' (Altman, 1991).

Table 21 Systematic review – Screening criteria questions

1. Is the study an original article in the English language? (i.e., not a secondary analysis or a review paper) "Yes" to include

2. Is the study population in human/adults (over 18 years)? "Yes" to include

3. Is the study of sleep conducted within the context of sleep disorders, drug trials, psychological therapy, medical illness/hospitalised patients, circadian rhythm disorders or shift work? "No" to include*

4. Does the study report a change in sleep or a measure of sleep on at least two occasions? "Yes" to include

5. Is the study design longitudinal? # "Yes" to include

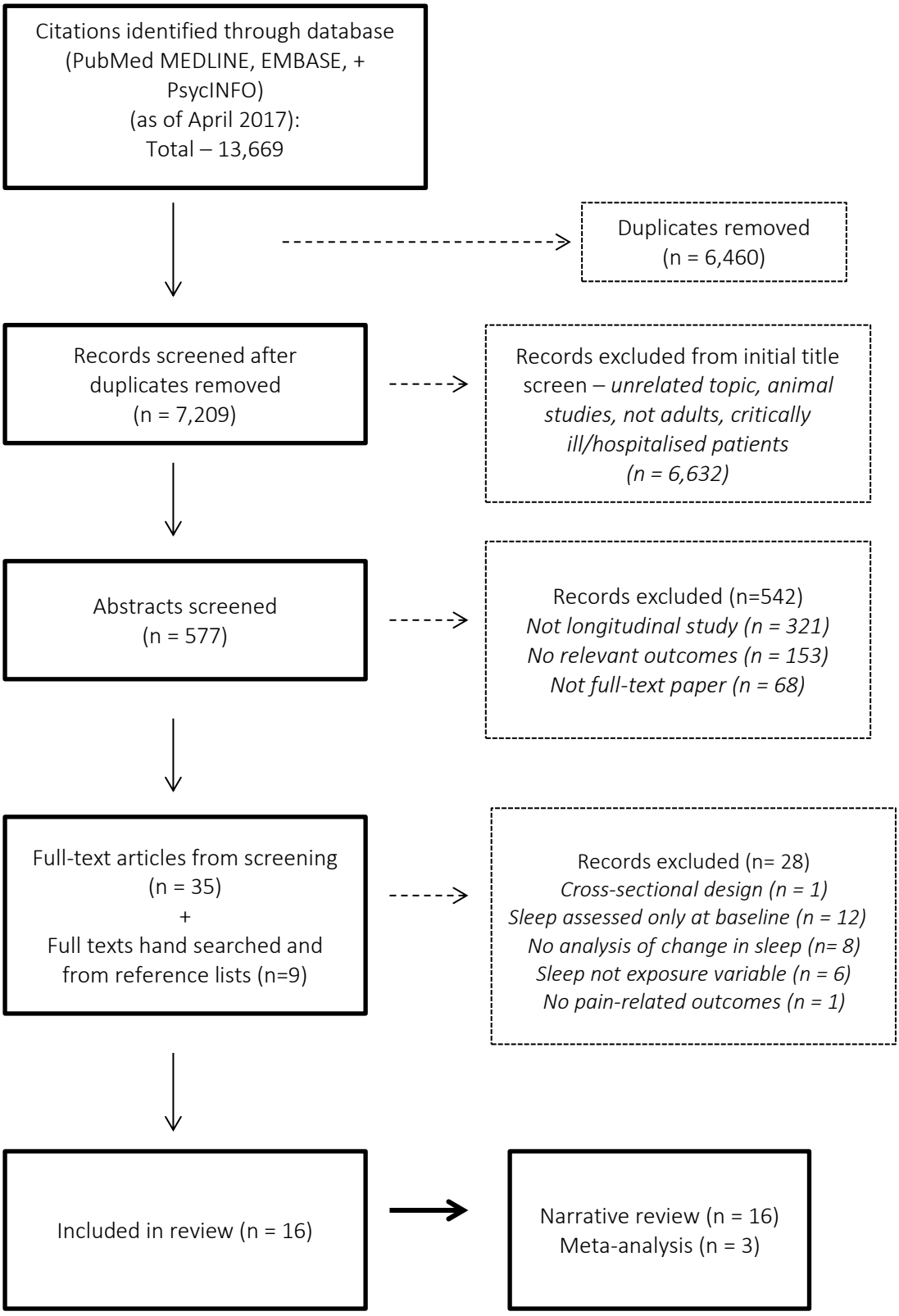
6. Does the study include an outcome measure of health? "Yes" to include

Note: *This excluded studies carried out on acutely ill and hospitalised medically ill or psychiatric patients but did not exclude populations within the general community with other pain or medical conditions. #This included studies where outcome is assessed prospectively OR where there is a sustained measure of the exposure and/or outcome over several assessment points in the same cohort of individuals.

6.2.3 Study selection

Figure 13 (flow diagram) depicts the search and screening process. After the initial title and abstract screen, 44 articles were selected for full-text screening. The full texts of these studies were then assessed for eligibility by the author as per the inclusion criteria, using the same aforementioned screening checklist, but with further emphasis on the following qualities: (i) the study had to have a follow-up design, (ii) that reported a change in sleep parameters using a measure of sleep, (iii) on at least two occasions (baseline and follow-ups) and (iv) that the association of change in sleep with a subsequent pain-related outcome was reported (See Figure 12).

Figure 13 Systematic review – Flowchart of study selection



Following the full-text screening, 28 studies were excluded because they did not meet all the inclusion criteria. Most were excluded as they only assessed sleep at baseline, did not report an analysis of change in sleep or sleep was not the main exposure or predicting variable. Sixteen studies met the full inclusion criteria and were selected for data extraction and data synthesis. All screened full-text articles and included studies were cross-checked for eligibility by a senior member of the review team (NT).

6.2.4 Predicting and outcome variables

The predicting/exposure variable was 'change in sleep' and outcome variable was 'pain-related health outcomes'. 'Change in sleep' was defined as change in any sleep parameters assessed in the study between two time points, e.g., change in sleep quantity, sleep quality, and/or insomnia symptoms. Change in sleep was derived from the difference in sleep at follow-up compared to sleep at baseline. 'Pain-related health outcomes' was operationalised as measures indicative of any pain conditions and/or pain symptoms. This included incidence or presence of pain-related health conditions (back pain, fibromyalgia, arthritis, hip fractures etc.), inflammatory and immune system biomarkers, pain intensity, pain interference, fatigue, pain-related psychosocial functioning, and quality of life. This diverse definition of pain-related health outcome covered different dimensions of the chronic pain experience and can be grouped into those representing (i) the diagnosis (given by health care professionals), (ii) the physiological underlying factors (indicated by relevant

biomarkers) and (iii) individuals' self-reported health-related perceptions and judgements (reflected by responses to questionnaires).

6.2.5 Data extraction

Characteristics of the included studies are presented in Table 2 which summarises the extracted details on study methodology (i.e. final sample size at follow-up, participants' characteristics, sleep assessment measure, outcome assessment measure, number of follow-up assessment and duration of follow-up, adjusted variables, and main results on the association of changes in sleep with outcome measure). For studies with multiple outcome measures, the main results included in this review were those related specifically to the association of change in sleep with a pain-related health outcome. When the relevant information was missing or not reported in the preferred formats in the original paper, the corresponding author of the article was contacted by email, with another follow-up email sent after three weeks if no response. Requests were sent out requesting additional information for seven (Ferrie et al., 2013; Irish, Dougall, Delahanty, & Hall, 2013; Rueggeberg, Wrosch, & Miller, 2012; Shakhar, Valdimarsdottir, Guevarra, & Bovbjerg, 2007; Silva et al., 2009; Suh et al., 2014; Zhang, Lam, Li, Li, & Wing, 2012) of the included articles. Five authors responded and three (Ferrie et al., 2013; Silva et al., 2009; Zhang et al., 2012) were able to provide the requested information.

6.2.6 Risk of bias assessment

Risk of bias was assessed qualitatively using a checklist adapted from: The Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines for reporting observational epidemiological studies (Sanderson, Tatt, & Higgins, 2007) and the modified Agency for Healthcare Research and Quality (AHRQ) quality assessment criteria for observational studies (Manchikanti, Singh, Smith, & Hirsch, 2009). All included studies were assessed for risk of bias using four categories: (i) methods of selecting and assessing study participants, (ii) measurement methods, (iii) design-specific issues (attrition and confounders), and (iv) statistical analysis methods (see Figure 14 for description of each category and the corresponding studies). This descriptive approach to risk of bias assessment provides details on the direction and magnitude of bias across the different methodological domains relevant to the study design and conduct. This approach has been used in other systematic reviews (Bernstein et al., 2016; Hertenstein et al., 2016) and follows the recommendation of the Cochrane collaboration (Higgins & Green, 2011), which advises against the use of summary scores and quality scales.

6.2.7 Data synthesis and analysis

All included studies were synthesised in a narrative form, organised by outcome and presented under three subsections: (i) change in sleep and risk of developing pain condition, (ii) change in sleep and inflammatory or immune function biomarkers, and (iii) change in sleep and self-reported pain-related health status. The primary aim of the systematic review was a narrative review, but we were able to pool

together a subset of the studies reporting the Physical Component Summary (PCS) score from the Short Form Health Survey-36 (SF-36) as a measure of pain-related health status for an exploratory meta-analysis. The SF-36 (Ware, 1993) is a validated measure of health-related quality of life and gives two summary scores: Mental Component Summary (MCS) and Physical Component Summary (PCS). For this review, we were interested in the PCS score which provided a composite score that is a combination of four of the SF-36 subscales (physical functioning, physical role functioning, bodily pain, and general health). Data were available from the three studies which assessed PCS as an outcome measure (Komada et al., 2012; Silva et al., 2009; Suh et al., 2014) and these were included as part of the exploratory meta-analysis to compare differences between associations of sleep change over time with self-reported physical health status.

For the meta-analysis, means and standard deviation of relevant outcome (PCS scores) were extracted for the individuals with no change or with change in sleep over the follow-up period. Change in sleep was a change in the reporting of sleep status at follow-up compared to the reported sleep status at baseline. Standardised mean differences (SMD) between those with change and those with no change in sleep were estimated using a random effect model. A similar method was used for an additional analysis comparing the PCS scores between persistent poor sleepers (i.e. no change in poor sleep between two time points) and persistent good sleepers (i.e. no change in good sleep between two time points). Statistical heterogeneity among the studies was assessed using the I^2 statistic along with visual inspection of the forest plot. Sensitivity

analysis was carried out when a meta-analysis showed significant heterogeneity (I^2 >50%) and involved omitting one study at a time to reveal the potential source of heterogeneity. All statistical analysis was performed using RevMan 5 (The Cochrane Collaboration).

6.3 Results

6.3.1 Characteristics of included studies

The 16 cohort studies included involved a total of 61,100 participants (female %: 50 - 100%; mean age: 30 – 80+ years) from 10 different countries (USA = 6, UK = 2, Israel, Sweden, Japan, Canada, Hong Kong, Finland, Korea and Singapore) and recruited from the community. The length across these studies ranged from 1 month to 23 years, with a median follow-up period of 4.5 years. See Table 22 for all study characteristics.

Table 22 Systematic review – Study characteristics

Citation Country	Final sample Gender Mean age (final sample) Ethnicity	Predicting variable	Pain-related health outcome	Follow-up duration	Timing of assessments	Adjusted variables	Results: sleep deterioration	Results: sleep improvement
Agmon & Armon (2014)[1] **Israel**	N = 2131 66% male 46.20 years Not stated	Change in self-reported insomnia symptoms from Athens Insomnia Scale.	Diagnosis of back pain (confirmed through medical records and medical interview with physician)	3.7 years	Predicting variable and pain-related health outcome assessed at three time points spread over a period of 3.7 years.	Age, gender, education, physical activity, self-rated health, smoking, BMI, levels of high-sensitivity C-reactive protein.	Increase in insomnia symptoms from Time 1 to Time 2 was associated with increased risk of diagnosis of back pain at Time 3 (OR = 1.40 94% CI 1.10-1.71).	None reported.
Campbell et al. (2013)[2] **UK**	N = 2622 42.1% male Not stated (range 50 – 80+ years) Not stated	Change in self-reported sleep quality (Jenkins Sleep Questionnaire).	Self-reported pain presence, persistence, interference and depressive symptoms.	6 years	Predicting variable and pain-related health outcome assessed at three time points (Baseline, 3 years and 6 years).	Age, gender, alcohol consumption, smoking, marital status, employment status, and BMI.	New onset of sleep problems associated with increased pain interference and increased risk of depression at follow-up.	None reported.

Ferrie et al. (2013)[2] UK	N = 5,003 71.8% male 49.3 years Not stated	Change in self-reported sleep quantity.	Immune marker – CRP and IL-6 levels.	5 years	Predicting variable and pain-related health outcome assessed at two time points (baseline and follow-up).	Age, gender, occupation, systolic blood pressure, BMI, total cholesterol, and diabetes.	Decrease in sleep quantity significantly associated with higher IL-6 levels but not CRP at follow-up.	Increase in sleep quantity not significantly associated with CRP and Il-6 levels at follow-up.
Foley et al. (1999)[4] USA	N = 6899 62% male Not stated (aged 65+ years) Not stated	Change in self-reported insomnia symptoms (difficulty falling asleep or early morning arousal).	Diagnosis of hip fracture by physician.	3 years	Predicting variable and pain-related health outcome assessed at two time points (baseline and follow-up).	Age, gender, community (state of residence), income, and education.	New incidence and persistence of insomnia symptoms significantly associated with newly reported presence of hip fracture at follow-up (OR = 2.08 95% CI 1.18, 3.65).	None reported.
Irish et al. (2013)[5] USA	N = 128 63% male 36.45 years 92% White	Change in self-reported sleep quality (Pittsburgh Sleep Quality Index [PSQI]).	Self-report physical symptoms. Immune marker – natural killer (NK) cell number and cytotoxicity (n=51).	12 months	Two time points. Predicting variable assessed at baseline and follow-up. Pain-related health outcome assessed only at follow-up.	None stated.	Deterioration of sleep quality not significantly correlated with pain-related health outcomes at follow-up.	Improvement in sleep quality not significantly correlated with pain-related health outcomes at follow-up.

Janson et al. (2001)[6] Sweden	N = 2602 100% male Not stated (range 30 – 69 years) Not stated	Change in self-reported insomnia symptoms (difficulty falling asleep and difficulty maintaining sleep).	Diagnosis of a medical disorder, including joint or low back disorders by physician.	10 years	Predicting variable and pain-related health outcome assessed at two time points (baseline and follow-up).	Age, BMI smoking, physical inactivity, alcohol dependence, and medical disorders.	Increase in insomnia symptoms associated with newly reported medical disorder at follow-up.	None reported.
Komada et al. (2012)[7] Japan	N = 1577 43% male 58.6 years Not stated	Change in self-reported sleep quality (Japanese version of PSQI – cut-off score of 5.5 indicating insomnia).	SF36 – PCS	2 years	Predicting variable and pain-related health outcome assessed at two time points (baseline and follow-up).	Age, gender, disease status, alcohol consumption, smoking habits, living status, sleep medication use, depression, MCS, PCS, and PSQI scores at baseline.	New incidence of insomnia symptom associated with a decline in PCS scores at follow-up.	Remission of insomnia symptoms not significantly associated with increase in PCS scores at follow-up.
Parthasarathy et al. (2015)[8] USA	N = 1409 45% male 47 years Not stated	Change in self-reported insomnia symptoms derived from ICSD insomnia diagnosis criteria.	Immune marker – CRP levels assessed in 722 participants.	6 years	Two time points. Predicting variable assessed at baseline and follow-up. Pain-related health outcome assessed only at 6-year follow-up.	Age, gender, BMI, smoking, physical activity, use of alcohol and medications to get to sleep, marital status, habitual snoring, diabetes mellitus and hypertension.	Persistence of insomnia symptoms associated with an increase in and higher CRP levels at follow-up compared to those with intermittent or no insomnia.	None reported.

Quan et al. (2005)[9] USA	N = 4667 40.9% male 72.3 years Not stated	Change in self-reported insomnia symptoms (trouble falling asleep, frequent awakenings and excessive daytime sleepiness).	Diagnosis of arthritis by physician.	1 – 4 years (mean 3.55)	Predicting variable and pain-related health outcome assessed at two time points (baseline and follow-up).	Age, gender, race, time interval between baseline and follow-up examinations.	New incidence of insomnia symptoms associated with baseline report of arthritis in women.	None reported.
Rueggeberg et al. (2012)[10] Canada	N = 157 48.40% male 71.71 years Not stated	Change in self-reported sleep quantity using items from Brief Pittsburgh Sleep Quality Index [PSQI].	Immune marker – diurnal cortisol secretion.	4 years	Predicting variable and pain-related health outcome assessed at three time points (Baseline, 2 years and 4 years).	Age, gender, partnership status, education, chronic illness, cortisol-related medication usage, BMI and smoking.	Decrease in sleep quantity associated with significant increases in cortisol secretion level at follow-up.	Increase in sleep quantity not significantly associated with changes in cortisol level at follow-up.
Ropponen et al. (2013)[11] Finland	N = 18979 47% male 45 years Not stated	Change in self-reported sleep quality and sleep quantity.	Diagnosis of back pain by physician and included in national register database on disability pension due to low back pain diagnosis.	23 years	Two time points. Predicting variable assessed at baseline and follow-up. Pain-related health outcome assessed only at follow-up.	Age, education, socioeconomic status, marital status, BMI, physical activity, musculoskeletal pain locations, smoking, alcohol, life satisfaction, use of hypnotic agents, diurnal type, and type of work.	Deterioration and persistent of poor sleep quality associated with higher risk of low back pain diagnosis at follow-up (HR = 1.84 95% CI 1.01-3.37). No association with decrease in sleep quantity.	Improvement in sleep quantity and quality not associated with risk of low back pain diagnosis at follow-up.

Shakhar et al. (2007)[12] USA	N = 45 0% male 39.7 years 47% White 40% Black	Change in self-reported sleep quantity.	Immune marker – Natural Killer Cell Activity (NKCA) levels.	1 month	Two time points. Predicting variable and pain-related health outcome assessed at both baseline and follow-up.	Self-reported POMS Depression and Tension subscales levels.	Decrease in sleep quantity not associated with NKCA levels at follow-up.	Increase in sleep quantity was significantly related to an increase in NKCA levels at follow-up.
Silva et al. (2009)[13] USA	N = 3078 45% male 67.3 years 75% White	Change in self-reported insomnia symptoms (difficulty initiating and maintaining sleep, daytime sleepiness.	SF36 – PCS	5 years	Predicting variable and pain-related health outcome assessed at two time points (baseline and follow-up).	Age, gender, BMI, smoking, sleeping pill use, PSG total sleep time, baseline coronary heart disease and respiratory disease.	Deterioration of insomnia symptoms was not associated with PCS scores. Increase in daytime sleepiness was associated with decline in PCS scores at follow-up.	Improvement of insomnia symptoms not significantly associated with PCS scores at follow-up.
Smagula et al. (2016)[14] Singapore	N = 8265 41.05% male 64.59 years 98.6% Asian	Change in self-reported sleep quantity.	Diagnosis of arthritis by physician and diagnosis of hip fracture recorded on hospital database.	12.7 years	Predicting variable and pain-related health outcome assessed at two time points (baseline and follow-up).	Age, gender, baseline sleep duration.	No association between change in sleep and arthritis. Increase in sleep quantity from 6-8 to >8hours linked with greater risk of hip fracture at follow-up (OR =	None reported.

							1.52 95% CI 1.16 – 2.00).	
Suh et al. (2014)[15] Korea	N = 1247 40.1% male 54.3 years Not stated	Change in self-reported insomnia symptoms (difficulty initiating and maintaining sleep, early morning awakenings and unrefreshed in the morning).	SF36 – PCS	2 years	Predicting variable and pain-related health outcome assessed at three time points spread over 2 years.	Age, gender, marital status, employment, smoking, alcohol, hypertension, diabetes, depression, PSQI and BMI score.	Deterioration and persistence of insomnia symptoms associated with significantly lower PCS scores at follow-up.	None reported.
Zhang et al. (2012)[16] Hong Kong	N = 2291 50% male 46.3 years Not stated	Change in self-reported insomnia symptoms (non-restorative sleep).	Subjective physical health status. Diagnosis of arthritis and other chronic pain condition by physician.	5 years	Predicting variable and pain-related health outcome assessed at two time points (baseline and follow-up).	Age, gender, education, family income, medication, and comorbid sleep problems (insomnia subtypes, habitual snoring, short sleep duration).	New incidence of insomnia symptoms significantly associated with higher risk of reporting a chronic pain condition at follow-up (OR = 2.47 95% CI 1.30-4.69)	Remission of insomnia symptoms associated with a relatively lowered risk of developing a chronic pain condition at follow-up (OR = 1.23, 95% CI 0.57-2.59).

6.3.2 Measures of sleep changes

Most studies assessed sleep twice, once at baseline and once at follow-up, except for four studies (Agmon & Armon, 2014; Campbell et al., 2013; Rueggeberg et al., 2012; Suh et al., 2014) that assessed sleep at three time points. Sleep was primarily assessed using self-report. Five of the studies (Foley, Monjan, Simonsick, Wallace, & Blazer, 1999; Janson, Lindberg, Gislason, Elmasry, & Borman, 2001; Quan et al., 2005; Suh et al., 2014; Zhang et al., 2012) assessed self-reported insomnia symptoms (difficulty falling asleep, difficulty maintaining sleep, early morning awakenings, symptoms of impaired daytime functioning, concern about not getting enough sleep and daytime sleepiness) and other similar general indicators of non-restorative sleep. *Parthasarathy* et al. (Parthasarathy et al., 2015) assessed these insomnia symptoms based on definitions derived from the International Classification of Sleep Disorders insomnia diagnostic criteria. A*gmon and Armon* (Agmon & Armon, 2014) used a validated questionnaire (Athens Insomnia Scale) to assess insomnia symptoms. Three studies used validated questionnaires, e.g., the Pittsburgh Sleep Quality Index (PSQI) (Irish et al., 2013; Komada et al., 2012) and the Jenkins Sleep Questionnaire (Campbell et al., 2013), to index sleep quality. Four studies (Ferrie et al., 2013; Rueggeberg et al., 2012; Shakhar et al., 2007; Smagula, Koh, Wang, & Yuan, 2016) assessed changes in sleep quantity by asking self-reported sleep duration at baseline and follow-up. One study (Ropponen et al., 2013) assessed sleep using both self-reported sleep quality and sleep quantity. Only one study (Silva et al., 2009) used both self-report and overnight polysomnography (PSG) to assess sleep. However, in this study, PSG was

only used to index overnight respiratory disturbance and no other objective sleep parameters were reported.

6.3.3 Measures of pain-related health outcomes

Seven studies (Agmon & Armon, 2014; Foley et al., 1999; Janson et al., 2001; Quan et al., 2005; Ropponen et al., 2013; Smagula et al., 2016; Zhang et al., 2012) focused on looking at change in sleep and risk of developing a pain-related health condition (namely; arthritis, back pain, general chronic pain, hip fractures) by means of self-report or using information from physician medical interviews, medical records, and linked national databases. Four studies (Ferrie et al., 2013; Parthasarathy et al., 2015; Rueggeberg et al., 2012; Shakhar et al., 2007) assessed changes in sleep in relation to physiological health status. This included assessments of inflammatory and immune system biomarkers. There was no restriction placed on the diversity of biomarkers, as long as they were immune or inflammatory biomarkers with established connection to pain conditions (Marchand et al., 2005). Three studies (Komada et al., 2012; Silva et al., 2009; Suh et al., 2014) assessed the effect of changes in sleep on self-reported pain-related health status, mostly using the Physical Component Summary and Bodily Pain scores derived from the SF-36. One study (Campbell et al., 2013) used a general health assessment questionnaire to determine pain presence and pain interference. Only one study (Irish et al., 2013) assessed changes in both self-reported physical pain symptoms and immune biomarkers.

6.3.4 Risk of bias assessment results

The results of the risk of bias assessment are graphically presented in Figure 14. Most of the reviewed studies were “low/medium risk” except for one (Foley et al., 1999), which was categorised as “high risk” in three out of the four risk categories. The main issues affecting the quality of the included studies were a heavy reliance on self-report and a lack of objective sleep/pain-related health outcome measures (i.e., polysomnography-determined sleep and quantitative sensory testing). In addition, some studies provided insufficient details on attrition, resulting in a lack of comparison with non-responding participants, which could affect the generalisability of association between variables and bias the interpretation of the results. Finally, other methodological issues included studies with small sample sizes (e.g., less than 50 in one study) and short follow-up period (i.e. 1 month). Small sample size in itself may not be an issue when combined with greater numbers of follow-up assessments as this would increase statistical power. However, statistical power to detect significant association will be limited in the case of both a small sample size and limited follow-up assessments.

Figure 14 Systematic review – Risk of bias checklist and rating

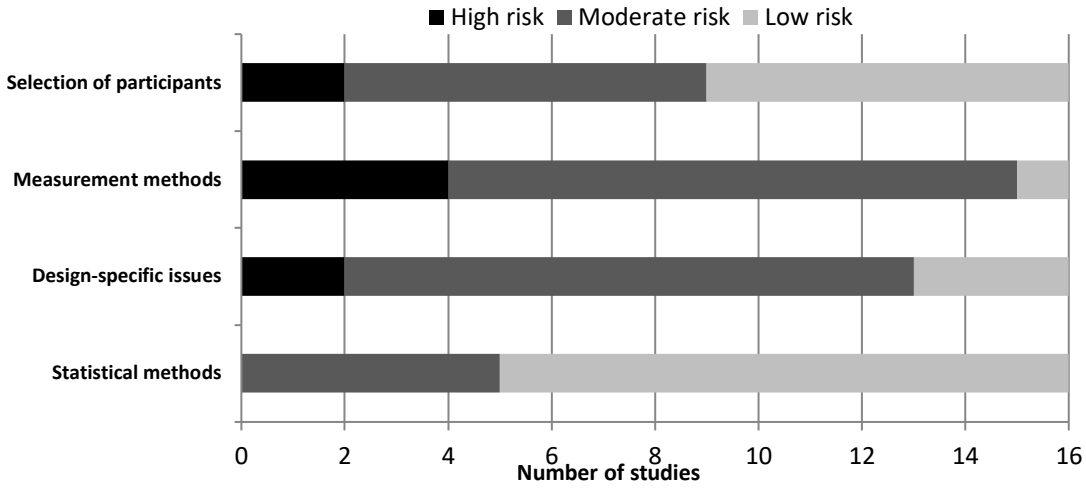


Figure Key:	High risk	Moderate risk	Low risk
Selection and assessment of participants	Minimal description of participants and inclusion characteristics. Sample size n < 100 with no justification given and two follow-up assessments. Ref: 4, 12	Some but insufficient description of participants and inclusion characteristics. Sample size n = 100 – 1000 and no justification given but at least two follow-up assessments. Ref: 6,7,10,16,5,8,14	Clear detailed description of participants and inclusion characteristics. Sample size n > 1000 or justification of sample size, and more than two follow-up assessments Ref: 9,13,2,3,11,1,15
Measurement methods	Uses only non-validated subjective measure of exposure or outcome. Ref: 4,6,9,16	Uses only validated subjective measure of exposure or outcome. Ref: 12,7,10,2,3,5,11, 1,15,8,14	Uses a standard objective and a validated subjective measure of exposure and outcome. Ref: 13
Design – specific issues	Attrition rate > 80%. Minimal description of attrition levels and comparison of non-responders with participating individuals. Very little/no confounding variables stated and controlled for. Ref: 4,14	Attrition rate 60 – 80%. Insufficient description of attrition levels and comparison of non-responders with participating individuals. Limited range of confounding variables stated and controlled for. Ref: 9,12,13,10,16,3, 5,11,1,15,8	Attrition rate < 60%. Clear description and comparison of non-responders with participating individuals. Describes and controls for a range of relevant confounding variables. Ref: 6,7,2
Statistical methods	Poorly described statistical analysis. Lack of appropriate significance testing and minimal justification for lack of further sensitivity analysis. Ref: N/A	Statistical analysis methods not sufficiently described. Insufficient details to justify lack of further sensitivity analysis. Ref: 6,12,5,15	Well-described and appropriate statistical analysis. Reports adjusted estimates, missing data, subgroups and other sensitivity analysis. Ref: 4,9,13,7,10,16 2,3,11,1,8,14

6.3.5 Association of change in sleep with the risk of developing a pain condition

Increase in insomnia symptoms

The reviewed studies conveyed the relationship between a negative change in insomnia symptoms and risk of developing a pain condition in those with no pain condition at baseline. Foley et al. (1999) reported that newly developed insomnia symptoms over a three-year period doubled the risk of the presence of self-reported hip fracture problems at follow-up (OR = 2.08 95% CI 1.18, 3.65). Zhang et al. (2012) also reported that incidence of insomnia symptoms and non-restorative sleep was associated with over a two-fold increase in risk of reporting a chronic pain disorder at five-year follow-up (OR = 2.47 95% CI 1.30-4.69). Agmon and Armon (2014) showed that increase in insomnia symptoms was associated with a 40% increased risk of new back pain diagnosis over a period of over 3 years (OR = 1.40 95% CI 1.10-1.71). With a much longer follow-up period of 23 years, Ropponen et al. (2013) reported an association of persistent poor sleep (HR = 1.84 95% CI 1.01-3.37) with an 84% increased risk of being included on the national register for disability pension due to low back pain diagnosis at follow-up. However, reduction in sleep quality (HR = 1.17, 95% CI 0.77-1.77) was not significantly associated with an increased risk. Janson et al. (2001) also found that an increase in insomnia symptoms over a ten-year period was associated with newly reported medical conditions including joint and low back pain disorder at follow-up, although the risk ratios were not specified in this report. In contrast to the other studies, Quan et al. (2005) did not find a link between the

development of insomnia symptoms over a four-year period and the presence of pain conditions at follow-up.

Decrease in insomnia symptoms

Notably, only Zhang et al. (2012) reported the effect of a positive change in insomnia symptoms. They reported an association of remission of insomnia symptoms with a 23% lowered risk of developing a chronic pain condition at follow-up, but this association was not significant (OR = 1.23, 95% CI 0.57-2.59).

Increase in sleep quantity

Ropponen et al. (2013) did not find an association between increased sleep quantity and risk of low back pain diagnosis over a 23-year follow-up period. Smagula et al. (2016) similarly, did not find a link between an increase in sleep quantity and developing arthritis at ten-year follow-up. However, these authors did report that an increase in nightly sleep quantity to > 8hrs was associated with a 52% greater risk of hip fracture problems as registered on a national hospital database (OR = 1.52 95% CI 1.16 – 2.00). The causal order of the relationship was unclear; the authors suggested that recent hip fractures and consequent low physical activity might be key determinants of the lengthened sleep duration.

Summary – change in sleep and risk of developing a pain condition

In the studies reviewed, reporting a negative change in insomnia symptoms was associated with a greater risk of developing and reporting a pain-related medical

condition. On the other hand, a remission or a positive change in insomnia symptoms did not necessarily neutralise or fully avert the risk of developing chronic pain. Moreover, an increase in sleep quantity might not be associated with a positive pain-related health outcome.

6.3.6 Association of change in sleep with inflammatory or immune biomarkers

Increase in sleep quantity and natural killer cells activities (NKCA)

Shakhar et al. (2007) and Irish et al. (2013) looked at the association between changes in sleep quantity and natural killer cells activities (NKCA). Natural killer cells play a physiologically protective role in activating immune responses to contain and clear viral infections. Low levels are linked to certain pain conditions such as fibromyalgia, and possibly contribute to exaggerated pain response in some individuals with chronic pain (Landis et al., 2004; Marchand et al., 2005). Shakhar et al. (2007) using a small sample (*n* = 45) with a short (1 month) follow-up found that an increase in sleep quantity was associated with an increase in NKCA levels. On the other hand, Irish et al. (2013) did not find a relationship between either an increase or decrease in sleep quantity and quality over 1-year with changes in natural killer cell levels. The analysis was carried out in a small subset (*n* = 51) of their sample and the standard deviation for mean NK cell number was quite large (Mean = 285.21, SD = 204.53).

Decrease in sleep quantity and cortisol levels

Cortisol is the body's primary stress hormone needed to activate the physiological 'flight or fight' response; however, high cortisol levels interfere with immune functions and are a risk factor for many illnesses (McEwen, 1998; McEwen & Kalia, 2010). Chronic pain states have been linked to sustained stress response and consequently higher cortisol levels (Vachon-Presseau et al., 2013). Rueggeberg et al. (2012) found that a decrease in sleep quantity (by 1 standard deviation) over the first two years of their study was associated with an increase in diurnal cortisol secretion over the total four-year follow-up period. By contrast, an increase in sleep quantity was not significantly associated with cortisol levels.

Decrease in sleep quantity and Interleukin-6(IL-6) and C-reactive protein (CRP) levels

IL-6 and CRP are markers of systemic inflammation, activated to combat infections (Watkins & Maier, 2000). They also possess a pain facilitatory effect and can alter pain modulation and pain processing (De Jongh et al., 2003; Irwin, 2011; Irwin et al., 2016). Persistent elevated presence of these markers has been observed in several chronic illnesses and implicated in the generation, maintenance and severity of chronic pain conditions (Lund Haheim, Nafstad, Olsen, Schwarze, & Ronningen, 2009; Marchand et al., 2005). Ferrie et al. (2013) analysing data from the UK Whitehall study, did not find an association between increases in sleep quantity and changes in levels of IL-6 and CRP. However, they revealed that a five-year decrease in sleep quantity was associated with higher levels of inflammatory markers. In the fully-adjusted

analysis controlling for age, sex, occupation, blood pressure, BMI, cholesterol level and presence of diabetes, each 1-hour decrease in sleep quantity was associated with a 2.7% higher level of IL-6. The reduction in sleep quantity was also associated with a 4.2% higher level of CRP, but this association was not statistically significant.

Summary – change in sleep and inflammatory or immune biomarkers

It appeared that a reduction in sleep quantity is temporally linked to elevated levels of inflammatory and immunological markers. However, a reverse association was not noted for an increase in sleep quantity. Only one study examined the effect of changes in insomnia symptoms and sleep quality on inflammatory and immunological markers indicative of pain. Parthasarathy et al. (2015) found that CRP levels were higher and increased at a greater rate in those with persistent insomnia compared with those with intermittent or no insomnia. It is important to note that the assessment of the biomarkers reviewed were not pain-specific. We cannot rule out other disease processes involving inflammation that might have affected the relationship of sleep changes with deterioration in health status.

6.3.7 Association of change in sleep with pain-related health status

Three of the reviewed studies (Komada et al., 2012; Silva et al., 2009; Suh et al., 2014) assessed perceived physical health status using the Physical Component Summary (PCS) from the SF-36. PCS is a summary of the SF-36 subscales that assess physical functioning, physical role functioning, bodily pain, and general physical health (Ware, 1993). Lower scores on the PCS and the bodily pain subscale indicates greater

physical health limitations and pain-related interference and disability. All three studies reviewed reported the PCS scores, but only the Silva et al. (2009) study provided the subcomponent bodily pain score separately.

Increase in insomnia symptoms

All three studies revealed an association of lowered PCS scores over time with an increase in or maintenance of insomnia symptoms. Silva et al. (2009) found that those who developed insomnia symptoms or whose insomnia symptoms persisted over a five-year follow-up period reported a decline in PCS scores and lower PCS scores at follow-up, compared with persistent good sleepers with no change in insomnia symptoms. Komada et al. (2012) used PSQI scores to assess those with newly developed insomnia symptoms over a two-year follow-up period. These individuals who reported increased insomnia symptoms over time reported a decline in PCS scores from baseline to follow-up and worse PCS scores at follow-up compared with persistent good sleepers. Suh et al. (2014) also reported a similar decrease in PCS score over a 2-year follow-up period for those with worsening and persistent insomnia symptoms.

Two studies used other forms of pain health assessment such as self-reported pain symptoms. Irish et al. (2013) did not find a one-year increase or decrease in PSQI to be related to physical pain symptoms. In their sample of rescue workers who performed rescue and clean-up operations at the site of a major airplane crash, the findings might have been affected by life stressors and other symptoms of

psychological distress following the crash. However, over 80% of the sample reported 'good' or 'excellent' physical health and had stable PSQI scores over the year. Campbell et al. (2013) on the other hand, found that new onset of sleep problems and insomnia symptoms in a chronic pain sample over three years significantly increased the risk of depression (relative risk 3.47) at six-year follow-up. Importantly, this risk was mediated by increased pain interference measured at three-year follow-up and the findings revealed a significant association between increased insomnia symptoms and increased pain interference.

Summary – change in sleep and pain-related health status

Compared to no change in good sleep, an increase in insomnia symptoms was associated with worse pain outcomes and physical functioning status over time.

6.3.8 Sleep change trajectories and PCS scores

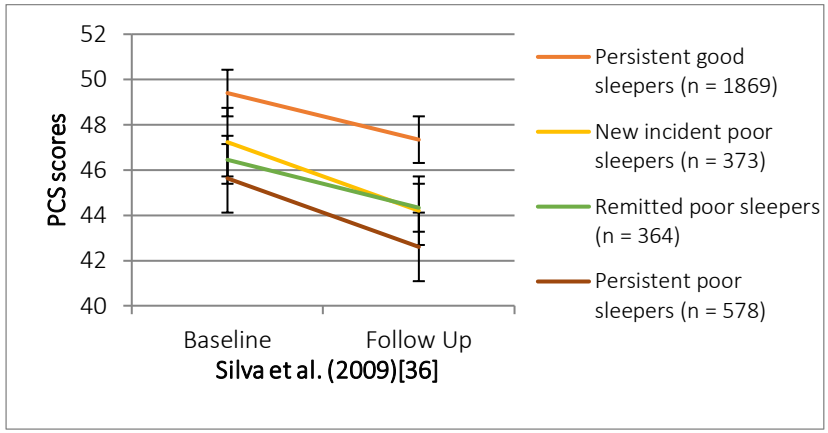
To further explore the observed trend of changes in sleep and physical functioning, the next step was to quantitatively and visually compare change in PCS from baseline to follow-up by sleep change trajectories (Figure 15). Namely, the four trajectories are (i) persistent good sleepers (no sleep disturbance at baseline and follow-up), (ii) new incident poor sleepers (developed sleep disturbance from baseline to follow-up), (iii) remitted poor sleeper (sleep disturbance resolved from baseline to follow-up), and (iv) persistent poor sleepers (sleep disturbance at baseline and follow-up).

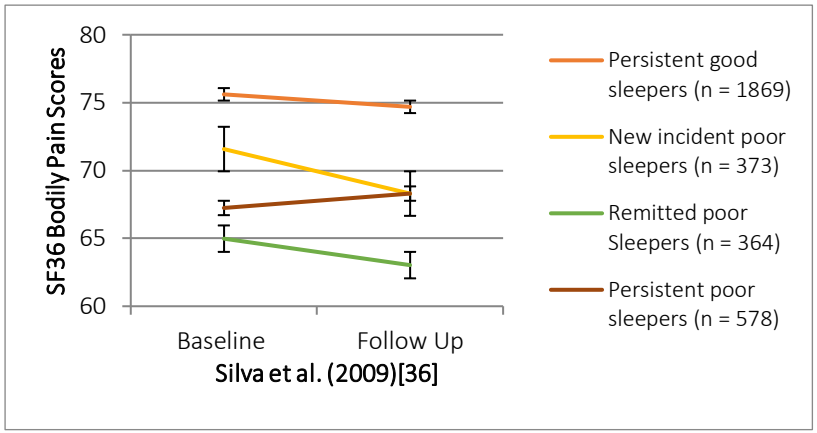
Across the three studies with this kind of data (Komada et al., 2012; Silva et al., 2009; Suh et al., 2014), persistent good sleepers fared the best and reported the highest PCS scores at both baseline and follow-up compared with the other trajectories. They also showed the greatest stability in PCS scores across both time points. New incident poor sleepers showed a decline in PCS scores. Whilst the PCS scores for remitted poor sleepers also showed fluctuations, the effect was not consistent across studies and the direction of the effect was unclear. Persistent poor sleepers fared the worst; they presented with the lowest PCS scores at both baseline and follow-up.

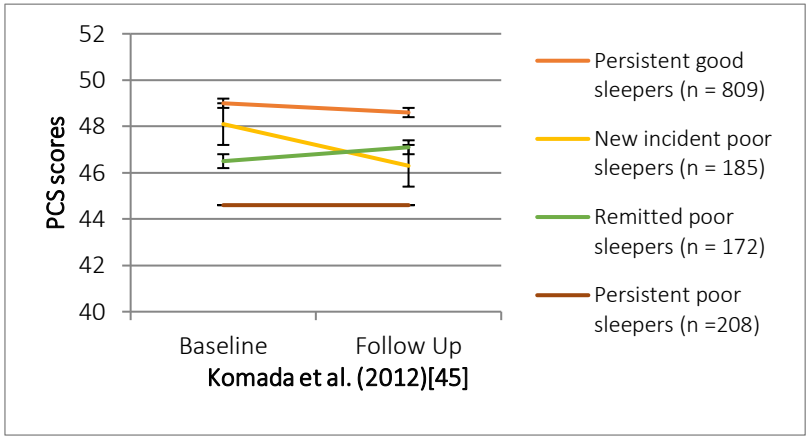
Subcomponent scores for bodily pain could not be extracted for all three studies, but using the data available from Silva et al. (2009), comparison of the different sleep change trajectories using the bodily pain subscale of the PCS was possible for this particular study. Remitted poor sleepers had the highest bodily pain score at baseline and this worsened at follow-up. However, the other patterns observed for the bodily pain subscale were similar to overall PCS scores; persistent good sleepers fared the best whereas new incident poor sleepers showed an increase in pain scores over time.

Figure 15 Systematic review – Sleep change trajectories and PCS scores

(Lower scores on the PCS and Bodily Pain subsection indicates greater physical health limitations and pain related interference and disability)







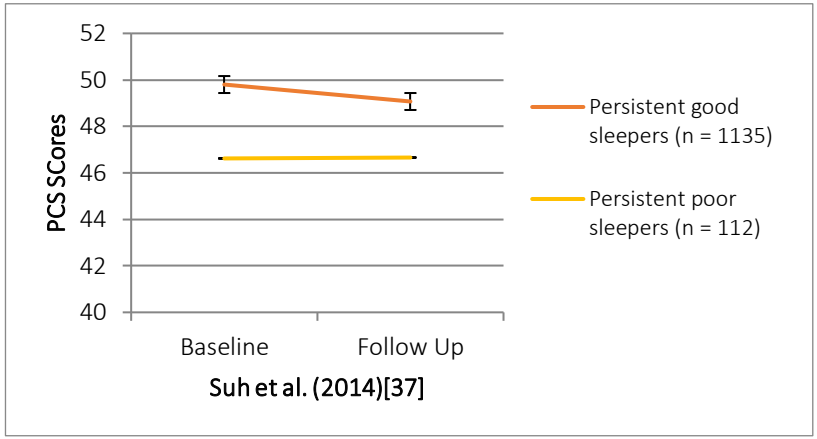


Figure 16 Systematic review – Exploratory meta-analyses

Figure 16a Forest plot of PCS scores at follow-up, comparing individuals who were 'persistent poor sleepers' with those who were 'persistent good sleepers'. Lower PCS scores represent worse physical functioning and health limitations.

	Persistent Poor Sleepers			Persistent Good Sleepers				Std. Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95% CI**
Komada et al 2012	44.6	7.8	268	48.6	6.2	809	33.4%	-0.60 [-0.74, -0.46]
Silva et al 2009	42.6	11.56	578	47.34	10.09	1869	41.1%	-0.45 [-0.55, -0.36]
Suh et al 2014	46.66	10.08	112	49.07	7.46	1135	25.5%	-0.31 [-0.51, -0.12]
Total (95% CI)			**958**			**3813**	**100.0%**	**-0.47 [-0.61, -0.33]**

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 6.08$, df = 2 (P = 0.05); $I^2 = 67\%$
Test for overall effect: Z = 6.55 (P < 0.00001)

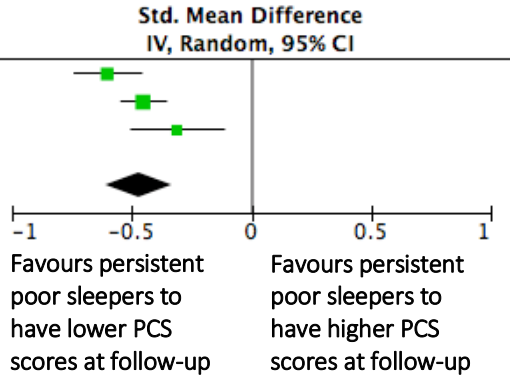


Figure 16b Forest plot of PCS scores at follow-up, comparing individuals who developed sleep disturbances over time ('new poor sleepers') with those who were 'persistent good sleepers' (i.e., evaluating the effect of negative sleep deterioration). Lower PCS scores represent worse physical functioning and health limitations.

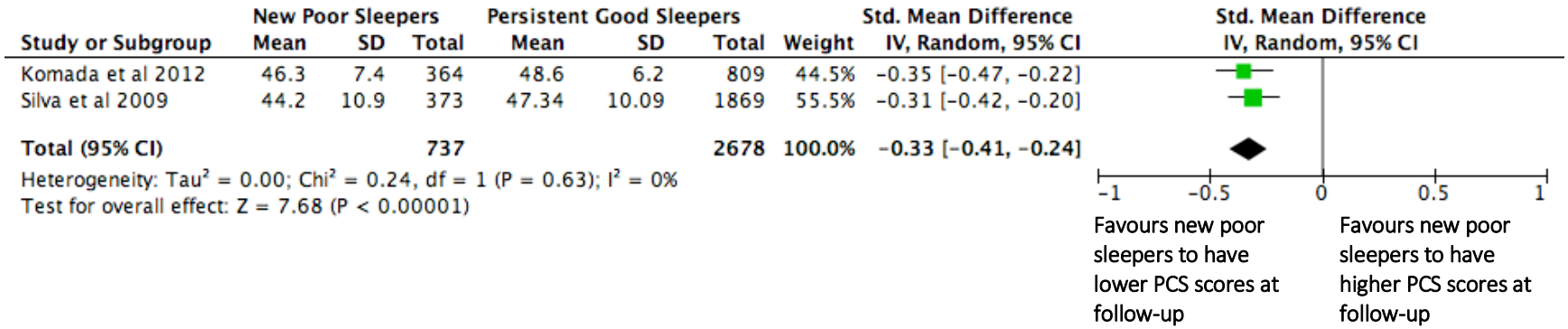
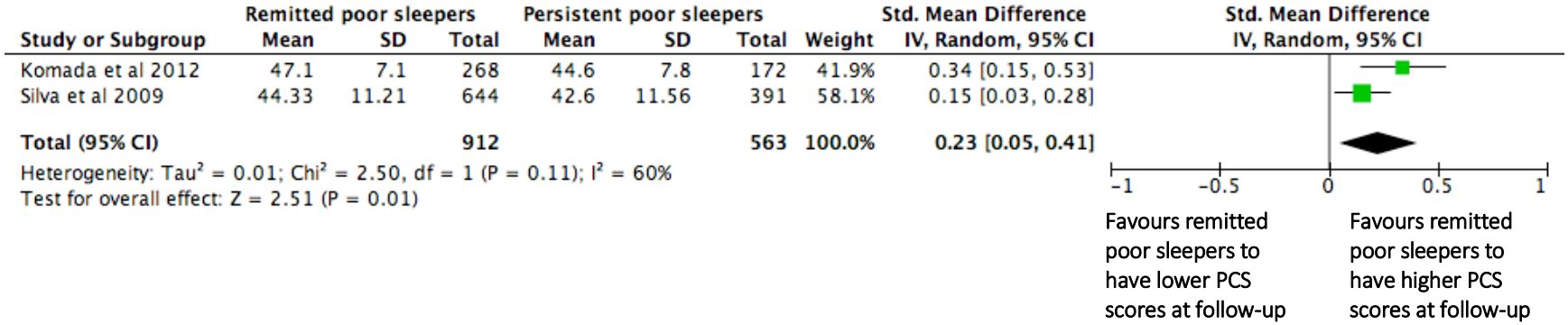


Figure 16c Forest plot of PCS scores at follow-up, comparing individuals whose sleep disturbances remitted over time ('remitted poor sleepers') with those who were 'persistent poor sleepers' (i.e., evaluating the effect of positive sleep improvement). Lower PCS scores represent worse physical functioning and health limitations.



6.3.9 Exploratory meta-analysis

Three exploratory meta-analyses were conducted to compare PCS score at follow-up to examine how different trajectories of sleep changes affected physical health. This was done using available data from the three studies (Komada et al., 2012; Silva et al., 2009; Suh et al., 2014) using PCS as an outcome measure. The total number of participants across the three studies was 5902 (female: 57.1%, mean age: 60 years) and the follow-up periods were 5 years and 2 years. An analytic approach was used that allowed comparison of the PCS scores at follow-up between persistence of poor sleep and good sleep, and then examine the separate association of sleep deterioration and sleep improvement with PCS scores. Statistics of these analyses are summarised with forest plots in Figures 16a-c.

Meta-analysis 1: Persistence of poor sleep and PCS scores

In comparing persistent poor sleep with persistent good sleep (Figure 16a), persistent poor sleep was significantly associated with lower PCS scores at follow-up. This analysis showed significant heterogeneity ($I^2 = 67\%$). Sensitivity analysis identified Komada et al. (2012) as the potential source, possibly due to the use of a Japanese version of the PSQI compared to individual questions for assessing insomnia symptom as used in the other studies. Omitting this study reduced I^2 from 67% to 39% and decreased the effect from -0.47 to -0.41 (95% CI -0.54, -0.25) $Z = 6.23$, $p < 0.00001$. This standardised mean difference indicates a medium effect size and that approximately 66% of those with persistent poor sleep had worse PCS scores at follow-up than those with persistent good sleep.

Meta-analysis 2: Sleep deterioration and PCS scores

New poor sleepers were compared with persistent good sleepers to assess the associations with sleep deterioration over time (Figure 16b). Developing insomnia symptoms was associated with significantly lower PCS scores at follow-up compared with persistent good sleep. There was no significant heterogeneity across the studies. A standardised mean difference of -0.33 (95% CI -0.41, -0.24) Z = 7.68, p < 0.00001 is a medium effect size indicating that approximately 62% of those who developed sleep problems from baseline to follow-up had worse PCS score at follow-up than those with persistent good sleep.

Meta-analysis 3: Sleep improvement and PCS scores

Finally, remitted poor sleepers were compared with persistent poor sleepers to assess the association with sleep improvement over time (Figure 16c). Remission of insomnia symptoms was significantly associated with higher PCS scores at follow-up compared with persistent poor sleepers whose sleep problems showed no improvement. However, the analysis did show heterogeneity across the two studies (I^2 = 60%). Given that only two studies were included in the analysis, we were unable to conduct a sensitivity analysis to identify the source of heterogeneity. The standardised mean difference effect of 0.23 (95% CI 0.05, 0.41) Z = 2.51, p < 0.01, which if heterogeneity was not an issue, suggests that approximately 58% of those with improvement in sleep from baseline to follow-up had better PCS scores at follow-up than those with persistent sleep problems.

Summary – exploratory meta-analyses

Findings from the exploratory meta-analyses suggest that incidence and persistence of sleep problems may be associated with worse physical health over

time. Remission of sleep disturbances was associated with better outcome, but the effect was weak. PCS scores usually have high test-retest reliability in the general population, yet, a drop in PCS scores was seen in those with persistent sleep problems and those who newly developed sleep problems. Such drop in PCS scores could be interpreted as signifying "some more" physical limitation among these individuals (Ware, 1993). Moreover, the PCS scores of these individuals at follow-up were comparable to levels of PCS scores observed in population groups with minor medical conditions or serious physical illnesses (Ware, 1993; Ware, Kosinski, & Keller, 1996). Together, these findings suggest a detrimental influence of deterioration in sleep quality and maintenance of sleep problems in contrast to persistent good sleep.

6.4 Discussion

6.4.1 Summary of findings

Findings from this systematic review and meta-analysis indicate that sleep deterioration is associated with pain-related health outcomes over time. There was, however, insufficient evidence to suggest a clear positive effect of sleep improvement on pain. Overall, the findings extend previous evidence highlighting poor sleep at baseline as a risk factor for developing a future pain condition (Gupta et al., 2007; McBeth et al., 2014; Mundal, Gräwe, Bjørngaard, LInaker, & Fors, 2014). A decline in sleep quality and sleep quantity was associated with a two- to three-fold increase in risk of developing a pain condition, small elevations in levels of inflammatory markers, and a decline in self-reported physical health status. An exploratory meta-analysis further revealed that deterioration in sleep was associated with worse self-reported

physical functioning (medium effect size), whilst improvement in sleep was associated with better physical functioning (small effect size). The review consolidates evidence that changes in sleep are prospectively associated with pain-related outcomes, adding weight to the argument for a causal association and highlighting the need for further longitudinal investigations on the long-term impact of sleep improvements.

6.4.2 Disentangling the effect of different sleep parameters

Sleep is a multidimensional construct and research has suggested that sleep quality and other aspects of sleep behaviours (e.g., use of sleep medications) may be more strongly associated with future health and well-being and should be considered alongside sleep quantity (Pilcher, Ginter, & Sadowsky, 1997; Tang, Fiecas, Afolalu, & Wolke, 2017). Notably, it emerged from this review that changes in sleep quality but not sleep quantity were associated with the risk of developing a pain condition and worse self-reported health outcomes. Whereas, changes in sleep quantity were mostly reported to be contributing to altered levels of pain-related biomarkers. These differing patterns of association reflect potential specificity in the roles of sleep quality and quantity on pain.

That said, there were considerable variations across studies in the way changes in insomnia symptoms, sleep quality and quantity were measured. Some studies reported changes in insomnia symptoms such as difficulty in initiating and maintaining sleep, some assessed only reports of non-restorative sleep, and others used questionnaires to assess sleep quality. For sleep quantity, some used predetermined

sleep duration categories, e.g., short (< 7 hours), average (7-8 hours), and long (> 8 hours), whilst others gathered single-item responses on average nightly sleep duration. In addition, these measures also vary in assessment of severity and chronicity of sleep problems, with studies assessing different sleep problems (e.g., mild vs. severe symptoms) across different time frames (e.g., currently, past month, past year, or in a lifetime). This further limit generalisation and meaningful comparisons.

Distinctions should also be made between insomnia symptoms and general dissatisfaction with sleep quality and quantity, as changes in insomnia symptoms and other sleep disturbance parameters may have differential effects on different health outcomes (Ohayon, 2002). Cross-sectional studies have provided some evidence to support this; Yokoyama et al. (2010) compared three sub-symptoms of insomnia – difficulty initiating sleep, early morning awakenings and difficulty maintaining sleep, and they found that difficulty initiating sleep was most strongly associated with depression than the other insomnia symptoms. Consequently, future studies exploring the association of sleep changes should consider not only assessing different parameters of sleep disturbances but also using standardised measures. Similar recommendations for assessing core outcome measures have been made for trials of chronic pain treatment efficacy and effectiveness. The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) proposed and encouraged the use of key standardised measures for assessing and reporting changes in pain intensity, physical functioning, emotional functioning and improvement and satisfaction with treatment (Dworkin et al., 2005). Whilst it is appreciated that aspects

of such proposal may be more applicable to clinical trials than longitudinal studies, the IMMPACT recommendations can be useful as an illustrative guideline on how core sleep outcomes could be measured, defined, and reported for improving comparability and interpretability across studies.

6.4.3 Mechanisms underlying the interaction between sleep and pain-related biomarkers

The current review shows that a negative change in sleep quantity may be a key predictor of elevated pro-inflammatory markers and deterioration of pain-related physical health over time. There is also some evidence suggesting that a negative change in insomnia symptoms is associated with raised inflammatory levels. These findings are consistent with longitudinal studies that have reported baseline sleep quality as a predictor for pathogenic levels of inflammatory markers at follow-up (Nakamura et al., 2014; Prather, Epel, Cohen, Neylan, & Whooley, 2013). That said, the observed association with these biomarkers may not be pain-specific but reflecting a decline in physiological health status in general. Future development of a more comprehensive biopsychosocial model linking sleep quality, pain, and inflammation would enable more rigorous examination of the underpinning physiological mechanisms (Smith, Quartana, Okonkwo, & Nasir, 2009). It is thought that the effects of sleep problems on pain responses are mediated by impaired immunity, elevated inflammatory responses, and raised cytokines levels such as those assessed by studies considered in this review, namely interleukin-6(IL-6), C-Reactive Protein (CRP), and cortisol (Haack et al., 2007; Vgontzas et al., 2004). However, their meditational roles are yet to be verified in the general population whereby sleep

disruptions and pain symptoms are assessed in a more naturalist way with ecological validity.

6.4.4 Clarifying the effect of sleep improvement on pain outcomes

Findings from this review suggest that deterioration in sleep and persistent poor sleep are key risk factors of poor health. However, the findings do not provide sufficient evidence that an improvement in sleep quality or an increase in sleep quantity has a protective function of mitigating disease risk, as many clinicians and researchers would assume. The meta-analysis revealed that the development of sleep problems over time has a negative association with self-reported physical health (Ware, 1993; Ware et al., 1996). The meta-analysis also showed that remission of sleep problems over time was associated with higher PCS scores at follow-up, but the effect size was small and was only significant when compared with those who reported persistent poor sleep. However, the amount of evidence available for the current review was limited due to the small number of studies examining positive sleep changes over time outside of the context of a clinical trial.

There is some evidence emerging to suggest that naturally occurring good sleep is a potential predictor of chronic pain remission in the general population. Aili, Nyman, Svartengren, and Hillert (2015) reported in their prospective analysis that out of 883 participants from the general population, for the 53 individuals who reported multi-site pain at baseline but not at follow-up, a lack of or minimal report of sleep disturbance at baseline was a significant predictor of the 'resolution' of their multi-site pain (adjusted OR 3.96 95% CI 1.69-9.31), after controlling for age, gender,

smoking, BMI, physical occupational risks, and psychosocial activities. However, the small size of the group limits the statistical power, risk estimation, and generalisability of these findings. Davies et al. (2008) similarly showed that self-reported restorative sleep at baseline was a predictive factor for the 'resolution' of chronic widespread pain (adjusted OR 2.0 95% CI 1.02-3.8) in 300 of the 679 participants presenting with pain at baseline but not at follow-up. However, the participants in this study who reported resolved widespread pain at follow-up still reported some regional pain. As such, the impact of restorative sleep on pain experience may have been overstated. What these studies are not able to say is whether resolution in pain are preceded by positive changes in sleep and to what extent improvement in pain is sustained. The current review has highlighted that there is room for further longitudinal studies with longer follow-up, to strengthen the evidence for the impact of sleep improvement on long-term pain outcomes.

6.4.5 Methodological considerations and recommendations

Although the included studies were mostly of low and medium risk of bias, there were some recurrent methodological issues that could affect the rigour and generalisability of the findings and conclusions drawn. Based on the findings of the risk of bias assessment in the current review, future studies could improve methodological rigour by clarifying the rate of participation and attrition and by ensuring sufficient statistical power for detecting significant (and meaningful) results over a sufficiently long follow-up period. Two further specific recommendations are offered below:

I. Improving research designs to substantiate the impact of changes in sleep on pain outcomes

One of the main methodological drawbacks noted in the included studies was a reliance on self-report and a lack of objective sleep and quantitative pain outcome measures. Objective sleep assessments beyond self-report are less vulnerable to reporting biases. It is important for future prospective studies to strive to include assessment of both objective and self-reported changes in sleep using polysomnography or actigraphy. This can then be used in combination with quantitative sensory testing that assesses normal and abnormal psychophysical pain responses and physiological pain sensitivity. Whilst these methods would increase research costs, they are often utilised in experimental studies and could have an equally important role to play in sleep epidemiology research that combines experimental laboratory studies with longitudinal follow-up assessments. This would provide clarity in our understanding of the physiological factors underlying sleep and pain disturbances.

In addition, the evidence from the meta-analysis was also restricted to a broad evaluation of general physical health and well-being scores derived from the SF-36. For example, only one of the included studies (Silva et al., 2009) provided data specifically on PCS bodily pain subcomponent scores over time, whereas none of the other studies with PCS scores as an outcome measure allowed for this level of detail for comparison. Future studies should consider incorporating direct pain measures to better demonstrate the long-term temporal relationship between sleep and pain intensity. Additional repeated ratings of pain (Jensen & Karoly, 2011) can mark the

trajectory of pain intensity over time and to clarify the influence of pain intensity, rather than pain interference, on health outcomes.

II. Improving longitudinal assessments of sleep and pain

A lot of the studies did not have an outcome that was measured only prospectively. Strictly speaking, to qualify as longitudinal studies, future studies should ensure that instead of having multiple assessments of the outcomes at different time points, their outcome should be assessed prospectively. Most of the reviewed studies also have just two assessment points. Two observations are the bare minimum needed to provide information about change over time, but this information is usually insufficient for a thorough understanding of the processes responsible for these changes. If the screening criteria only allowed for the inclusion of studies with more than two assessment time-points, only four studies would have met this requirement. This highlights the need for additional waves of assessment for investigating the temporal relationship between changes in sleep and pain outcomes and for revealing the trajectories of health status over time within groups of individuals with different patterns of sleep. Cross-lagged and cluster analysis could be applied to these multi-wave data to establish directions of causality (Kenny, 1975).

Finally, the findings from these longitudinal studies were mostly drawn from analyses at the general population level to maximise generalisability. Future studies may benefit from incorporating subgroup analyses to dissect the sleep and pain relationship, for example, through stratification by age, by gender, by those with malignant and non-malignant chronic pain conditions, and by those with chronic pain but no sleep problems. This would help reveal the context in which a change in sleep

is a contributing factor to the development, perpetuation, or alleviation of these conditions. It would also provide new insights into the potential of sleep as an amenable treatment target in the management of these conditions across different spectra of the population.

6.4.6 Limitations of the review

Some limitations in the present review and meta-analysis should be acknowledged. First, the number of studies included in the review and the meta-analysis was limited due to a lack of access to required data and the stringent inclusion criteria. The results of the meta-analysis should thus be considered as exploratory. That said, the stringent inclusion criteria were necessary to capture only studies with an appropriate longitudinal design that addresses and analyses the association of change in sleep with pain-related outcomes. Second, the high level of heterogeneity observed in the analysis was possibly due to variations in research methodologies, but the small number of studies eligible for meta-analysis has made it impossible to pin down the source of heterogeneity at this stage. Also, not all studies assessed sleep in the same way despite having similar outcome measures and there was consequently no consistent definition of what denotes sleep stability, sleep deterioration and sleep improvements.

Finally, as inherent in most systematic reviews, there is a risk of publication bias although there was no obvious evidence of publication bias. Funnel plots were visually inspected to detect the presence of bias, including publication bias in the

meta-analysis, however, formal statistical tests which exist for detecting asymmetry in a funnel plot (e.g. Egger's test) were not conducted (Egger, Davey Smith, Schneider, & Minder, 1997). Given the few studies available for meta-analysis (three studies), these tests would have had very low power for funnel plot asymmetry detection and are generally not recommended in such a case (Sterne et al., 2011). The studies reviewed were limited to texts in English even though studies included in the review involved cities/countries that are not English-speaking. There appeared to be no indication that cultural differences in pain reports distort the sleep-pain association being examined. Nevertheless, future studies should consider the possible influence of culture on the perception of sleep and pain.

6.5 Conclusion

The current evidence provides moderate support that negative changes in sleep may be associated with detrimental health effects and that consistently good sleep may favour better pain-related health outcomes. Although there is emerging preliminary evidence for the relationship between changes in sleep status and pain-related health outcomes, full understanding of the mechanisms underlying the causal relationship between sleep and pain remains incomplete. In this review, improvements in sleep quantity and sleep quality were not consistently associated with better health outcomes. The jury is out regarding whether positive changes in sleep could lead to a reduction of, or even full recovery from, pain symptoms.

7 Changes in insomnia symptoms and their association with physical and mental health outcomes within the general population and among individuals with arthritis

7.1 Introduction

Chapter 6 (6.4.1) of this thesis presented a systematic review of studies highlighting the negative association of sleep deterioration over time on both objective and self-reported pain-related outcomes and the potential benefits of sleep improvements. Specifically, the review uncovered the need to conduct further studies to examine the association of both negative and positive changes in sleep with pain-related health outcomes. The sleep-pain associations demonstrated in the studies reviewed in Chapter 6 were based primarily on data from a general pain-free population. The study presented in this chapter aimed to incorporate a more focused analysis by respondents' characteristics and evaluate if such associations also applies to individuals who are already affected by chronic pain. Finally, studies from the review in Chapter 6 adopted a wide range of operationalisation of sleep quality, sleep quantity and insomnia symptoms, which makes it difficult to compare findings and draw generalisable conclusions across studies. The study reported in this chapter aimed to address these issues by detangling the differential association of changes in insomnia symptoms with health outcomes.

7.1.1 Insomnia symptoms in arthritis

It is essential to describe the sleep characteristics and associated health outcomes not just in the healthy populations but for those with chronic pain conditions for whom sleep disturbance is often a co-occurring problem impacting on

functioning and quality of life. It is possible that compared with pain-free individuals, those with persistent chronic pain may show differences in trajectory of sleep and self-reported health status over time. Separate explorations of patterns by pain status of sleep changes would clarify if insomnia onset and aggravation of insomnia symptoms are associated with health and functioning status in this population.

This present analysis sought to extract data from a panel study of the UK population consisting of individuals reporting a diagnosis of arthritis. Arthritis is a common chronic pain condition and leading cause of health-related disability (1.3.3). In spite of this, not a lot of studies focus on changes in sleep over time and in those with arthritis as evidence is still limited to cross-sectional overviews from a single time-point. Wolfe, Michaud, and Li (2006) reported an increased prevalence of general sleep disturbance in 8,676 rheumatoid arthritis participants living in the community, explaining that 25% - 42% of their sleep disturbance can be uniquely attributed to the condition. In addition, these sleep problems were linked to pain, mood, and disease activity. Westhovens, Van der Elst, Matthys, Tran, and Gilloteau (2014) also found an association between increased RA disease activity and poor sleep quality determined from PSQI scores and decreased daytime sleepiness. However, the study was another cross-sectional study with 305 patients presently seeking treatment from and attending a rheumatology clinic. It has also been suggested that emotional disturbance such as depression may be mediating the associations between sleep disturbance and symptoms in this population. Nicassio et al. (2012) reported that poor physical and mental functioning derived from the SF-36, predicted sleep disturbance and higher PSQI scores in 106 RA patients from a pain clinic. Furthermore,

this association was mediated by increased report of depressive symptoms. These findings pave the way for further studies to consider the associations of long-term changes in insomnia symptoms with mental and physical health-related outcomes in those with arthritis.

7.1.2 Differentiating the effect of insomnia symptoms on health outcomes

Poor sleep has been shown to have a direct effect on emotional appraisal and is a persistent predictor of life dissatisfaction (Paunio et al., 2009). Sivertsen et al. (2009) presented one of the largest cross-sectional investigations into the patterns of insomnia symptoms and association with physical and mental health in the general population. The study comprised data from 47,700 Norwegian individuals from the HUNT-2 survey and the researchers reported a 13.5% prevalence of insomnia within the study sample. They found the strongest association of insomnia with mental health conditions (anxiety and depression), followed by pain conditions with uncertain organic aetiology (e.g., fibromyalgia), general chronic pain conditions (e.g., arthritis) and the weakest association with somatic conditions (e.g., asthma). The study assessed individual symptoms of insomnia; frequency of sleep onset problems, waking up too early, and experiencing non-restorative sleep. However, it was not a full insomnia diagnostic measure and they had no information to verify middle of the night awakenings and sleep-related daytime impairments. Nevertheless, they showed that reports of insomnia symptoms were generally strongly associated with psychological and psychosomatic health problems in the general population. These findings provide a preliminary understanding of the association of deterioration in sleep with physical and emotional functioning within the general population.

However, as the review in Chapter 6 highlighted, there are often inconsistencies in observational and epidemiological studies in how poor sleep and change in sleep is defined and operationalised. The diagnosis of insomnia incorporates several symptoms and components that may have differential associations and it is important to clarify the differences in both stability and changes in these symptoms over time. Insomnia is defined as long-term and continuous difficulty falling and staying asleep, dissatisfaction with sleep and resultant daytime impairments (DSM-5, 2013; ICSD-3, 2014). Hence, Ohayon (2002) suggested distinguishing symptomatic aspects of insomnia and breaking down elements of insomnia diagnosis in order to better understand how they may affect health outcomes in the general population. One of the studies from the systematic review (Silva et al., 2009) extensively studied patterns of poor sleep and daytime sleepiness over 5 years in 3078 participants and the association of these changes with SF-36 scores. Worsening of difficulty initiating and maintaining sleep (a key part of insomnia diagnosis) was related to poorer MCS scores, while worsening daytime sleepiness was related to both poorer MCS and PCS scores. Their analysis consisted of a sample of just over 3000 individuals but was restricted to a specific cardiovascular and respiratory disease cohort (Sleep and Heart Health Study) of those over 40 years of age. The current study aimed to present an extension of the findings with a larger general population sample. Previous work by Tang et al. (2017) has also examined changes in sleep quantity, sleep quality and use of sleep medication in the UK general population and associations with health and well-being outcomes (SF-12 and GHQ). Not only was sleep deterioration associated with poorer health outcomes but positive changes were also associated with better

perceived health and well-being. Importantly, associations of changes in sleep quality with health outcomes had the greatest effect size when assessing the associations between perceived physical and mental health.

7.1.3 Aims

Tang et al. (2017) explored individual factors such as sleep duration, sleep quality, and use of sleep medication but not symptoms that match with insomnia diagnostic presentation. This current study aimed to extend their findings by examining changes in insomnia symptoms (prolonged sleep onset latency, frequency of overnight and early morning awakenings and daytime sleepiness) over 4 years (Waves 1-4) using the same dataset, for their associations with Wave 4 physical and mental health outcomes. In addition, the current analysis also explored changes in these insomnia symptoms in a subset of the cohort reporting a chronic pain condition (arthritis).

7.2 Methods

7.2.1 Study Design – UK Household Longitudinal Survey (UKHLS) background

This analysis used data from the Understanding Society UK Household Longitudinal Survey (UKHLS). UKHLS is a household panel study commenced in 2009, building up from and incorporating the existing British Household Panel Survey (BHPS). The BHPS was commenced in 1991, with boosted Scottish and Welsh sample added in 1999 and boosted Northern Irish sample added in 2001 (Buck & McFall, 2012). Ethical approval for the panel study was granted by the University of Essex and data use for this study was granted under an end user licence from UK Data Service

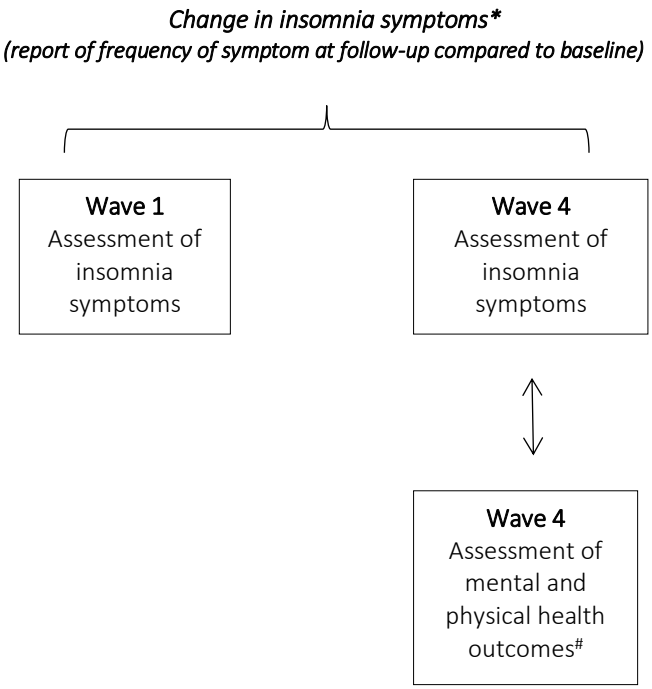
(University of Essex Institute for Social and Economic Research, NatCen Social Research, & Kantar Public, 2016).

The UKHLS provides an understanding of the trajectories of individuals' health, wellbeing, social, environmental and economic behaviours, and psychological attributes. UKHLS is a large survey, with a rough target of 40,000 households across the country. It has the advantage of being a household panel design in that it represents a sample of the entire population of all ages across the country. In addition, the UKHLS also has a unique consideration for the multi-ethnic nature of current UK society and aimed for a greater coverage of ethnic minority populations through oversampling of a booster ethnic sample and having additional ethnicity related measures. A total of 18 waves of data collection are planned for the UKHLS. Data is collected with annual measurements and each wave of data is collected over two years due to the large sample size. Presently, the first six waves of data have been released, however, only Wave 1 and Wave 4 are used for this analysis. At the time of planning for the analysis, Wave 4 was the first and only available wave repeating the same rotating sleep and well-being module first administered in Wave 1.

Wave 1 and Wave 4 samples included the general population (GP) sample and the ethnic minority booster (EMB) sample. The GP sample were drawn using a stratified, clustered, equal probability approach from residential addresses across the UK, however, the Northern Ireland sample were selected systematically from property agency lists. The ethnic booster sample was identified by over-sampling geographic areas with at least 5% density of the targeted five largest ethnic minority groups

(Indian, Pakistani, Bangladeshi, Caribbean, and African). Data collection for the UKHLS was carried out through Computer Assisted Personal Interviewing (CAPI). The initial four waves of data collection were done face-to-face to boost initial compliance and response rates. The interview schedule and questions were made available across a range of languages including Bengali, Punjabi, Welsh, Arabic, Somali, Cantonese, Urdu, and Gujarati. One person from an eligible household completed the household list and household interview. Everyone over the age of 16 then completed an individual adult interview and self-completion questionnaire. The self-completed questionnaire contained the questions on health, well-being, sleep habits and health conditions that were used for the current analysis. Further details and discussion on the design, conduct and sample of the UKHLS can be found in the design overview (Buck & McFall, 2012). For the current analysis, the focus was on using the UKHLS panel data to explore the association of change in reported insomnia symptoms in the same cohort of individuals from Wave 1 to Wave 4 with perceived health outcomes assessed at Wave 4. Figure 17 shows the design methodology for the analysis.

Figure 17 UKHLS analysis – Design methodology

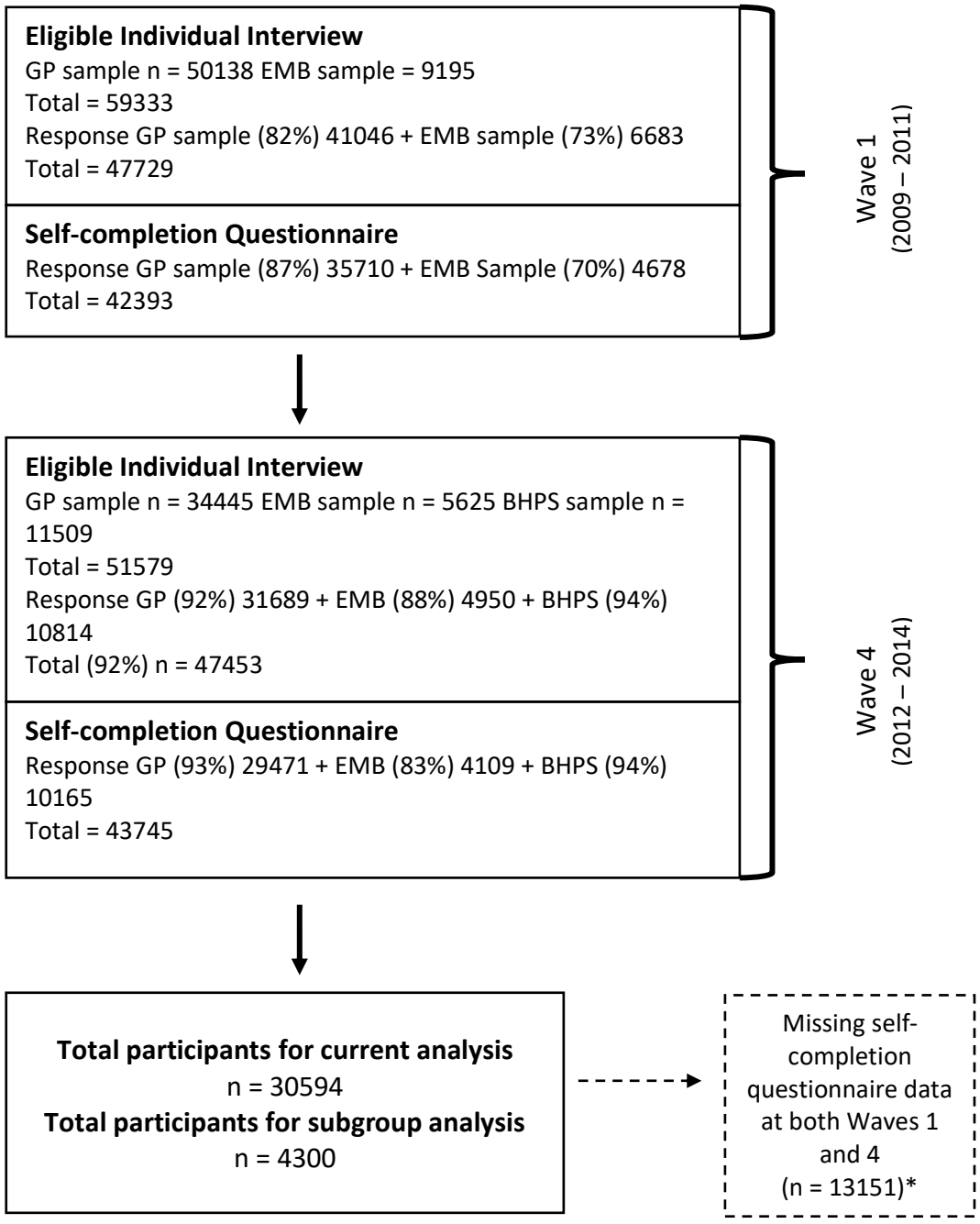


Note: *Change in insomnia symptoms refers to change in frequency of (i) sleep onset latency (ii) overnight awakenings and (iii) daytime sleepiness symptoms.
#Mental and physical health outcome refers to measures and scores of General Health Questionnaire (GHQ) and Short Form Health Survey-12 [Mental Health Component(MCS) and Physical Health Component (PCS)] at Wave 4.

Figure 18 summarises the response and participation rates respectively at the household and individual levels at Wave 1 and Wave 4 and resulting sample size for the current analysis derived from the survey technical reports (Boreham, Boldysevaite, & Killpack, 2012; Jessop & Oskala, 2014). **At Wave 1**, 45,431 GP and 10,253 EMB sample households were identified as eligible at Wave 1. Response rate for the household interview was 57% for the GP sample and 40% for the EMB sample. Of the total eligible adults of 59,333, there was 82% response rate in the GP sample and 73% for the EMB sample. From these, 87% of adults from the GP sample and 70% from the EMB subsequently also completed the self-completion questionnaire, giving

a total of 42,393 individuals at Wave 1. **At Wave 4**, 31,447 households were eligible for the recurring repeat assessment, these also included a sample of 6,840 household from the BHPS sample who were introduced into UKHLS in Wave 2. Total response rates the household level was 82% and 92% at the individual level. From this, the response rate for the self-completing questionnaire was 93%, 83%, and 94% respectively for the GP, EMB, and BHPS sample, leaving a total of 43,745 eligible individuals at Wave 4. Taking away the BHPS sample and other individuals that do not have matching self-completion questionnaire data at both Wave 1 and Wave 4 leaves **a total of 30,594 participants** considered for this current analysis. Of these, **4,300** individuals had reported having a chronic pain health condition (arthritis) at Wave 1 and were used for the subgroup analysis.

Figure 18 UKHLS analysis – UKHLS survey flowchart



Notes: *Includes the former BHPS sample introduced at Wave 2, but these participants' data were not included in the current analysis as their Wave 1 data were missing.

7.2.2 Measures – Exposure, Outcomes, Confounders

Exposure

As shown in Figure 17, the sleep parameters and insomnia symptoms of interests were – frequency of sleep onset latency of more than 30 minutes (henceforth – 'sleep onset latency'), frequency of overnight and early morning awakenings (henceforth – 'awakenings'), and frequency of difficulty staying awake during the day (henceforth – 'daytime sleepiness'). These sleep variables were considered since they were closest to the (DSM-5, 2013) and (ICSD-3, 2014) diagnostic criteria for insomnia disorder; dissatisfaction with sleep quantity or quality due to one or more: difficulty initiating sleep, difficulty maintaining sleep and early-morning awakenings, and daytime difficulties and impairments including fatigue, poor concentration, low mood, or impaired ability to perform social, occupational or caregiving responsibilities). However, the information from this dataset cannot determine if sleep difficulty occurs on at least three nights per week for at least 3 months, despite adequate opportunity to sleep, and if symptoms are better explained by other co-occurring medical or mental condition (DSM-5, 2013; ICSD-3, 2014)

At Wave 1 and Wave 4, frequency of 'sleep onset latency' problem was assessed using the question – 'During the past month, how often have you had trouble sleeping because you cannot get to sleep within 30 minutes'. Frequency of problem with 'awakenings' was assessed using the question – 'During the past month, how often have you had trouble sleeping because you woke up in the middle of the night or early in the morning'. Frequency of 'daytime sleepiness' symptoms was assessed using the question – 'During the past month, how often have you had trouble staying

awake, while driving, eating meals or engaging in social activities'. The response formats to these questions were the same – 'not during the past month', 'less than once a week', 'once or twice a week' and 'three or more times a week'. The measure of exposure were derived variables reflecting changes in these insomnia symptoms between Wave 1 and Wave 4. These derived categories were 'increase', 'no change' and 'decrease', denoting a change in the frequency of problems with sleep onset latency, awakenings, and daytime sleepiness symptoms. These questions were adapted for the UKHLS survey from the Pittsburgh Sleep Quality Index (PSQI); the time scale, word choice, and response scale are all similar to the PSQI. The original PSQI is a valid and established measure of general sleep quality and insomnia symptoms (4.2.3.2)

Outcomes

The outcome variables were health and well-being, measured with total scores from the 12-item General Health Questionnaire (GHQ-12) and the 12-item Short-Form Health Survey (SF-12) at Wave 4.

General Health Questionnaire (GHQ-12) (Goldberg et al., 1997)

The GHQ-12 is an established measure of psychological and mental well-being. It assesses psychological distress and minor psychiatric symptoms within the general population, in a community setting, and general non-psychiatric clinical setting. It has a range of 12 questions on normal functioning and behavioural patterns associated with psychological distress with items such as 'ability to concentrate', 'constantly under strain' and 'enjoy normal activities', with responses ranging from 'less than

usual' to 'much more than usual'. In the UKHLS, it was scored using a Likert scale with score ranging from 0-3 for each item instead of the usual 1-4 for each individual item. Items are summed, and total scores range from 0 (least distress) to 36 (most distress). The GHQ-12 has shown reliability with alpha coefficients ranging from 0.82 to 0.90 across studies, and sensitivity (83.4%) and specificity (76.3%) to detect minor psychiatric symptoms and is correlated with other measures of psychological distress such as the Beck's Depression Inventory (BDI) and Spielberger's State Trait Anxiety Index (STAI).

Short-Form Health Survey (SF-12) (Ware et al., 1996)

The SF-12 is the shortened version of SF-36, another well-validated scale for measuring health-related quality of life, and functional physical and mental health and well-being. It was originally developed for a longitudinal study of patients with chronic conditions but has since been applied and widely used in large population health surveys. The SF-12 provides two component scores: Physical Component Scores (PCS) and Mental Component Score (MCS) from eight domains assessing physical and mental health. PCS items assess physical functioning, role interference due to physical problems, bodily pain, and general health. The MCS items assess vitality, social functioning, role interference due to emotional problems and mental health. Scores from each component ranges from 0 – 100 with higher scores indicating higher and better level of health and functioning (Ware, 1993). The PCS and MCS were used as separate outcomes variables for this current analysis. The SF-12 has shown internal consistency and reliability with Cronbach's α of 0.81 for the PCS and 0.84 for the MCS

(Lim & Fisher, 1999) and test-retest reliability of 0.86 for the PCS and 0.77 for the MCS and validity estimates of 0.67 for the PCS and 0.97 for the MCS (Ware et al., 1996).

Confounders

Several potential confounding variables were adjusted for and were selected in accordance to possible associations with sleep and mental and physical health functioning and according to previously published studies (Ferrie et al., 2013; Silva et al., 2009; Tang et al., 2017). These included baseline demographic information from Wave 1: age (determined from date of birth or age at last birthday), sex, ethnicity (selected from a list of 14 ethnic origins and for this analysis, ethnicity was pooled into five main groups by order of size – White, Asian, Black, mixed and other), education (selected from a list of highest qualification achieved, for this analysis, responses were pooled into degree level or above, any other qualification below degree level and no qualification), and employment status (selected from a list asking about current employment situation and for this analysis, responses were pooled into full-time, part-time and not in employment). Body mass index (BMI) was also assessed as a cofounding variable, it was a variable derived by UKHLS from self-reported weight and 'height without shoes'. Lastly, baseline (Wave 1) value of the relevant insomnia symptoms variables, and baseline (Wave 1) scores of GHQ-12, PCS, and MCS were also considered to adjust for differences in symptom presentation.

7.2.3 Analysis

All analyses were carried out in R (R Core Team, 2016). The main analysis was to determine how Wave 4 scores of each outcome (GHQ-12, PCS, and MCS) were

associated with changes in each insomnia symptom (sleep onset latency, awakenings, daytime sleepiness). Analysis was only carried out for participants who have all the sleep variables as well as confounders of interest to match the three outcome variables at both Wave 1 and Wave 4. Analysis for each outcome was a multivariate linear regression on the outcome score at Wave 4 on each of the change in insomnia symptom parameters (increase or decrease), adjusted for baseline outcome score, confounders and baseline measure of the insomnia symptom parameter concerned.

Potential confounding factors were adjusted for in the multivariate regression analysis. Reference indicator categories were created for the categorical variables. For the confounders, this was 'female' for sex, 'white' for ethnicity, 'full-time' for employment, and 'degree level or above' for education. For the change in insomnia symptom parameter, this was 'no change'. For each of the regression analysis, biases in the survey sample were accounted for by applying longitudinal weights computed by the UKHLS. These weights are particularly relevant for the adult self-completion questionnaire data from Wave 1 to Wave 4. They represent adult population who continued to live in the UK at both time points and were computed to account for potential sampling biases, participants' non-response, and unequal selection probability (Knies, 2014).

In addition, local effect sizes (Cohen's f^2) were calculated for each change in insomnia symptom predictor. This provides an estimate of how much more adding the change in insomnia symptom predictor to the regression model with confounders alone explained the variance in the outcome measure. This method of effect size

calculation quantifies one variable's effect size within the context of the multivariate regression model (Cohen, 1988). Cohen's f^2 is interpreted as small (approx. 0.02 or 2% of variance), medium (approx. 0.15 or 13% of variance) and large (approx. 0.35 or 26% of variance). Essentially, Cohen's f^2 reflects the proportion of variance uniquely accounted for by 'change in insomnia symptom' over and above that of all the other confounders. Not only does it help interpret the influence of the change in insomnia symptoms, it also provides a gauge of which change in insomnia symptom had the greatest association with health and well-being outcomes.

Chronic pain subgroup analysis

The subgroup analysis was restricted to those with a chronic pain condition namely, arthritis). The presence of a chronic pain condition was assessed at Wave 1 with the following question – 'Has the doctor or another health professional ever told you that you have any of the conditions listed?' Arthritis was listed as one of the conditions and the response to the question was 'mentioned', 'don't know' or not mentioned'. A similar process for the multivariate linear regression analysis explained above was repeated for the subgroup analysis.

Sensitivity analysis

To account for the number of observations with missing data across the dataset, the Multiple Imputation by Chained Equation (MICE) technique was applied as an additional sensitivity analysis. This imputed analysis is only reported for the subgroup analysis given the considerably smaller number of participants and a higher rate of missing observation across all the predicting, confounders and outcome

variables. MICE is an established method of dealing with missing data and is based on a posterior predictive distribution model, in which the imputed values depend on values of the outcome and covariate variables to create a prediction of missing values (van Buuren, 2012; van Buuren & Groothuis-Oudshoorn, 2011). The combined standard errors produced from multiple imputation methods such as MICE are greater and fairly accurate compared to single imputations and account for statistical uncertainties created by estimating missing values (Azur, Stuart, Frangakis, & Leaf, 2011). For this analysis, the procedure included all the variables (predictors, confounders and outcomes) used in the subsequent analysis. The regression analysis was then performed on each of the imputed data sets for the arthritis subgroup analysis. Effect size (Cohen f^2) was computed for each imputed dataset and this was summarised using the mean effect size, this approach to compute and pool effect size of the imputed datasets was informed by Little and Rubin (2002).

The multiple imputation by chained equation (van Buuren & Groothuis-Oudshoorn, 2011) procedure was also utilised by Tang et al. (2017) and is described as follows:

- All missing value in the dataset are initially temporarily replaced by random sampling of mean observed values (predictive mean matching).
- The values for the first variable (‘a’) that will be imputed are then replaced back to missing. The variable (‘a’) is regressed upon the other variables in the dataset and the missing values for ‘a’ are then replaced with the imputations (posterior predictive distribution) from the regression model.

- These steps are then repeated for the next variables ('a', 'b', 'c' and so forth) using the previously imputed values. This continual looping through the variables stabilises the results.
- At the end of these cycles, all the missing values have then been replaced with the predictions from the regression models, giving a final complete imputed dataset that represents the interactions apparent in the data.
- Given the large data size, the MICE procedure was repeated multiple times (5 rounds of imputations and 50 iterations) for this analysis to produce the final imputed dataset, it has been reported that this number of rounds is enough imputations to obtain valid results (Little & Rubin, 2002).

7.3 Results

7.3.1 Full sample

Sample characteristics

Table 23 shows the baseline characteristics of the whole sample and complete cases of participants providing data for all combined outcomes, exposure, and confounders. The baseline demographic characteristics and reports of insomnia symptoms were similar across analyses. Based on the complete cases, just over half of the sample was female (53.17%), mean age of 44.65 years, and mean BMI of 25.89. Most of the sample were white (87.43%), just over half were in full-time employment (50.60%) and less than half were with below degree-level education (48.27%). Mean score for GHQ-12 was 10.02, 52.48 for PCS, and 52.42 for MCS and all these values were within the normative range for the general population (Ware, 1993).

Baseline insomnia symptoms

For the sleep parameters, at baseline, the majority of the sample did not report sleep onset difficulties in the previous month (48.89%), 27.01% reported difficulties less than once a week, 16.79% reported difficulties once or twice a week, and only 7.31% reported difficulties three of more times a week. The prevalence of frequency of problems with overnight and early morning awakenings were fairly evenly split with 29.9% reporting no problems in the past month, 24.4% reporting problems less than once a week, 26.0% reporting problems once or twice a week, and 20.64% reporting problems three or more times a week. A large majority of the sample (86.72%) reported no daytime sleepiness symptoms during the past month, 9.35% reported symptoms less than once a week, 3.25% reported symptoms once or twice a week, and 0.67% reported symptoms three or more times a week.

Table 23 UKHLS analysis – Full sample baseline characteristics		GHQ analysis (n = 12,350)	PCS analysis (n = 12,533)	MCS analysis (n= 12,533)	Complete case (n = 12,326)
Sex, n female (% female)		6569 (53.19%)	6667 (53.19%)	6667 (53.19%)	6554 (53.17%)
Age, mean (sd)		44.67 (15.98)	44.57 (16.01)	44.57 (16.01)	44.65 (15.97)
BMI, mean (sd)		25.89 (4.73)	25.88 (4.73)	25.88 (4.73)	25.89 (4.73)
Ethnicity	**White, n (%)**	10797 (87.42%)	10925 (87.17%)	10925 (87.17%)	10777 (87.43%)
	Asian, n (%)	841 (6.81%)	873 (6.97%)	873 (6.97%)	838 (6.80%)
	Black, n (%)	385 (3.12%)	396 (3.16%)	396 (3.16%)	384 (3.12%)
	Mixed, n (%)	174 (1.41%)	181 (1.44%)	181 (1.44%)	174 (1.41%)
	Other, n (%)	153 (1.24%)	158 (1.26%)	158 (1.26%)	153 (1.24%)
Employment	**Full time, n (%)**	6242 (50.54%)	6318 (50.41%)	6318 (50.41%)	6237 (50.60%)
	Part time, n (%)	2162 (17.51%)	2197 (17.53%)	2197 (17.53%)	2158 (17.51%)
	Not in employment, n (%)	3946 (31.95%)	4018 (32.06%)	4018 (32.06%)	3931 (31.89%)
Education	**Degree level or above, n (%)**	5329 (43.15%)	5398 (43.07%)	5398 (43.07%)	5317 (43.14%)
	Any other qualification, n (%)	5957 (48.23%)	6054 (48.30%)	6054 (48.30%)	5950 (48.27%)
	No qualification, n (%)	1064 (8.62%)	1081 (8.63%)	1081 (8.63%)	1059 (8.59%)
Sleep latency (> 30 mins)	**Not during the past month, n (%)**	6040 (48.91%)	6122 (48.84%)	6122 (48.84%)	6026 (48.89%)
	Less than once a week, n (%)	3336 (27.01%)	3378 (26.95%)	3378 (26.95%)	3330 (27.01%)
	Once or twice a week, n (%)	2073 (16.76%)	2109 (16.83%)	2109 (16.83%)	2069 (16.79%)
	Three or more times a week, n (%)	901 (7.30%)	924 (7.37%)	924 (7.37%)	901 (7.31%)
Awakenings	**Not during the past month, n (%)**	3594 (29.10%)	3649 (29.12%)	3649 (29.12%)	3582 (29.06%)
	Less than once a week, n (%)	2989 (24.20%)	3037 (24.23%)	3037 (24.23%)	2988 (24.24%)
	Once or twice a week, n (%)	3219 (26.06%)	3267 (26.07%)	3267 (26.07%)	3212 (26.06%)
	Three or more times a week, n (%)	2548 (20.63%)	2580 (20.59%)	2580 (20.59%)	2544 (20.64%)
Daytime sleepiness	**Not during the past month, n (%)**	10709 (86.71%)	10861 (86.66%)	10861 (86.66%)	10690 (86.72%)
	Less than once a week, n (%)	1115 (9.35%)	1177 (9.39%)	1177 (9.39%)	1152 (9.35%)
	Once or twice a week, n (%)	403 (3.26%)	408 (3.26%)	408 (3.26%)	401 (3.25%)
	Three or more times a week, n (%)	83 (0.67%)	87 (0.69%)	87 (0.69%)	83 (0.67%)
GHQ-12, Mean (SD)		10.02 (4.24)	-	-	10.02 (4.24)
PCS, Mean (SD)		-	52.47 (8.35)	-	52.48 (8.33)
MCS, Mean (SD)		-	-	52.42 (7.86)	52.42 (7.85)

Notes: Summary statistics for the full samples and restricted to complete cases for Wave 1 and Wave 4 measurements for each outcomes and predictors as well as confounders. Complete case data in the last column refers to sample characteristics restricted to all combined outcomes, exposures, and confounders.

Changes in insomnia symptoms from Wave 1 to Wave 4

Tables 24-26 describe the pattern of changes in the frequency of insomnia symptoms for all participants with insomnia symptoms measurements (sleep onset latency, awakenings, and daytime sleepiness) at both Wave 1 and Wave 4. The most common trajectory was stability in reports of the frequency of insomnia symptoms. Of 19,032 general population sample presenting data for sleep onset latency problems, 48.03% reported no change from Wave 1 to Wave 4, 23.48% reported an increase in the frequency of problems and 28.48% reported a decrease. For the 15,793 reporting on problems with overnight and early morning awakenings, 37% reported no change in presentation of symptoms, while 25.30% reported an increase and 37.7% reported a decrease in the frequency of symptoms. Finally, for the 24,316 individuals reporting on daytime sleepiness symptoms, a large majority (79.33%) reported no change in symptoms, while 8.13% reported an increase in symptoms and 12.53% reported a decrease in the frequency of symptoms.

Table 24 UKHLS analysis – Full sample: Changes in insomnia symptoms for participants with sleep onset latency measurements at both Wave 1 and Wave 4.

Sleep onset latency "cannot get to sleep within 30 minutes"		Wave 4 Not during the past month	Less than once a week	Once or twice a week	Three or more times a week	
Wave 1	Not during the past month	No change n=6,305	Increase n=1,442	Increase n=767	Increase n=485	n = 8,999
	Less than once a week	Decrease n=2,209	No change n=1,397	Increase n=850	Increase n= 398	n = 4,854
	Once or twice a week	Decrease n=1,190	Decrease n=767	No change n=893	Increase n=527	n = 3,377
	Three or more times a week	Decrease n=519	Decrease n=286	Decrease n=450	No change n=547	n = 1,802
		n = 10,223	n = 3,892	n = 2,960	n = 1,957	**n = 19,032**

Table 25 UKHLS analysis – Full sample: Changes in insomnia symptoms for all participants with awakenings measurements at both Wave 1 and Wave 4.

Awakenings "woke up in the middle of the night or early in the morning"		Wave 4 Not during the past month	Less than once a week	Once or twice a week	Three or more times a week	
Wave 1	Not during the past month	No change n=2,619	Increase n=774	Increase n=617	Increase n=431	n = 4,441
	Less than once a week	Decrease n=1,428	No change n=970	Increase n=755	Increase n=528	n = 3,681
	Once or twice a week	Decrease n=1,275	Decrease n=876	No change n=1,122	Increase n=891	n = 4,164
	Three or more times a week	Decrease n=922	Decrease n=592	Decrease n=861	No change n=1,132	n = 3,507
		n = 6,244	n = 3,212	n = 3,355	n = 2,982	**n = 15,793**

Table 26 UKHLS analysis – Full sample: Changes in the sleep parameters of all participants with daytime sleepiness measurements at both Wave 1 and Wave 4.

Daytime sleepiness "trouble staying awake while driving, eating meals, or engaging in social activities"		Wave 4 Not during the past month	Less than once a week	Once or twice a week	Three or more times a week	
Wave 1	Not during the past month	No change n=18,876	Increase n=889	Increase n=508	Increase n=319	n = 20,592
	Less than once a week	Decrease n=1,805	No change n=256	Increase n=133	Increase n=65	n = 2259
	Once or twice a week	Decrease n=758	Decrease n=124	No change n=103	Increase n=63	n = 1048
	Three or more times a week	Decrease n=266	Decrease n=41	Decrease n=54	No change n=56	n = 417
		n = 21,705	n = 1,310	n = 798	n = 503	**n = 24,316**

Changes in insomnia symptoms and Wave 4 GHQ-12

Table 27 presents a summary of the parameter estimates (β) of all the sleep exposure variables included in the multivariable regression models assessing the association with Wave 4 GHQ-12 score, controlling for Wave 1 GHQ score and all potential confounders. An increase in the frequency of sleep onset problems was associated with higher GHQ scores at Wave 4 (β = 1.646 [95% CI 1.456, 1.836]), indicative of greater psychiatric symptoms and mental distress. Decrease in the frequency of symptoms was associated with lower GHQ scores (β = -1.066 [95% CI -1.284, -0.849). Increase in the frequency of awakenings was associated with higher Wave 4 GHQ scores (β = 1.078 [95% CI 0.864, 1.293]) and a decrease in symptoms with lower Wave 4 GHQ scores (β = -0.967 [95% CI -1.177, -0.756]). An increase (β = 1.585 [95% CI 1.299, 1.869]) in frequency of daytime sleepiness symptoms was significantly associated with higher Wave 4 GHQ scores but a decrease in symptoms was not significant. Of the three parameters, changes in sleep onset problems had the greatest effect and yielded a small effect size of $f^2 = 0.04$.

Table 27 UKHLS analysis – Full sample: Summary of regression models of associations with Wave 4 GHQ score by potential confounders and changes in insomnia symptoms (analysis using complete cases)

	Model 1 Wave 1 GHQ + confounders + change in sleep onset latency (n = 16,515) Parameter estimate (β)	Model 2 Wave 1 GHQ + confounders + change in awakenings (n = 13,759) Parameter estimate (β)	Model 3 Wave 1 GHQ + confounders + change in daytime sleepiness (n = 20,866) Parameter estimate (β)
Wave 1 GHQ	**0.422 (0.404, 0.439)**	**0.422 (0.402, 0.441)**	**0.450 (0.435, 0.465)**
Male	**-0.550 (-0.705, -0.395)**	**-0.672 (-0.843, -0.501)**	**0.829 (-0.982, -0.675)**
Age	**-0.012 (-0.017, -0.008)**	**-0.019 (-0.024, -0.013)**	**-0.021 (-0.026, -0.016)**
Asian	**0.478 (0.124, 0.832)**	**0.810 (0.443, 1.178)**	**0.687 (0.341, 1.034)**
Black	-0.150 (-0.743, 0.442)	-0.159 (-0.802, 0.484)	**-0.586 (-1.172, -0.0005)**
Mixed	**-1.459 (-2.151, -0.766)**	**-0.736 (-1.459, -0.014)**	**-0.975 (-1.663, -0.287)**
Other	0.223 (-0.524, 0.970)	0.249 (0.574, 1.071)	0.365 (-0.394, 1.123)
BMI	**0.024 (0.008, 0.039)**	**0.026 (0.008, 0.044)**	**0.045 (0.030, 0.060)**
Any other qualification	-0.054 (-0.216, 0.109)	0.098 (-0.079, 0.274)	**0.213 (0.047, 0.379)**
No qualification	-0.159 (-0.423, 0.104)	-0.111 (-0.415, 0.194)	0.241 (-0.012, 0.494)
Part-time employment	-0.167 (-0.389, 0.055)	**-0.244 (-0.483, -0.004)**	**-0.229 (-0.454, -0.003)**
Not in employment	**0.205 (0.022, 0.387)**	**0.216 (0.016, 0.415)**	**0.459 (0.277, 0.640)**
Sleep onset latency – Increase	**1.646 (1.456, 1.836)**		
Sleep onset latency – Decrease	**-1.066 (-1.284, -0.849)**		
Awakenings – Increase		**1.078 (0.864, 1.293)**	
Awakenings – Decrease		**-0.967 (-1.177, -0.756)**	
Daytime Sleepiness – Increase			**1.585 (1.299, 1.869)**
Daytime Sleepiness – Decrease			-0.471(-0.969, 0.027)
	Effect size (f^2) 0.04	*Effect size (f^2) 0.03*	*Effect size (f^2) 0.01*

Notes: Model parameter estimates (β) and 95% confidence intervals (CI) in parentheses for each of the considered models in the complete case analysis. Significant results in bold. A higher GHQ score indicates more psychological distress, hence risk factors = positive estimates and protective factors = negative estimates. Effect size = local effect size (Cohen's $f2$) - proportion of variance explained by adding a sleep exposure variable to the model with confounders alone.

Changes in insomnia symptoms and Wave 4 PCS

Table 28 presents a summary of the parameter estimates (β) of all the sleep exposure variables included in the multivariable regression models assessing the association with Wave 4 PCS scores, controlling for Wave 1 PCS score and all potential confounders. An increase in the frequency of sleep onset problems was associated with lower PCS scores at Wave 4 (β = -0.905 [95% CI -1.230, -0.575]), indicative of poorer physical health status and functioning and a decrease in frequency of symptom was not significant. An increase in the frequency of awakenings was associated with lower PCS scores (β = -0.555 [95% CI -0.908, -0.201]) and a decrease in symptoms with higher PCS scores (β = 0.609 [95% CI [0.261, 0.956]). An increase (β = -2.563 [95% CI -3.034, -2.092]) in frequency of daytime sleepiness was significantly associated with lower Wave 4 PCS scores and a decrease was not significant. Of the three parameters, changes in daytime sleepiness had the greatest effect and yielded a small effect size of $f^2 = 0.01$.

Table 28 UKHLS analysis – Full sample: Summary of regression models of associations with Wave 4 PCS score by potential confounders and changes in insomnia symptoms (analysis using complete cases)

	Model 1 Wave 1 PCS + confounders + change in sleep onset latency (n = 16,793) Parameter estimate (β)	Model 2 Wave 1 PCS + Confounders + change in awakenings (n = 13,985) Parameter estimate (β)	Model 3 Wave 1 PCS + Confounders + change in daytime sleepiness (n = 21,250) Parameter estimate (β)
Wave 1 PCS	**-0.435 (-0.449, -0.420)**	**-0.472 (-0.488, -0.455)**	**-0.410 (-0.423, -0.398)**
Male	-0.031 (-0.299, 0.237)	-0.084 (-0.365, 0.197)	0.177 (-0.076, 0.430)
Age	**-0.102 (-0.111, -0.094)**	**-0.082 (-0.090, -0.072)**	**-0.100 (-0.108, -0.092)**
Asian	**-2.187 (-2.792, -1.581)**	**-2.129 (-2.730, -1.529)**	**-1.810 (-2.376, -1.243)**
Black	**-1.290 (-2.316, -0.263)**	**-1.454 (-2.506, -0.402)**	**-1.135 (-2.093, -0.177)**
Mixed	-0.620 (-1.816, 0.576)	**-1.985(-3.171, -0.798)**	**-1.222 (-2.353, -0.092)**
Other	0.312 (-0.982, 1.607)	0.337 (-1.013, 1.687)	-0.348 (-1.593, 0.897)
BMI	**-0.127 (-0.155, -0.099)**	**-0.115 (-0.144, -0.086)**	**-0.128 (-0.153, -0.103)**
Any other qualification	**-0.792 (-1.075, -0.510)**	**-0.833 (-1.125, -0.541)**	**-1.014 (-1.289, -0.739)**
No qualification	**-1.928 (-2.385, -1.471)**	**-2.194 (-2.698, -1.691)**	**-1.893 (-2.311, -1.474)**
Part-time employment	-0.353 (-0.739, 0.032)	-0.351 (-0.745, 0.043)	**-0.459 (-0.832, -0.086)**
Not in employment	**-1.668 (-1.988, -1.347)**	**-1.577 (-1.910, -1.245)**	**-2.028 (-2.332, -1.724)**
Sleep onset latency – Increase	**-0.905 (-1.230, -0.575)**		
Sleep onset latency – Decrease	-0.093 (-0.470, 0.284)		
Awakenings – Increase		**-0.555 (-0.908, -0.201)**	
Awakenings – Decrease		**0.609 (0.261, 0.956)**	
Daytime Sleepiness – Increase			**-2.563 (-3.034, -2.092)**
Daytime Sleepiness – Decrease			0.541 (-0.282, 1.364)
	Effect size (f^2) 0.006	*Effect size (f^2) 0.004*	*Effect size (f^2) 0.01*

Notes: Model parameter estimates (β) and 95% confidence intervals (CI) in parentheses for each of the considered models in the complete case analysis. Significant results in bold. A higher PCS score indicates better physical health/functioning, hence protective factors = positive estimates and risk factors = negative estimates. Effect size = local effect size (Cohen's $f2$) - proportion of variance explained by adding a sleep exposure variable to the model with confounders alone.

Changes in insomnia symptoms and Wave 4 MCS

Table 29 presents a summary of the parameter estimates (β) of all the exposure variables included in the multivariable regression models assessing the association with Wave 4 MCS scores, controlling for Wave 1 MCS score and all potential confounders. An increase in the frequency of sleep onset latency problems was associated with lower MCS scores at Wave 4 (β = -2.548 [95% CI -2.894, -2.203]) indicative of poorer mental health status and psychological functioning. Decrease in the frequency of sleep onset problems was associated with higher Wave 4 MCS scores (β = 1.279 [95% CI 0.883, 1.673]). Increase in the frequency of awakening was associated with lower MCS scores (β = -1.698 [95% CI -2.085, -1.312]) and a decrease with higher MCS scores (β = 1.199 [95% CI [0.819, 1.579]). An increase in frequency of daytime sleepiness (β = -2.563 [95% CI (-3.889, -2.882]) was associated with lower Wave 4 MCS scores and a decrease (β = 0.959 [95% CI (0.081 – 1.838]) with higher MCS score. Of the three parameters, changes in sleep onset problems had the greatest effect and yielded a small effect size of $f^2 = 0.04$

Table 29 UKHLS analysis – Full sample: Summary of regression models of associations with Wave 4 MCS score by potential confounders and changes in insomnia symptoms (analysis using complete cases)

	Model 1 Wave 1 MCS + confounders + change in sleep onset latency (n = 16,793) Parameter estimate (β)	Model 2 Wave 1 MCS + confounders + change in awakenings (n = 13,985) Parameter estimate (β)	Model 3 Wave 1 MCS + confounders + change in daytime sleepiness (n = 21,250) Parameter estimate (β)
Wave 1 MCS	**-0.612 (-0.628, -0.595)**	**-0.610 (-0.628, -0.591)**	**-0.591 (-0.605, -0.576)**
Male	**0.955 (0.673, 1.236)**	**1.037 (0.729, 1.346)**	**1.306 (1.035, 1.577)**
Age	**0.073 (0.064, 0.081)**	**0.088 (0.078, 0.098)**	**0.089 (0.080, 0.097)**
Asian	**-0.912 (-1.548, -0.278)**	**-1.712 (-2.368, -1.055)**	**-1.155 (1.760, -0.550)**
Black	0.499 (-0.576, 1.574)	0.085(-1.065, 1.236)	0.878 (-0.145, 1.902)
Mixed	1.040 (-0.213, 2.294)	0.087(-1.212, 1.386)	0.643 (-0.565, 1.852)
Other	-0.414 (-1.770, 0.942)	-0.440 (1.917, 1.036)	-0.473 (1.804, 0.857)
BMI	-0.021 (-0.049, 0.007)	-0.007 (-0.038, 0.025)	**-0.045 (-0.072, -0.018)**
Any other qualification	**0.479 (0.184, 0.775)**	0.239 (0.080, 0.558)	**-0.060 (-0.354, 0.232)**
No qualification	0.275 (-0.201, 0.751)	-0.135 (-0.682, 0.411)	**-0.688 (-1.132, -0.243)**
Part-time employment	-0.302 (-0.634, 0.031)	-0.318 (-0.678, 0.042)	**-0.843 (-1.163, -0.524)**
Not in employment	**0.439 (0.035, 0.843)**	**0.556 (0.125, 0.987)**	**0.572 (0.173, 0.970)**
Sleep onset latency – Increase	**-2.548 (-2.894, -2.203)**		
Sleep onset latency – Decrease	**1.279 (0.883, 1.673)**		
Awakenings – Increase		**-1.698(-2.085, -1.312)**	
Awakenings – Decrease		**1.199 (0.819, 1.579)**	
Daytime Sleepiness – Increase			**-3.386 (-3.889, -2.882)**
Daytime Sleepiness – Decrease			**0.959 (0.081 – 1.838)**
	Effect size (f^2) 0.04	*Effect size (f^2) 0.02*	*Effect size (f^2) 0.02*

Notes: Model parameter estimates (β) and 95% confidence intervals (CI) in parentheses for each of the considered models in the complete case analysis. Significant results in bold. A higher MCS score indicates better mental health/functioning, hence protective factors = positive estimates and risk factors = negative estimates. Effect size = local effect size (Cohen's f^2) - proportion of variance explained by adding a sleep exposure variable to the model with confounders alone.

Sensitivity analysis

Each of the analysis described above was also performed with imputed datasets computed using the MICE procedure to check the sensitivity of the results. Tables 30, 31, and 32 present a summary of the parameter estimates (β) of all the sleep exposure variables included in the multivariable regression models assessing the associations with Wave 4 GHQ, PCS and MCS scores, controlling for Wave 1 MCS score and all potential confounders using the imputed datasets. Overall, the pattern of results did not differ from the complete case analysis. The only difference observed was that the association of decrease in frequency of sleep onset problems with Wave 4 MCS score was no longer significant.

Table 30 UKHLS analysis – Full sample: Summary of regression models of associations with Wave 4 GHQ score by potential confounders and changes in insomnia symptoms (analysis combining results from imputed dataset)

	Model 1 Wave 1 GHQ + confounders + change in sleep onset latency (n = 30,414) Parameter estimate (β)	Model 2 Wave 1 GHQ + confounders + change in awakenings (n = 30,414) Parameter estimate (β)	Model 3 Wave 1 GHQ + confounders + change in daytime sleepiness (n = 30,414) Parameter estimate (β)
Wave 1 GHQ	**0.437 (0.421, 0.454)**	**0.447 (0.432, 0.462)**	**0.449 (0.434, 0.464)**
Male	**-0.655 (-0.803, -0.508)**	**-0.693 (-0.849, -0.537)**	**-0.852 (-1.001, -0.703)**
Age	**-0.016 (-0.020, -0.011)**	**-0.025 (-0.030, -0.021)**	**-0.020 (-0.024, -0.015)**
Asian	**0.458 (0.129, 0.787)**	**0.547 (0.205, 0.889)**	**0.468 (0.135, 0.801)**
Black	-0.461 (-0.992, 0.071)	-0.399 (-0.936, 0.138)	-0.543 (-1.077, -0.008)
Mixed	**-1.077 (-1.742, -0.412)**	**-0.869 (-1.539, -0.199)**	**-1.048 (-1.718, -0.378)**
Other	0.418 (-0.352, 1.189)	0.582 (-0.164, 1.327)	0.444 (-0.292, 1.179)
BMI	**0.040 (0.025, 0.056)**	**0.042 (0.027, 0.057)**	**0.042 (0.026, 0.057)**
Any other qualification	0.100 (-0.063, 0.264)	0.180 (0.019, 0.341)	**0.219 (0.056, 0.381)**
No qualification	0.115 (-0.126, 0.355)	0.256 (0.013, 0.499)	**0.287 (0.044, 0.530)**
Part-time employment	**0.412 (0.235, 0.589)**	**0.494 (0.319, 0.669)**	**0.443 (0.267, 0.618)**
Not in employment	-0.207 (-0.424, 0.010)	-0.221 (-0.442, 0.0003)	-0.244 (-0.463, -0.025)
Sleep onset latency – Increase	**1.710 (1.504, 1.916)**		
Sleep onset latency – Decrease	**-0.454 (-0.783, -0.124)**		
Awakenings – Increase		**1.060 (0.694, 1.427)**	
Awakenings – Decrease		**-0.7010 (-1.086, -0.333)**	
Daytime Sleepiness – Increase			**1.529 (1.243, 1.814)**
Daytime Sleepiness – Decrease			-0.517 (1.016, -0.019)
	Mean effect size (f^2) 0.04	*Mean effect size (f^2) 0.02*	*Mean effect size (f^2) 0.01*

Notes: Model parameter estimates (β) and low/high 95% confidence intervals (CI) in parentheses for each of the considered models in the datasets imputed using multivariate imputation by chained equation (mice). Significant results in bold. A higher GHQ score indicates more psychological distress, hence risk factors = positive estimates and protective factors = negative estimates. Effect size = mean local effect size (Cohen's $f2$) for the imputed datasets - proportion of variance explained by adding a sleep exposure variable to the model with confounders alone.

Table 31 UKHLS analysis – Full sample: Summary of regression models of associations with Wave 4 PCS score by potential confounders and changes in insomnia symptoms (analysis combining results from imputed dataset)

	Model 1 Wave 1 PCS + confounders + change in sleep latency (n = 30,414) Parameter estimate (β)	Model 2 Wave 1 PCS + confounders + change in awakenings (n = 30,414) Parameter estimate (β)	Model 3 Wave 1 PCS + Confounders + change in daytime sleepiness (n = 30,414) Parameter estimate (β)
Wave 1 PCS	**-0.408 (-0.421, -0.395)**	**-0.405 (-0.418, -0.392)**	**-0.413 (-0.425, -0.401)**
Male	0.098 (-0.150, 0.346)	0.107 (-0.146, 0.360)	0.260 (0.014, 0.507)
Age	**-0.101 (-0.109, -0.094)**	**-0.091 (-0.099, -0.083)**	**-0.099 (-0.107, -0.092)**
Asian	**-1.790 (-2.345, -1.234)**	**-1.881 (-2.436, -1.327)**	**-1.771 (-2.324, -1.218)**
Black	**-1.233 (-2.118, -0.347)**	**-1.287 (-2.174, -0.400)**	**-1.125 (-2.007, -0.244)**
Mixed	-0.844 (-1.954, 0.265)	-1.009 (-2.118, 0.099)	-0.755 (-1.860, 0.349)
Other	-0.675 (-1.897, 0.546)	-0.762 (-1.985, 0.460)	-0.599 (-1.813, 0.615)
BMI	**-0.130 (-0.155, -0.105)**	**-0.130 (-0.155, -0.106)**	**-0.129 (-0.154, -0.104)**
Any other qualification	**-0.910 (-1.183, -0.637)**	**-0.963 (-1.236, -0.689)**	**-1.025, (-1.295, -0.755)**
No qualification	**-1.701 (-2.106, -1.295)**	**-1.809 (-2.223, -1.395)**	**-1.822 (-2.227, -1.417)**
Part-time employment	**-0.418 (-0.781, -0.056)**	-0.401 (-0.766, -0.037)	-0.392 (-0.754, -0.029)
Not in employment	**-2.005 (-2.299, -1.709)**	**-2.104 (-2.401, -1.808)**	**-2.035 (-2.329, -1.740)**
Sleep onset latency – Increase	-0.954 (1.377, -0.531)		
Sleep onset latency – Decrease	-0.359 (-0.890, 0.173)		
Awakenings – Increase		-0.808 (1.659, 0.042)	
Awakenings – Decrease		**0.548 (0.003, 1.093)**	
Daytime Sleepiness – Increase			**-2.584 (-3.057, -2.111)**
Daytime Sleepiness – Decrease			0.578 (-0.230, 1.387)
	Mean effect size (f^2) 0.007	*Mean effect size (f^2) 0.007*	*Mean effect size (f^2) 0.007*

Notes: Model parameter estimates (β) and low/high 95% confidence intervals (CI) in parentheses for each of the considered models in the datasets imputed using multivariate imputation by chained equation (mice). Significant results in bold. A higher PCS score indicates better physical health/functioning, hence protective factors = positive estimates and risk factors = negative estimates. Effect size = mean local effect size (Cohen's f^2) for the imputed datasets - proportion of variance explained by adding a sleep exposure variable to the model with confounders alone.

Table 32 UKHLS analysis – Full sample: Summary of regression models of associations with Wave 4 MCS score by potential confounders and changes in insomnia symptoms (analysis combining results from imputed dataset)

	Model 1 Wave 1 MCS + confounders + change in sleep onset latency (n = 16,793) Parameter estimate (β)	Model 2 Wave 1 MCS + confounders + change in awakenings (n = 13,985) Parameter estimate (β))	Model 3 Wave 1 MCS + confounders + change in daytime sleepiness (n = 21,250) Parameter estimate (β)
Wave 1 MCS	**-0.592 (-0.606, -0.578)**	**-0.583 (-0.597, -0.569)**	**-0.591 (-0.605, -0.577)**
Male	**0.914 (0.648, 1.1803)**	**0.975 (0.707, 1.244)**	**1.293 (1.029, 1.558)**
Age	**0.081 (0.073, 0.090)**	**0.099 (0.091, 0.108)**	**0.087 (0.079, 0.095)**
Asian	**-1.049 (-1.642, -0.456)**	**-1.255 (-1.849, -0.662)**	**-1.033 (-1.622, -0.444)**
Black	0.783 (-0.162, 1.729)	0.607 (-0.336, 1.550)	0.906 (-0.037, 1.850)
Mixed	0.654 (-0.528, 1.836)	0.247 (-0.939, 1.433)	0.701 (-0.482, 1.884)
Other	-0.511 (-1.814, 0.791)	-0.721 (-2.040, 0.598)	-0.439 (-1.741, 0.862)
BMI	**-0.045 (-0.072, -0.019)**	**-0.047 (-0.073, -0.021)**	**-0.044 (-0.070, -0.018)**
Any other qualification	0.206 (-0.080, 0.492)	0.078 (-0.210, 0.365)	-0.018 (-0.305, 0.269)
No qualification	-0.387 (-0.829, 0.055)	**-0.626 (-1.060, -0.191)**	**-0.670 (-1.101, -0.240)**
Part-time employment	0.451 (0.065, 0.836)	**0.494 (0.102, 0.887)**	**0.536 (0.147, 0.924)**
Not in employment	**-0.787 (-1.108, -0.465)**	**-0.939 (-1.249, -0.628)**	**-0.848 (-1.159, -0.537)**
Sleep onset latency – Decrease	0.306 (-0.151, 0.763)		
Awakenings – Increase		**-1.802 (-2.160, -1.445)**	
Awakenings – Decrease		**0.891 (0.418, 1.364)**	
Daytime Sleepiness – Increase			**-3.223 (-3.731, -2.716)**
Daytime Sleepiness – Decrease			**1.033 (0.166, 1.900)**
	Mean effect size (f^2) 0.03	*Mean effect size (f^2) 0.02*	*Mean effect size (f^2) 0.03*

Notes: Model parameter estimates (β) and low/high 95% confidence intervals (CI) in parentheses for each of the considered models in the datasets imputed using multivariate imputation by chained equation (mice). Significant results in bold. A higher MCS score indicates better mental health/functioning, hence protective factors = positive estimates and risk factors = negative estimates. Effect size = mean local effect size (Cohen's $f2$) for the imputed datasets - proportion of variance explained by adding a sleep exposure variable to the model with confounders alone.

7.3.2 Arthritis subgroup

Sample characteristics

Table 33 shows the baseline characteristics of the arthritis subgroup by analysis and complete cases of participants providing data for all combined outcomes, predictors and confounders. Based on the complete cases, majority of the sample was female (53.17%), with mean age of 60.02, and mean BMI of 27.42. Most of the sample were white (95.48%), not in employment (56.48%) and just under half had below degree level education (47.52%). Mean score for GHQ-12 was 10.45, 43.85 for PCS, and 53.22 for MCS, values for GHQ and MCS were within the normative range for the general population but PCS values were in the indicative range for those with a 'minor medical condition' (Ware et al., 1996). This gives further support for the chronic pain subgroup classification. Comparing the arthritis subgroup to the full sample, they showed no significant differences in baseline insomnia symptoms, GHQ, and MCS mean scores. However, the arthritis group were significantly older and showed poorer baseline PCS mean scores.

Arthritis subgroup – baseline insomnia symptoms

For baseline insomnia symptoms, the arthritis subgroup showed a similar pattern of symptom prevalence as the full sample. 44.54% of the arthritis sample did not report sleep onset difficulties in the previous month, 27.82% reported difficulties less than once a week, 18.77% reported difficulties once or twice a week, and 8.87% reported difficulties three or more times a week. The frequency of overnight and early morning awakenings was evenly distributed among categories, with 20.65% reporting no problems in the past month, 22.27% reporting problems less than once a week,

28.75% reporting problems once or twice a week, and 28.33% reporting problems three or more times a week. The majority (88.23%) reported no daytime sleepiness during the past month, 8.28% reported symptoms less than once a week, 2.99% reported symptoms once or twice a week and a very small number (0.52%) reported symptoms three or more times a week. The frequency of symptoms presentation was similar to the full sample, although a higher percentage in the arthritis group reported symptoms of sleep onset latency and awakening three or more times a week. This is suggestive of greater insomnia symptoms intensity.

Table 33 UKHLS analysis – Arthritis subgroup baseline sample characteristics		GHQ analysis (n = 1,177)	PCS analysis (n = 1,195)	MCS analysis (n = 1,195)	Complete case (n = 1,172)
Sex, n Female (% Female)		725 (61.60%)	737 (61.67%)	737 (61.67%)	721 (61.52%)
Age mean (sd)		60.02 (12.86)	60.02 (12.89)	60.02 (12.89)	60.02 (12.88)
BMI mean (sd)		27.43 (4.86)	27.45 (4.86)	27.45 (4.86)	27.42 (4.85)
Ethnicity	White, n (%)	1123 (95.41%)	1140 (93.40%)	1140 (93.40%)	1119 (95.48%)
	Asian, n (%)	31 (2.63%)	32 (2.68%)	32 (2.68%)	31 (2.65%)
	Black, n (%)	12 (1.02%)	11 (0.92%)	11 (0.92%)	11 (0.94%)
	Mixed, n (%)	7 (0.59%)	8 (0.67%)	8 (0.67%)	7 (0.60%)
	Other, n (%)	4 (0.34%)	4 (0.33%)	4 (0.33%)	4 (0.34%)
Employment	Full time, n (%)	348 (29.57%)	351 (29.37%)	351 (29.37%)	347 (29.61%)
	Part time, n (%)	163 (13.85%)	169 (14.14%)	169 (14.14%)	163 (13.91%)
	Not in employment, n (%)	666 (56.58%)	675 (56.49%)	675 (56.49%)	662 (56.48%)
Education	Degree level or above, n (%)	388 (32.97%)	395 (33.05%)	395 (33.05%)	386 (32.94%)
	Any other qualification, n (%)	560 (47.58%)	564 (47.20%)	564 (47.20%)	557 (47.52%)
	No qualification, n (%)	229 (19.46%)	236 (19.75%)	236 (19.75%)	229 (19.53%)
Sleep latency (>30 mins)	Not during past month, n (%)	524 (44.52%)	531 (44.44%)	531 (44.44%)	522 (44.54%)
	Less than once a week, n (%)	327 (27.78%)	329 (27.53%)	329 (27.53%)	326 (27.82%)
	Once or twice a week, n (%)	222 (18.86%)	229 (19.16%)	229 (19.16%)	220 (18.77%)
	Three or more times a week, n (%)	104 (8.84%)	106 (8.87%)	106 (8.87%)	104 (8.87%)
Awakenings	Not during the past month, n (%)	244 (20.73%)	248 (20.75%)	248 (20.75%)	242 (20.65%)
	Less than once a week, n (%)	261 (22.18%)	264 (22.09%)	264 (22.09%)	261 (22.27%)
	Once or twice a week, n (%)	338 (28.72%)	342 (28.62%)	342 (28.62%)	337 (28.75%)
	Three or more times a week, n (%)	334 (28.34%)	341 (28.54%)	341 (28.54%)	332 (28.33%)
Daytime sleepiness	Not during the past month, n (%)	1037 (88.11%)	1053 (88.12%)	1053 (88.12%)	1034 (88.23%)
	Less than once a week, n (%)	99 (8.41%)	99 (8.28%)	99 (8.28%)	97 (8.28%)
	Once or twice a week, n (%)	35 (2.97%)	35 (2.93%)	35 (2.93%)	35 (2.99%)
	Three or more times a week, n (%)	6 (0.51%)	8 (0.67%)	8 (0.67%)	6 (0.52%)
GHQ-12, Mean (SD)		10.44(4.43)	-	-	10.45 (4.44)
PCS, Mean (SD)		-	43.69 (12.41)	-	43.85 (12.37)
MCS, Mean (SD)		-	-	53.20 (8.70)	53.22 (8.69)

Notes: Summary statistics for the arthritis subgroup restricted to complete cases for Wave 1 and Wave 4 measurements for each outcomes and predictors as well as confounders. Complete case data in the last column refers to arthritis subgroup characteristics restricted to all combined outcomes, exposures, and confounders.

Arthritis subgroup – changes in insomnia symptoms from Wave 1 to Wave 4

Tables 34-36 describe the pattern of changes in the frequency of insomnia symptoms for participants within the arthritis subgroup with insomnia symptoms measurements (sleep onset latency, awakenings, and daytime sleepiness) at both Wave 1 and Wave 4. As also observed in the full sample, stability in reports of the frequency of insomnia symptoms was still the most common trajectory. However, in this group, there was more reports of improvement rather than deterioration of symptoms. Of 2,324 presenting data for sleep onset problems, 43.89% reported no change from Wave 1 to Wave 4, 24.66% reported an increase in the frequency of problems, and 31.45% reported a decrease. For the 1,647 reporting problems with overnight and early morning awakenings, 34.55% reported no change in presentation of symptoms, while 27.32% reported an increase, and 38.13% reported a decrease in the frequency of symptoms. Finally, for the 3,600 individuals reporting on daytime sleepiness, the majority (78.36%) reported no change in symptoms, while 9.72% reported an increase in symptoms, and 11.92% reported a decrease in the frequency of symptoms.

Table 34 UKHLS analysis – Arthritis subgroup: Changes in insomnia symptoms for arthritis subgroup participants with sleep onset latency measurements at both Wave 1 and Wave 4.

Sleep onset latency "cannot get to sleep within 30 minutes"		Wave 4 Not during the past month	Less than once a week	Once or twice a week	Three or more times a week	
Wave 1	Not during the past month	No change n=672	Increase n=136	Increase n=95	Increase n=80	n = 983
	Less than once a week	Decrease n=299	No change n=129	Increase n=99	Increase n=58	n = 585
	Once or twice a week	Decrease n=154	Decrease n=98	No change n=112	Increase n=105	n = 469
	Three or more times a week	Decrease n=70	Decrease n=30	Decrease n=80	No change n=107	n = 287
		n = 1195	n = 393	n = 386	n = 350	**n = 2,324**

Table 35 UKHLS analysis – Arthritis subgroup: Changes in insomnia symptoms for arthritis subgroup participants with awakenings measurements at both Wave 1 and Wave 4.

Awakenings "woke up in the middle of the night or early in the morning"		Wave 4 Not during the past month	Less than once a week	Once or twice a week	Three or more times a week	
Wave 1	Not during the past month	No change n=173	Increase n=61	Increase n=61	Increase n=50	n = 345
	Less than once a week	Decrease n=109	No change n=73	Increase n=68	Increase n=82	n = 332
	Once or twice a week	Decrease n=133	Decrease n=79	No change n=120	Increase n=128	n = 460
	Three or more times a week	Decrease n=132	Decrease n=70	Decrease n=105	No change n=203	n = 510
		n = 547	n = 283	n = 354	n = 463	**n = 1,647**

Table 36 UKHLS analysis – Arthritis subgroup: Changes in insomnia symptoms for arthritis subgroup participants with daytime sleepiness measurements at both Wave 1 and Wave 4.

Daytime sleepiness "trouble staying awake while driving, eating meals, or engaging in social activities"		Wave 4 Not during the past month	Less than once a week	Once or twice a week	Three or more times a week	
Wave 1	Not during the past month	No change n=2,750	Increase n=100	Increase n=98	Increase n=94	n = 3,042
	Less than once a week	Decrease n=209	No change n=28	Increase n=20	Increase n=19	n = 276
	Once or twice a week	Decrease n=114	Decrease n=18	No change n=22	Increase n=19	n = 173
	Three or more times a week	Decrease n=68	Decrease n=8	Decrease n=12	No change n=21	n = 109
		n = 3141	n = 154	n = 152	n = 153	**n = 3,600**

Arthritis subgroup – Changes in insomnia symptoms and Wave 4 GHQ-12

Table 37 presents a summary of the parameter estimates (β) of all the sleep exposure variables included in the multivariable regression models for imputed datasets assessing the association with Wave 4 GHQ-12 score in the arthritis subgroup, controlling for Wave 1 GHQ score, and all potential confounders. An increase in the frequency of sleep onset latency problems was associated with higher GHQ scores at Wave 4 (β = 1.035 [95% CI 0.241, 1.828]), indicative of greater psychiatric symptoms and mental distress. Increase in the frequency of awakening was associated with higher Wave 4 GHQ scores (β = 1.539 [95% CI 0.616, 2.462]). An increase in frequency of daytime sleepiness symptoms (β = 2.031 [95% CI 1.280, 2.783]) was significantly associated with higher Wave 4 GHQ scores. A decrease in the frequency of all of the symptoms was not significant. Of the three parameters, change in daytime sleepiness had the greater effect and yielded a small effect size of $f^2 = 0.03$.

Table 37 UKHLS analysis – Arthritis subgroup: Summary of regression models in arthritis subgroup of associations with Wave 4 GHQ score by potential confounders and changes in frequency of insomnia symptoms (analysis combining results from imputed dataset)

	Model 1 Wave 1 GHQ + confounders + change in sleep onset latency (n = 4,120) Parameter estimate (β)	Model 2 Wave 1 GHQ + confounders + change in awakenings (n = 4,120) Parameter estimate (β)	Model 3 Wave 1 GHQ + confounders + change in daytime sleepiness (n = 4,120) Parameter estimate (β)
Wave 1 GHQ	**0.441 (0.381, 0.502)**	**0.460 (0.402, 0.517)**	**0.431 (0.389, 0.473)**
Male	**-0.689 (-1.135, -0.244)**	**-0.864 (-1.299, -0.429)**	**-0.977 (-1.408, -0.547)**
Age	**-0.066 (-0.086, -0.046)**	**-0.072 (-0.093, -0.050)**	**-0.067 (-0.086, -0.047)**
Asian	-0.399 (-1.886, 1.088)	-0.319 (-2.103, 1.465)	-0.518 (-1.959, 0.923)
Black	-0.821 (-2.251, 0.608)	-0.388 (-1.997, 1.221)	-1.138 (-2.654, 0.378)
Mixed	0.905 (-1.999, 3.809)	0.613 (-2.355, 3.582)	0.589 (-2.361, 3.539)
Other	1.486 (-1.855, 4.827)	2.011 (-1.266, 5.288)	1.547 (-1.506, 4.600)
BMI	**0.058 (0.022, 0.094)**	**0.053 (0.017, 0.090)**	**0.051 (0.011, 0.091)**
Any other qualification	0.065 (-0.446, 0.577)	0.174 (-0.385, 0.733)	0.133 (-0.371, 0.636)
No qualification	0.020 (-0.569, 0.609)	0.172 (-0.427, 0.772)	0.105 (-0.484, 0.694)
Part-time employment	-0.196 (-0.973, 0.581)	-0.085 (-0.856, 0.685)	-0.182 (-0.957, 0.593)
Not in employment	**0.853 (0.234, 1.467)**	**0.974 (0.385, 1.563)**	**0.844 (0.256, 1.432)**
Sleep onset latency – Increase	**1.035 (0.241, 1.828)**		
Sleep onset latency – Decrease	0.251 (-0.625, 1.128)		
Awakenings – Increase		**1.539 (0.616, 2.462)**	
Awakenings – Decrease		0.351 (-1.114, 0.412)	
Daytime sleepiness – Increase			**2.031 (1.280, 2.783)**
Daytime sleepiness – Decrease			-0.846 (-2.730, 1.038)
	Mean effect size (f^2) 0.02	*Mean effect size (f^2) 0.02*	*Mean effect size (f^2) 0.03*

Notes: Model parameter estimates (β) and low/high 95% confidence intervals (CI) in parentheses for each of the considered models in the datasets imputed using multivariate imputation by chained equation (mice). Significant results in bold. A higher GHQ score indicates more psychological distress, hence risk factors = positive estimates and protective factors = negative estimates. Effect size = mean local effect size (Cohen's $f2$) for the imputed datasets - proportion of variance explained by adding a sleep exposure variable to the model with confounders alone.

Arthritis subgroup – Changes in insomnia symptoms and Wave 4 PCS

Table 38 presents a summary of the parameter estimates β) of all the sleep exposure variables included in the multivariable regression models for imputed datasets assessing the association with Wave 4 PCS scores in the arthritis subgroup, controlling for Wave 1 PCS score and all potential confounders. An increase in the frequency of sleep onset latency problems was associated with lower PCS scores at Wave 4 (β = -1.066 [95% CI (-2.068, -0.064]), indicative of poorer physical health status and functioning. An increase in frequency of daytime sleepiness symptoms was also associated with lower PCS scores at Wave 4 (β = --1.514 [95% CI (-3.201, 0.173]). A decrease in sleep onset latency symptoms and daytime sleepiness and changes in frequency of problems with awakenings were not significantly associated with Wave 4 PCS scores. Of the three parameters, change in sleep onset latency and daytime sleepiness had the greater effect and both yielded a small effect size of $f^2 = 0.01$.

Table 38 UKHLS analysis – Arthritis subgroup: Summary of regression models in arthritis subgroup of associations with Wave 4 PCS score by potential confounders and changes in frequency of insomnia symptoms (analysis combining results from imputed dataset)

	Model 1 Wave 1 PCS + confounders + change in sleep onset latency (n = 4,120) Parameter estimate (β)	Model 2 Wave 1 PCS + confounders + change in awakenings (n = 4,120) Parameter estimate (β)	Model 3 Wave 1 PCS + confounders + change in daytime sleepiness (n = 4,120) Parameter estimate (β)
Wave 1 PCS	**-0.386 (-0.416, -0.356)**	**-0.382 (-0.413, -0.351)**	**-0.389 (-0.419, -0.359)**
Male	-0.037 (-0.949, 0.875)	0.215 (-0.683, 1.112)	0.349 (-0.540, 1.238)
Age	-0.025 (-0.064, 0.013)	-0.018 (-0.055, 0.020)	-0.026 (-0.064, 0.012)
Asian	**-2.598 (-5.041, -0.155)**	**-2.702 (-5.236, -0.169)**	-2.499 (-5.258, 0.260)
Black	-1.101 (-4.490, 2.287)	-1.318 (-4.878, 2.243)	-0.870 (-3.998, 2.258)
Mixed	2.030 (-4.130, 8.190)	1.909 (-3.965, 7.784)	2.409 (-3.558, 8.375)
Other	1.694 (-2.940, 6.328)	1.155 (-3.298, 5.608)	1.498 (-3.026, 6.021)
BMI	**-0.131 (-0.203, -0.059)**	**-0.124 (-0.195, -0.054)**	**-0.116 (-0.189, -0.043)**
Any other qualification	-0.446 (-1.626, 0.733)	-0.578 (-1.816, 0.661)	-0.578 (-1.755, 0.599)
No qualification	**-1.976 (-3.244, -0.709)**	**-2.101 (-3.313, -0.890)**	**-2.033 (-3.334, -0.732)**
Part-time employment	-1.019 (-2.424, 0.387)	-1.032 (-2.464, 0.401)	-1.060 (-2.465, 0.345)
Not in employment	**-3.791 (-4.934, -2.648)**	**-3.908 (-5.034, -2.782)**	**-3.845 (-4.955, -2.735)**
Sleep onset latency – Increase	**-1.066 (-2.068, -0.064)**		
Sleep onset latency – Decrease	-0.408 (-1.769, 0.953)		
Awakenings – Increase		0.006 (-2.032, 2.043)	
Awakenings – Decrease		0.559 (-0.745, 1.862)	
Daytime sleepiness – Increase			**-1.514 (-3.201, 0.173)**
Daytime sleepiness – Decrease			**1.008 (-1.647, 3.663)**
	Mean effect size (f^2) 0.01	*Mean effect size (f^2) 0.005*	Mean effect size (f^2) 0.01

Notes: Model parameter estimates (β) and low/high 95% confidence intervals (CI) in parentheses for each of the considered models in the datasets imputed using multivariate imputation by chained equation (mice). Significant results in bold. A higher PCS score indicates better physical health/functioning, hence protective factors = positive estimates and risk factors = negative estimates. Effect size = mean local effect size (Cohen's $f2$) for the imputed datasets - proportion of variance explained by adding a sleep exposure variable to the model with confounders alone.

Arthritis subgroup – Changes in insomnia symptoms and Wave 4 MCS

Table 39 presents a summary of the parameter estimates (β) of all the sleep exposure variables included in the multivariable regression models for imputed datasets assessing the association with Wave 4 MCS scores in the arthritis subgroup, controlling for Wave 1 MCS score and all potential confounders. An increase in the frequency of sleep onset latency problems was associated with lower MCS scores at Wave 4 (β = -2.539 [95% CI -4.366, -0.713]) indicative of poorer mental health status and psychological functioning. Decrease in the frequency of sleep onset latency problems was also associated with lower Wave 4 MCS scores (β = -1.566 [95% CI -2.776, -0.356]). Increase in the frequency of awakening was associated with lower MCS scores (β = -1.980 [95% CI -3.402, -0.558]), and a decrease in symptoms was not significant. An increase in frequency of daytime sleepiness symptoms (β = -4.143 [95% CI -5.748, -2.537]) was associated with Wave 4 MCS scores and a decrease in symptoms was not significant. Of the three parameters, change in sleep onset latency and daytime sleepiness had the greater effect and both yielded a small effect size of $f^2 = 0.03$.

Table 39 UKHLS analysis – Arthritis subgroup: Summary of regression models in arthritis subgroup of associations with Wave 4 MCS score by potential confounders and changes in frequency of insomnia symptoms (analysis combining results from imputed dataset)

	Model 1 Wave 1 MCS + confounders + change in sleep onset latency (n = 4,120) Parameter estimate (β)	Model 2 Wave 1 MCS + confounders + change in awakenings (n = 4,120) Parameter estimate (β)	Model 3 Wave 1 MCS + confounders + change in daytime sleepiness (n = 4,120) Parameter estimate (β)
Wave 1 MCS	**-0.605 (-0.639, -0.571)**	**-0.585 (-0.619, -0.551)**	**-0.607 (-0.641, -0.572)**
Male	0.152 (-0.790, 1.094)	0.569 (-0.453, 1.590)	0.870 (-0.100, 1.840)
Age	**0.121 (0.084, 0.158)**	**0.132 (0.090, 0.174)**	**0.123 (0.083, 0.163)**
Asian	-0.438 (-3.399, 2.523)	-0.697 (-3.356, 1.963)	-0.071 (-2.733, 2.591)
Black	0.114 (-2.823, 3.052)	-0.564 (-3.619, 2.491)	0.695 (-2.173, 3.564)
Mixed	-0.544 (-6.387, 5.299)	-0.572 (-6.571, 5.428)	0.015 (-5.725, 5.755)
Other	-1.355 (-6.072, 3.361)	-2.380 (-7.066, 2.305)	-1.299 (-5.898, 3.230)
BMI	-0.052 (-0.121, 0.018)	-0.046 (-0.125, 0.034)	-0.034 (-0.107, 0.040)
Any other qualification	0.664 (-0.238, 1.565)	0.438 (-0.510, 1.385)	0.452 (-0.467, 1.371)
No qualification	-0.087 (-1.235, 1.061)	-0.380 (-1.530, 0.770)	-0.225 (-1.393, 0.943)
Part-time employment	0.493 (-0.977, 1.962)	0.302 (-1.180, 1.784)	-0.225 (-1.393, 0.943)
Not in employment	**-1.481 (-2.647, -0.314)**	**-1.824 (-2.995, -0.654)**	**-1.474 (-2.640, -0.307)**
Sleep onset latency – Increase	**-2.539 (-4.366, -0.713)**		
Sleep onset latency – Decrease	**-1.566 (-2.776, -0.356)**		
Awakenings – Increase		**-1.980 (-3.402, -0.558)**	
Awakenings – Decrease		-0.159 (-1.275, 0.956)	
Daytime Sleepiness – Increase			**-4.143 (-5.748, -2.537)**
Daytime Sleepiness – Decrease			-0.051, (-2.479, 2.376)
	Mean effect size (f^2) 0.03	*Mean effect size (f^2) 0.01*	*Mean effect size (f^2) 0.03*

Notes: Model parameter estimates (β) and low/high 95% confidence intervals (CI) in parentheses for each of the considered models in the datasets imputed using multivariate imputation by chained equation (mice). Significant results in bold. A higher MCS score indicates better mental health/functioning, hence protective factors = positive estimates and risk factors = negative estimates. Effect size = mean local effect size (Cohen's $f2$) for the imputed datasets - proportion of variance explained by adding a sleep exposure variable to the model with confounders alone.

7.4 Discussion

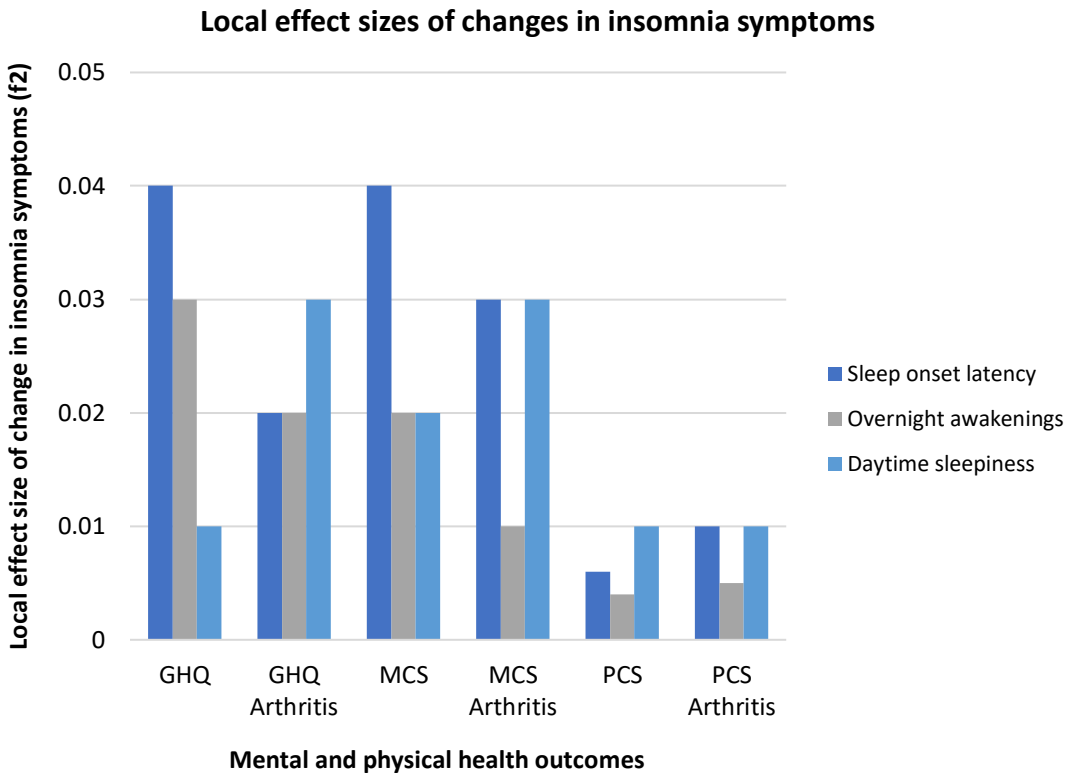
7.4.1 Summary of findings

Findings from this study provided some evidence for the differential association of changes in different insomnia symptoms with perceived health status in the general population and an arthritis chronic pain subgroup within this population. The most prevalent insomnia symptoms were problems with prolonged sleep onset latency and overnight/early morning awakenings, both of which are key criteria in diagnosing insomnia disorder. Certain demographics variables were also consistently associated with mental and physical health outcomes in the analysis. Across all analysis, male sex and older age tended to be associated with better outcomes, whereas Asian race, increased BMI, and unemployment were associated with worse outcomes.

Table 40 provides a summary and comparison of the pattern of results for changes in insomnia symptoms across the full sample and arthritis subgroup. The results suggest that overall, worsening of insomnia symptoms over a 4-year period was associated with poorer health outcomes, especially perceived mental health and psychological well-being. A weaker effect was observed for association between increase in frequency of all insomnia symptoms and poorer physical health outcome at Wave 4. In the arthritis group, an increase in sleep onset latency and daytime sleepiness symptoms were associated with poorer physical health outcome at Wave 4. Generally, associations of improvement in insomnia symptoms with better mental and physical health outcomes were of lesser magnitude, and often not significant compared to worse symptoms at Wave 4. As shown in Figure 19, changes in sleep

onset latency seems to be a key insomnia symptom driving the association with mental health outcomes, functioning and well-being, and yielded the biggest effect size for the associations with mental health outcomes for the full sample and arthritis subgroup. Changes in daytime sleepiness symptoms were also particularly relevant within the arthritis subgroup.

Figure 19 UKHLS analysis – Local effect sizes of changes in insomnia symptoms



Notes: Graphical summary of the local effect sizes of changes in insomnia symptoms between Wave 1 and Wave 4 assessments, by mental and physical health outcomes at Wave 4. The local effect sizes shown above quantify the proportion of variance explained by adding a sleep-change exposure variable to the model with confounders alone.

Table 40 UKHLS analysis – Summary of pattern of results for full sample and arthritis subgroup

	Full sample	Arthritis subgroup
Increase in frequency of insomnia symptoms:		
	Mental health outcomes	**Mental health outcomes**
Sleep onset latency	Worse GHQ + MCS at Wave 4	Worse GHQ + MCS at Wave 4
Overnight awakenings	Worse GHQ + MCS at Wave 4	Worse GHQ + MCS at Wave 4
Daytime sleepiness	Worse GHQ + MCS at Wave 4	Worse GHQ + MCS at Wave 4
	Physical health outcomes	**Physical health outcomes**
Sleep onset latency	Worse PCS at Wave 4	Worse PCS at Wave 4
Overnight awakenings	Worse PCS at Wave 4	No significant association
Daytime sleepiness	Worse PCS at Wave 4	Worse PCS at Wave 4
Reduction in frequency of insomnia symptoms:		
	Mental health outcomes	**Mental health outcomes**
Sleep onset latency	Better GHQ + MCS at Wave 4	Worse MCS at Wave 4
Overnight awakenings	Better GHQ + MCS at Wave 4	No significant association
Daytime sleepiness	Better MCS at Wave 4	No significant association
	Physical health outcomes	**Physical health outcomes**
Sleep onset latency	No significant association	No significant association
Overnight awakenings	Better PCS at Wave 4	No significant association
Daytime sleepiness	No significant effect	Better PCS at Wave 4

7.4.2 Change in insomnia symptoms and perceived mental health

The finding that change in insomnia symptoms were associated with perceived mental health was similar to Silva et al. (2009). They found that worsening of difficulty in initiating and maintaining sleep over five years was most strongly associated with lower mental health-related quality of life assessed with MCS scores. A similar pattern emerges here, not only for MCS scores but also for GHQ scores, another validated measure of psychological well-being that has not been commonly assessed in relation to sleep and changes in insomnia symptoms.

Poor self-rated mental health as captured in the GHQ and MCS are perhaps a contributing factor in how poor sleep and insomnia are risk factor for mental health problems such as depression and anxiety. Baglioni et al. (2011) meta-analysis of 21 longitudinal studies revealed that healthy individuals with no depression and insomnia symptoms at baseline were at greater risk (OR 2.10 95% CI 1.86 – 2.38) of developing depression over time. Li, Wu, Gan, Qu, and Lu (2016) updated this meta-analysis to 34 cohort longitudinal studies with over 172,007 participants and average follow-up of 5 years (range 3.5 months – 34 years) again found this risk to be almost doubled (pooled RR 2.27, 95% CI 1.89 – 2.71). The risk was prevalent even across subgroups analysis by gender, location, insomnia definition, type of depression measure used, follow-up duration, sample size, and controlling for age, socioeconomic status, smoking, alcohol consumption, and body mass index. On a day-to-day level, poor sleep can affect mood and contribute to dysfunctional emotional reactivity and impaired socio-emotional functioning (Beattie, Kyle, Espie, & Biello, 2015; Dinges et al., 1997; Franzen, Siegle, & Buysse, 2008). The current findings provided additional insights into the associations

of changes in problems with sleep onset, awakenings, and daytime sleepiness in the long-term, which may in ways impact perceived mental well-being and risk for subsequent depression.

This relationship between sleep and mental functioning was also observed in the chronic pain subgroup which also further corroborate previous findings. These findings highlight the pervasive and interactive nature of sleep and emotional disturbances in those with chronic pain and supports evidence for the daily influence of negative affect on daytime disabilities and impaired functioning associated with insomnia and poor sleep (Kothari, Davis, Yeung, & Tennen, 2015). O'Brien et al. (2011) assessed three chronic pain groups with back pain, facial pain, and fibromyalgia using daily monitoring of mood, pain rating and sleep with actigraphy and sleep diaries and found a relationship between self-reported poor sleep and increased pain ratings. Importantly, they found that negative mood was a moderator influencing this association. Poor sleep can have an impact on daily thoughts and the contents of those thoughts, leading to a tendency for brain processing to become skewed towards loops of repetitive negative thinking. These short-term sleep disruptions if they continue could contribute and lay the stage for long-term negative thinking, depressive and anxiety provoking thoughts, emotional problems, and general dissatisfaction with mental health (Gruber & Cassoff, 2014; Harvey, Murray, Chandler, & Soehner, 2011; Neckelmann, Mykletun, & Dahl, 2007; Palmer & Alfano, 2017). The longer the sleep problems persist, the greater the psychological consequences. The current findings illustrate that even in a general population, prolonged sleep problems or worsening of sleep problems may consequently be associated with general life satisfaction and

mental well-being. In addition, once insomnia symptom is present, an improvement over a period of four years was associated with only some improvement in mental well-being and not by as much magnitude as worsening of symptoms. As sleep difficulties may further be a contributory causal factor in the long-term occurrence of mental health problems and other comorbidities, recent trials have found that even in those with chronic pain conditions, improving sleep could benefit psychological health of the population by improving symptoms of depression and anxiety (Freeman et al., 2017; Luik et al., 2017).

7.4.3 Difficulty getting to sleep and mental health in the general population

In this current study, problems with sleep onset latency had the greatest association with mental health (GHQ and MCS scores) in the general population. In differentiating the effects of varying insomnia symptoms, Yokoyama et al. (2010) compared three sub symptoms of insomnia – they also found that difficulty initiating sleep was more associated with depression symptoms compared with early morning awakenings and difficulty maintaining sleep in their analysis of Japanese older adults over 65 years old and living in the community. These findings are possibly reflective of the presleep thoughts and cognitions that usually accompanies insomnia and sleep disturbance. People dissatisfied with their sleep or presenting with insomnia symptoms usually tend to report greater mental activities near bedtime. For example, it has been hypothesised that insomnia patients tend to overestimate how long it takes them to fall asleep because of enhanced sensory and information processing around sleep onset, leading to elevated cortical arousal and inability to disengage from sleep disruptive sensory and cognitive processes (Perlis, Giles, Mendelson,

Bootzin, & Wyatt, 1997). Cognitive models of insomnia further highlight these cognitive-behavioural mechanisms and explains how these psychosocial and physiological processes maintain insomnia disorder by prompting excessive negative-toned cognitive activity, psychological arousal, distress, worrying, and rumination (Espie, Broomfield, MacMahon, Macphee, & Taylor, 2006; Harvey, 2002; Riemann et al., 2010).

These excessive negative thinking centred around getting to sleep may contribute to problems with insomnia and related health outcomes. This current analysis highlights the potential relevance of sleep onset latency problems and need for further research to explore this association. Especially since it was not possible to directly compare these findings with other studies due to paucity of analysis on associations of sleep onset difficulties with perceived mental health. Problems with sleep onset latency may also be a prominent symptom of a certain type of insomnia that is particularly vulnerable to poorer physical and mental health, in comparison with other types of insomnia or sleep disorders featured by awakenings and excessive daytime sleepiness (e.g., sleep apnoea) (Chung, 2005).

7.4.4 Improvements of insomnia symptoms in the general population

This current study found the greatest associations of health outcomes with worsening than improvement of insomnia symptoms. Worsening of insomnia symptoms was associated with lower MCS scores of almost 3 points indicating 'some more' mental and emotional role limitation compared to baseline. On the other hand, improvement of symptoms was associated with higher scores by 1 – 2 points

indicating ‘a little less’ limitation (Ware, 1993; Ware et al., 1996). For GHQ scores, the results show deterioration of health status and reduction by 1.6 points when symptoms get worse and increase of 1.0 points when improvements in symptoms were observed. This GHQ score compare with those observed in a trial where mental health professionals who underwent an 8-week mindfulness based cognitive therapy showed increased psychological well-being at 20-week follow-up and experienced a GHQ score increase of 1.6 points (Ruths et al., 2012).

As observed, there is already some associations of ‘natural’ improvements in sleep, this also conveys that there could be some value in exploring the curative effect of improving sleep in the general population by investigating public health strategies to boost sleep and identifying avenue to implement these strategies. There are established CBT-I effective to tackle chronic insomnia in clinical populations (Trauer et al., 2015) but it is yet to be seen how this can be translated into meaningful strategies to reduce insomnia symptoms in non-clinical populations, and raise public awareness to the consequences and prevalence of disturbed sleep and symptoms of insomnia. There is some evidence to support the use of this manner of therapy in a community setting for those with sub-clinical and mild insomnia symptoms.

There may be some value for CBT-I approaches to be delivered in an adapted manner as a public health strategy to address the prevalence and burden of mild insomnia symptoms. Swift et al. (2012) reported the effects of a 1-day intensive psychoeducational CBT sleep workshop. Participants from the general public were randomly assigned to attend an experimental workshop and follow up sessions

immediately (n=75), or to the waitlist control group (n=76). The CBT-I workshops were significantly effective in reducing insomnia symptoms among participants at a 3-month follow-up. According to ratings on the insomnia severity index, symptoms reduced 17.6% in the experimental group, but only 3.5% in the control group. The workshops were delivered in large groups of around 30 participants and were easily accessible by the public. Adapting sleep management approaches in such manners means it can be readily delivered quickly and effectively in communities, does not require as much specialist knowledge as CBT-I for insomnia and thus bypasses the issue of lack of readily available health care professionals extensively trained to deliver more dedicated one-to-one non-pharmacological therapy for insomnia. It may help remediate mild symptoms such as problems initiating sleep and hereby then prevent development of clinical levels of insomnia. However, further trials with longer follow-up and a broader set of outcome measures are still warranted to establish the effectiveness and efficiency of such a community-based therapy. There is also a need to explore which aspects of the broad construct of insomnia and sleep quality can be successfully addressed and improved and how this will impact on risk of developing clinical insomnia, health-related quality of life, and overall well-being of the population.

7.4.5 Daytime sleepiness and perceived health outcomes in chronic pain

In the arthritis subgroup, as well as sleep onset latency, it was changes in daytime sleepiness that translated to greater associations with health outcomes. As well as being related to chronic sleep loss, daytime sleepiness is often linked with organic sleep disorders like sleep apnoea, circadian rhythm sleep disorders, sleep

related movement disorders, hypersomnias (e.g., narcolepsy), and it could also be symptoms of underlying medical conditions such as stroke, brain injuries, other neurological disorder or use of medications and illicit substances (Tsai, 2010). In this chronic pain group, daytime sleepiness symptoms may reflect the dissatisfaction with daytime impairment not just related to sleep but also to their pain condition such as changes in pain intensity, flare-ups, and consequent decline in social and physical activity. In addition, those with chronic pain may also misperceive fatigue and physical exhaustion associated with their pain condition for sleepiness (Ancoli-Israel & Martin, 2006; Shekleton, Rogers, & Rajaratnam, 2010). It may be helpful to assess separately and tease apart the respective contribution of sleep problems, physical pain symptoms, and fatigue in contributing to daytime sleepiness. Consequently, targeting this symptom and improving sleep in this population may help in drawing attention as to how sleep affects not only pain but also daily functioning, mood, engagement in physical activity, pain appraisal and coping (Gerhart et al., 2016; Kothari et al., 2015; Tang & Sanborn, 2014).

7.4.6 Preventing worsening of insomnia symptoms in chronic pain

It is also worth noting that in the arthritis subgroup, the associations of natural improvement in sleep was not as prominent compared to the patterns of findings in the full sample. Even an improvement in sleep onset latency problems over time was still associated with worse health outcome. However, this analysis was carried out on imputed datasets, so this may have contributed to the result. Although, it may also be possible that a history of sleep disturbance in this group predicts stronger impairments in health status even if symptoms remits and resolves. The combined

effect of a chronic pain condition comorbid with poor sleep could lead to a predisposition to heightened sleep reactivity, sleep system sensitisation, increased vulnerability to insomnia symptoms, and psychological distress (Kalmbach, Pillai, Arnedt, Anderson, & Drake, 2016; Smith & Haythornthwaite, 2004). Hence, for those with a chronic pain condition, there may be a need for more targeted hybrid interventions that considers aspects of pain and sleep management to improve sleep in the long-term. Vitiello et al. (2014) were already able to show that 6 weekly sessions of CBT-I in those with arthritis led to short-term improvements in sleep measures 2 months later across measures of insomnia severity, sleep quality and fatigue. Furthermore, for those showing improvement in sleep, the improvements further predicted sustained long-term improvement in sleep quality 18-months later, compared to those whose sleep did not initially improve.

7.4.7 Limitations

The current study highlights the associations of changes in insomnia symptoms with physical and mental health outcomes and is strengthened by the UKHLS large representative sample, availability of repeated assessment of measures in same individuals, derived weighting to control for sample attrition, and the measures of sleep and validated health outcomes. However, some limitations of the current analysis should also be noted. Whilst the study provided further investigation of the association of changes in sleep (i.e. a sustained exposure) with health outcomes, it lacked the specific longitudinal design (measurement of the outcome measure only prospectively) which would have further strengthened the causal relationship between sleep symptoms and health outcomes. Further longitudinal studies and

analyses of further waves of the UKHLS panel cohort data are required to establish if there is a temporal and causal prospective association between changes in sleep and these outcomes.

The current analysis is also unable to provide an insight into what drove the changes in insomnia symptoms, it could be a case of reverse causality and that it was actually changes in the physical and mental outcomes and associated psychological distress and depression leading to worse or better sleep (Phelan, Love, Ryff, Brown, & Heidrich, 2010). To combat this, the current analysis controlled for Wave 1 measure of health outcomes, however, it was not possible to control for other changes in health outcomes during the 4-year period. In addition, each of the insomnia symptoms (sleep latency, awakenings and daytime sleepiness) were assessed independently for their relationship with health outcome at Wave 4 and whilst each analysis was adjusted for various confounding variables, the remaining insomnia symptoms were not included in the model and this may affect the specificity of the observed results.

Furthermore, for the full sample analysis there was a difference noted for the MCS and sleep onset latency analysis for the imputed analysis. When comparing the imputed and complete case analysis, the association of decrease in frequency of sleep onset latency problems with Wave 4 MCS score was no longer significant. This inconsistency suggests that perhaps missingness may be an issue for this analysis and begs the question of why responses for these particular items were missing in the first place. Missingness is often a common issue in panel studies with substantial follow-up assessments. Attention should be paid to methods to deal with missingness and

consequent results should be interpreted with caution. Here for the full sample, the imputed data sets and complete cases analysis were compared to highlight any potential inconsistencies in estimates, confidence intervals and interferences. Further efficient techniques and statistical methods to address and appropriately interpret the issue of missing data in these types of studies would be a worthwhile research effort.

Notably, assessment of sleep, outcomes, and even report of arthritis in the current analysis was based on self-report which is subject to recall and reporting biases. Some of items embedded within outcome measures (for example the sleep item in the GHQ-12) may also have an undetected impact on the observed associations between changes in sleep and the GHQ-12 outcome measure. In addition, Arthritis was not determined by clinical diagnosis and this arthritis subgroup within the general population were also as healthy as the population except for differences in PCS scores. This suggests they may present with less comorbidity with sleep issues compared with other clinical chronic pain patients. The current analysis also did not explore comorbidity with other health conditions reported in UKHLS (diabetes, asthma, cancer, epilepsy, depression, coronary heart disease etc.) and use of medications which may all contribute to different health states and differential effect on sleep. Furthermore, the comparison between the full sample and the arthritis subgroup was not as distinct since the full and subgroup sample were still overlapping to some extent.

For assessment of insomnia symptoms, the UKHLS also does not have information on other organic sleep disorder such as sleep apnoea, hypersomnia, REM

behaviour disorders, and the sleep assessment did not include items on duration of insomnia symptoms beyond the past month. Absence of other potential confounding sleep disorders, short period for report of insomnia symptoms, and lack of information on impact of sleep impairment on work and social participation and daytime functioning does not allow the assessment to meet full insomnia diagnostic criteria as per DSM-5 (2013) and ICSD-3 (2014). This may reduce the specificity of the current assessment of insomnia symptoms and associations to capture the full spectrum of insomnia trajectories and health outcomes. Perhaps, future research or cohort study design can add a few further questions on self-reported assessment of sleep and sleep disorders to get an elaborate measure of clinical insomnia.

7.5 Conclusion

The current analysis revealed the association between changes in insomnia symptoms (both worsening and improvement) and perceived mental and physical functional well-being in the general population, and an arthritis subgroup. As new waves of data are released for the UKHLS, future analysis can perhaps also use advanced statistical techniques like latent modelling and latent class cluster analysis to follow insomnia symptoms over more than 2 – 3 time points, examine the rate of change in sleep over time and from this analysis determine further detailed curvilinear relationships between sleep and health outcomes. Fine-tuned latent class analysis can also explore the pattern and change in prevalence of different symptoms and relative contribution to different dimensions of physical and psychological well-being and pain-related health outcomes (Collins & Lanza, 2010).

8 General discussion

"Sleep is that golden chain that ties health and our bodies together"

Thomas Dekker (1577–1632)

8.1 Summary of main findings

This thesis sought to explore the interrelationship between sleep disturbance and the experience of pain. In particular, it considered the associations between sleep and pain and the mechanisms and factors underlying the association between the two processes. A brief summary of the relevant findings from the studies presented in the preceding chapters of the thesis is below.

Chapter 4 – This experimental study supported the utility of conditioned pain modulation as a marker of pain inhibitory processes by exploring the reliability and validity of the procedures to elicit conditioned pain modulation response. It considered factors such as the type of conditioning stimuli used to elicit pain, distraction, pain catastrophising, and sleep that could impact the efficiency of endogenous pain inhibitory response. Findings support the validity of CPM as a process relatively independent of cognitive distraction. Importantly, this study also revealed that less efficient CPM response may be associated with self-reported day-to-day sleep disruptions (less total sleep time and longer sleep onset latency) in a sample of healthy young adults.

Chapter 5 – This quasi-experimental study further explored the associations between sleep disturbances and pain by comparing sleep and pain-related parameters in clinical chronic pain groups with healthy controls. Whilst the chronic pain groups reported poor self-reported sleep, findings did not find distinct differences in characteristics of sleep disturbance assessed using actigraphy, and polysomnography between two chronic pain conditions (fibromyalgia and chronic back pain) compared with healthy controls. However, the study offered some extension of the aims from Chapter 4. Namely that objective sleep disturbance (less total sleep time, more overnight arousals, and longer sleep onset latency) may be associated with less efficient CPM response and pain inhibitory processes in individuals with fibromyalgia and chronic back pain.

Whilst Chapter 4 extended evidence of the validity of CPM as a marker of pain inhibition response, it also coveys the potential association of CPM with self-reported sleep. Chapter 5 did not reveal substantial differences in characteristics between chronic pain and non-chronic pain controls and pain inhibition processes. Nevertheless, these experimental chapters explored the potential associations of sleep disturbances with pain and provide a basis to further consider the role of pain inhibition and inflammation as possible mechanisms underlying the associations. Taken together, Chapter 4 and 5 provide an insight into the short-term cross-sectional relationship between sleep and pain variables and in small specific samples. To expand on this, this thesis moved on to examine the interrelationship between sleep and pain-related variables over time in the general population. A systematic review and further epidemiological analyses were carried out and it was hoped this would add another

layer of perspective to deepen understanding of the potential long-term associations between sleep and pain outcomes.

Chapter 6 – This systematic review and exploratory meta-analysis consolidates extant evidence that changes in sleep are associated with several dimensions of the pain experience (risk of developing a pain condition, elevations in levels of inflammatory markers, and a decline in self-reported physical health status). Findings from this review suggest that deterioration in sleep and persistent poor sleep are key risk factors of poor health. However, the findings do not provide sufficient evidence that an improvement in sleep quality has a reverse protective function. The review highlighted key issues that suggest that there is room for further longitudinal studies with longer and more frequent follow-up assessments, allowing for a proper evaluation of the impact of dynamic changes in sleep on long-term pain outcomes.

Several methodological considerations arising from the systematic review also formed the focus of the analysis presented in Chapter 7. The review in Chapter 6 revealed considerable variations across studies in the way changes in insomnia symptoms, sleep quality and quantity were measured, which limited interpretability and generalisation. Hence, the need for an investigation into how changes in different sleep parameters may have differential associations with health outcomes. The studies reviewed also focused mainly on general populations. This leaves room to consider incorporating subgroup analyses (e.g., those with chronic pain) in future studies to dissect how change in sleep is associated with the pain-related physical and mental health functioning in a high risk clinical group.

Chapter 7 – This analysis using the UKHLS dataset revealed an association between changes in sleep and different insomnia symptoms over a 4-year period from Wave 1 – Wave 4 (prolonged sleep onset latency, overnight and early morning awakenings, and daytime sleepiness) and perceived physical and psychological well-being at Wave 4. In both the general population and people with arthritis, worsening of insomnia symptoms over the 4-year period was associated with subsequent poorer health outcomes, especially perceived mental health and psychological well-being. Associations with improvement in insomnia symptoms on health outcomes were, however, of lesser magnitude and often not significant compared to worsening of symptoms. These findings suggest that poorer sleep may be associated with worse psychological well-being and pain-related comorbidities in the general population and in those living with a chronic pain condition.

8.2 Emerging findings, implications, and research recommendations

Overall, the findings of this thesis provide further support for the associations between sleep and pain outcomes and offer some ideas on the processes through which this happens. The studies reported in this thesis assessed the relationship from two different angles (experimental and observational). These different but complementary research methodologies enrich and contextualise our understanding of the interrelationship between sleep, pain, and related health outcomes.

Specifically, from the two experimental studies, we see the possible associations of sleep disturbance with pain response through several possible mechanisms

including central pain processing and inflammation. The exact roles of these mechanisms remain unspecified and further empirical investigations are warranted to establish their role in the causal links between sleep and pain. That said, the systematic review and analysis of the UKHLS dataset provided some evidence to support both the long-term associations between sleep and pain problems and the mechanisms involved from an epidemiological point of view. Further research into understanding the temporal effects and long-term relationship between the two may subsequently be used to determine and predict disease prognosis of these problems and impact on population health.

Sleep disturbances and pain inhibition processes

From the experimental studies discussed in this thesis, sleep disruptions seem to be associated with enhanced responses to pain and diminish the efficacy of descending pain inhibitory pathway. As reported in Chapter 4, self-reported total sleep time was correlated with CPM response and shorter in CPM non-responders than non-responders. Other markers of sleep disturbance, namely, sleep onset latency and wake after sleep onset were also longer in CPM non-responders but were not statistically significant possibly due to lack of statistical power and mismatch in the cell sizes of responders (n = 44; n = 91) and non-responders (n = 10; n = 12).

The study presented in Chapter 5 combined self-reported sleep assessment with objective PSG sleep parameters and the findings of this study further revealed potential association of patterns of sleep disturbances with measures of pain threshold and pain inhibition. Here, we see that objective sleep disturbance may also

be associated with pain inhibitory processes in a chronic pain population. Less total sleep time may be associated with lower CPM response and greater arousal index with lower pressure pain threshold assessed the next morning in chronic back pain patient. In the fibromyalgia group, longer sleep onset latency and increased arousal index overnight may also be related to lower pressure pain thresholds and next day CPM response. Of course, these are only correlations which were no longer significant after Bonnferroni corrections and coming from a study of a small sample size. Further clarification of the causal link is required in larger studies in both healthy and clinical populations.

Nevertheless, one cannot discount the possibility that short-term sleep disruptions may not only be associated with acute pain responses but could also contribute to an increased risk for future chronic pain conditions (Iacovides, George, Kamerman, & Baker, 2017). If self-reported poor sleep quality and even objectively measures sleep are associated with insufficient CPM, it raises the question whether interventions that aim to improve sleep quality and protect sleep duration could alter pain inhibition response? Roehrs, Harris, Randall, and Roth (2012) for example, randomised 18 healthy participants with mild sleep disturbance (sleep efficiencies < 85% on screening PSG) to either extended bedtime over 4 nights to 10 hours or 4 nights of sleep diary reported habitual times. The extended bedtime group showed an increase in total sleep time and reduced sleepiness as assessed by daytime multiple sleep latency tests (MSLT) and this was correlated with reduced pain sensitivity and greater pain threshold to a heat pain stimulus. These findings highlight the need for further work both in healthy and clinical population to determine how and if changes

in sleep can lead to better pain and health outcomes. The finding from this thesis point to insufficient sleep quantity as a factor associated with pain inhibition impairments. Future investigations may further assess the feasibility of protecting or extending sleep duration or addressing sleep continuity disturbances on pain inhibition impairments in pain conditions.

This would also ideally provide a platform to assess the temporal relationship between the processes of sleep and pain over a period of a couple of weeks for example, by combining ambulatory PSG, self-reported sleep, and daytime lab visits for quantitative sensory testing and to assess CPM response. Combining assessments of sleep and pain parameters may have clinical utility in enabling the development of personalised assessment of sleep disturbance, inflammation, and psychophysical pain modulation profile. It has been suggested that greater pro-nociceptive profile may be linked with higher risk of pain acquisition, intense pain syndrome and greater resistance to therapeutic methods, and greater impairments in the overall psychosocial experience of pain. Whereas an anti-nociceptive profile may be more indicative of lower chances of acquiring pain, and lower intensity of pain syndromes and symptoms (Granovsky & Yarnitsky, 2013; Yarnitsky, 2015). This has implications for pain therapy as it may provide predictive indicators of the individual's psychophysical pain behaviour and response to medications and other preventive treatments. Essentially, by establishing differential pain profiles, research can explore if sleep disturbance is a risk factor for a pro-nociceptive or anti-nociceptive profile and if this association is also mediated by factors such as inflammation. In addition, the concurrent presence of sleep disturbances and pain syndrome may further facilitate

a change in pain modulation state and profile, shifting it towards pro-nociception (Granovsky & Yarnitsky, 2013). The effect of addressing sleep continuity disturbances may thus differ based on the presenting pain profile or pain inhibition impairments in an individual presenting with a pain condition. Knowledge of how sleep influences an individual's pain experience may promote personalised integrated interventions and management by sleep phenotype. As the systematic review in Chapter 6 also revealed, these associations between sleep and pain inhibition profiles have also not yet been explored from a longitudinal perspective. This would further inform the epidemiological evidence on the development, perpetuation, or alleviation of pain experience.

Sleep disturbances and pain-related disease risk

The systematic review in Chapter 6 illuminated that a decline in sleep quality and sleep quantity over time was generally associated with a greater risk of developing a pain condition, small elevations of inflammatory markers, and a decline in self-reported physical health status. Levels of inflammatory cytokine consistently emerges as one of the potential mechanisms through which sleep influences short- and long-term disease risk. The study in Chapter 5 also suggested that profiles of inflammation and levels of cytokines may differ and be elevated in those with chronic pain and poor sleep compared with pain-free controls. Other studies have suggested that subclinical elevations in inflammation cytokine levels such as hs-CRP are often related to increased pain sensitivity, suggesting a potential role of inflammation in experimental pain and which may be of importance for the development of clinical pain (Schistad, Stubhaug, Furberg, Engdahl, & Nielsen, 2017).

The studies included in the systematic review tend to evaluate findings related to sleep and these physiological biomarkers either in isolation or in relation to mortality risk or another health conditions such as cardiovascular disease (Cappuccio et al., 2011; Miller & Cappuccio, 2007) but not specifically in relation to pain or even specifically within a chronic pain population. Evidence from further epidemiological studies is required to substantiate how sleep could trigger and activate stress response, stimulate pro-inflammatory markers, and consequently facilitate and worsen pain experience (Smith et al., 2009). Much of the included studies lacked the specificity and research design required to clarify the underlying direction of the association between sleep and pain and how sleep alters physiological biomarkers and influences pain experience. To pin down the role of these biomarkers, future investigations would need to expand on the relevance of these biomarkers and how they specifically relate to aspects of the physiological and psychological sleep and pain experience (e.g., pain inhibition, conditioned pain modulation, pain catastrophising, quality of life), in both short- and long-term.

Sleep disturbances and long-term physical and mental health

The evidence from the experimental studies in this thesis focused primarily on examining the within-person association between sleep and pain within relatively healthy and small clinical groups. Although the studies provide in-depth explorations and support for a relationship between sleep disturbances and pain. The generalisability of the findings from such studies to the general population needs to be further reinforced by prospective studies with longer follow-up periods. By

considering an epidemiological perspective, this thesis generated further insight on the trajectory of sleep deterioration and sleep improvement and associations with pain related outcomes. Evaluating changes in sleep allowed for simulation of sleep deterioration and improvement and different sleep trajectories over time, enabling a better gauge of the potential value of sleep interventions in the prevention and management of chronic pain in the general population.

The exploratory meta-analysis from the systematic review presented in Chapter 6 and the UKHLS analysis results in Chapter 7 suggested that new incidence and persistence of sleep problems may be associated with poor perceived physical and mental health over time. Whereas, the remission of sleep disturbances was only associated with a slight improvement in health outcomes. Such findings suggest that it is logical to hypothesise that improvements in sleep may help to mitigate pain-related health factors. Hence, future studies should not only focus on the negative effect of sleep on pain or the association between sleep problems and propensity towards the risk of developing a pain condition. It is equally important to characterise these dynamic natural improvements in sleep and determine why and how they are associated with positive pain-related health outcomes.

Promoting good sleep and well-being within clinical pain and general population

In clinical settings, sleep is increasingly gaining relevance as an assessment and treatment target within pain management. The growing body of evidence on the specifics of the relationship between the two garnered from this thesis supports further development of ongoing non-pharmacological treatments for sleep problems

such as hybrid cognitive behavioural therapy for insomnia and pain to tackle sleep and pain problems (Tang, Goodchild, & Salkovskis, 2012). Further experimental work would provide insight and further conceptualisation of the sleep and pain relationship and relevant bio-psychological mechanisms at play as well as their role in the inception in sleep problems and other physical and functional impairments in chronic pain. At the general population level, there may also be some value for CBT-I approaches to be delivered in an adapted manner as a strategy to address the burden of mild insomnia symptoms prevalent within the population and targeting at-risk population groups. Indeed, further work is needed on how this can impact the health of the population positively.

Future studies can also look into differences between those with worsening and improvement of sleep problems to gain further understanding of what triggers these changes in sleep. Different lifestyle factors such as day-to-day activities, exercise, and diet could be conducive to better sleep or predictive of different patterns of change and thus indicative of how to promote better sleep and health-related quality of life. Studies have suggested that behavioural interventions and approaches (e.g. Tai Chi) that target sleep may not only improve sleep, but also improve physical health and wellbeing (Irwin et al., 2015). Currently, we do not know what produces these effects and a key and interesting extension of this work could possibly focus on the mechanisms through which these approaches (exercise, diet etc.) impact on biologic processes and interactions between sleep and pain (Davidson, 2015). Consequently, the goal of further sleep and pain epidemiological studies in this area is to inform understanding of the development, evolution and progression of

these problems in the population and use this epidemiological knowledge to enhance societal health and well-being.

8.3 Looking forward

Poor sleep and chronic pain conditions both contribute largely in determining societal health and present a major public health challenge due to their pervasive impact on daily functioning and well-being. Further experimental studies are needed to verify the specific causal links between sleep, inflammatory processes, and the experience of pain and the interaction between these processes in causing the altered pain perception and hyperalgesia induced by sleep disturbances. In addition, screening for sleep disturbances and psychological risk factors and addressing acute insomnia and sleep problems in the short-term may lessen the risk and transition to long-term chronic pain comorbidity. It has been suggested that timely identification and response to acute insomnia to lessen the aggravation and development occurrence of chronic insomnia is possible and feasible (Ellis, Cushing, & Germain, 2015; Ellis, Gehrman, Espie, Riemann, & Perlis, 2012). This could be carried out for example during hospitalisation for pain surgery or whenever symptoms of acute insomnia are first identified by the primary care giver. Although, it is also reliant on the availability of a treatment infrastructure which recognises acute insomnia as a problem, and knowledgeable health-care providers with the expertise to assess and treat the problem (Ellis, Gehrman, et al., 2012).

It would also be desirable to further investigate the effectiveness of interventions, e.g., cognitive behavioural therapies and exercise programmes as possible tools to enhance pain-related health outcomes and quality of life in general via promoting sleep. This can serve as further tests of the causal association between sleep, pain, and wellbeing. Although, in order to implement interventions and strategies to promote better sleep and good sleep quality, there is a need to disentangle and examine which aspects of sleep fluctuates and is also most feasibly amenable to changes and improvements that would lead to better quality of life.

The need for more longitudinal research and knowledge of the processes underlying sleep and pain is also consistently emphasised throughout the thesis (Lee, 2016). Importantly, further evidence is required to understand the trajectory of sleep characteristics and health outcomes in the general population and in those with a chronic pain condition. Longitudinal studies enable understanding of the natural evolution of poor sleep, its symptoms, development and progression from acute to chronic insomnia, transition from good sleep to poor sleep and vice-versa and causal consequences and associations of these trajectories and transitions with pain-related health outcomes (Ellis, Perlis, Neale, Espie, & Bastien, 2012; Kyle, Morgan, & Espie, 2010; Morin et al., 2009). Longitudinal studies with more than two follow-up assessments and appropriate corresponding cross-lagged analysis would provide a suitable platform to substantiate the temporal relationship between changes in sleep and pain outcomes and to provide a framework to examine the trajectories of health status over time across individuals with different patterns of sleep changes.

8.4 Limitations of the thesis

The studies and findings presented in this thesis are limited by a number of factors that require consideration:

i. The scope of this thesis did not cover in detail other domains of sleep-wake behaviour for example, the role of chronotypes and biological circadian rhythms in the association between sleep and pain. There is limited but emerging evidence concerning the involvement of chronotypes and diurnal variations in pain syndromes, pain perception, related inflammatory processes, and pain management (Junker & Wirz, 2010; Keller et al., 2009). Circadian variations have also been observed in chronic pain conditions; the pain intensity and pain perception is often dependent on time of day (Junker & Wirz, 2010). Chronotypes are also often linked to circadian rhythms and diurnal variations. Some cross-sectional studies have revealed that both early and late chronotypes type with fibromyalgia reported poorer sleep quality and subjective pain than intermediate types and that late chronotypes had amplified fibromyalgia related symptoms (Kantermann, Theadom, Roenneberg, & Cropley, 2012). In terms of pain perceptions, evening types also tend to show lower pain thresholds and greater sensitivity to pain than morning types all day long and this could also be partially associated with affective functioning, negative affect, differences in cortisol, and sleep debts (Jankowski, 2013). This could have implications for the findings reported in this thesis related to the assessment of pain inhibition, inflammatory markers, sleep disturbances, and affective variables. On the other hand, these existing studies are also few and often limited either by small restricted sample sizes

or cross-sectional designs. Further studies should seek to further clarify the interrelationship between subjective and objective pain assessment and sleep disturbances and also individual chronotypes. Considering the role of biological rhythms may be another part of the puzzle in understanding the links between sleep and better individualized pain assessment and management.

ii. Findings from the experimental studies in the chronic pain population is limited by small sample size, mismatch between groups, recruitment difficulties, and subsequent lack of control in some aspects of the design. Although studies using PSG sleep assessment do not usually tend to have extremely large sample size. As encountered during the course of recruitment for this study, it may often be hard to recruit patients for extensive overnight sleep studies solely for research purposes. In addition, academic research department may also be constrained by the scope of how many participants can be tested at once due to limited resources, compared to dedicated sleep disorders clinics within hospitals. Looking forward, and with the emergence and popularity of 'big data' analysis, there could be scope for building a database of experimental PSG studies within and across sleep laboratories (Bianchi et al., 2017). This would then inform a collation of sleep data to be assessed for microstructural features to distinguish pain-free healthy with those with pain conditions.

iii. Despite the multi-methodological approach used in this thesis and given that perception of sleep quality and pain are inherently subjective experiences, the

thesis lacked some exploration of the participants' and patients' phenomenological perspective. For example, some chronic pain patients do not report sleep problem, or their sleep difficulty was not a cause of great burden or interference. Why this is the case would be interesting to know. When the thesis explored self-reported change in sleep, it may have also been informative to qualitatively consider how the changes in sleep are important or meaningful to participants and how the changes contribute to the perception of functioning and well-being. It may also have been the reverse and that it was changes in perceived health and functioning that contributed to these changes. Further studies may further elaborate if it is sleep pattern and behaviours that fundamentally change in the long-term and lead to changes in health outcomes or if individuals learn to cope better with poor sleep and adapt their function accordingly. Future studies incorporating qualitative analyses and utilising mixed-methods approaches as used in health sciences research may provide further insight into this (Ostlund, Kidd, Wengstrom, & Rowa-Dewar, 2011).

8.5 Concluding remarks

The strength of this thesis was the exploration of the interaction between the sleep and pain experience using several methodological approaches and providing different levels of empirical evidence. From observational quasi-experimental studies to a systematic review and analysis of a cohort dataset; these approaches complemented each other and enabled the utilisation of different empirical methodologies to explore the influence of sleep fluctuations on pain in both the short

and long-term and the underlying relationship between the two. The thesis also highlighted future research needs crucial to the implementation and translation of scientific knowledge of sleep to improve pain and related health outcomes. These include investigations into beneficial interventions aimed at addressing the negative health outcomes associated with poor sleep, and the need to incorporate sleep assessment into pain management approaches.

Emerging recommendations from the thesis also include the need for epidemiological investigations to understand the evolution and consequences of changes in sleep quality and the impact of this on pain conditions and the health of the population. For example, given accumulating evidence to support the importance of sleep in influencing cardiovascular health (Cappuccio et al., 2011), it has been suggested that poor sleep could be included in the list of leading modifiable cardiovascular disease risk factors (Lallukka & Kronholm, 2017; Redline & Foody, 2011). A similar conceptualisation can perhaps be applied to pain research to establish the importance of sleep as a health attribute integral to many physiological and behavioural factors implicated in pain and related health outcomes. Subsequently, this would enable the prioritisation of sleep as an important health issue and help target interventions to promote better sleep, reduce pain-related disease risks, and improve population health.

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Appendices

1: CPM Experiment 1 – Informed Consent Form

THE UNIVERSITY OF WARWICK

Participant identification number:

CONSENT FORM

Project Title: Experiment 23 – Sleep & Functioning

Name of Researcher: Esther Afolalu. Department of Psychology, University of Warwick, Coventry, CV4 7AL, United Kingdom.
Tel: (024) 765 23158. E-mail: e.f.afolalu@warwick.ac.uk

I confirm that I have read and understood the study information and have had the opportunity to ask any questions I may have.
I agree to take part in the above study and am willing to: *Complete study diaries & questionnaires, carry out the sensory testing, physical functioning tasks and cognitive testing.*
I understand that my information will be held as per the University of Warwick's Research Code of Conduct and may be processed for the following purposes: r*esearch findings published in journals, presented at conferences and shared anonymously with other researchers.* I understand that my participation in the study will be kept confidential and anonymous and that I will not be identified personally in any presentation or publication and only the research team will have access to my personal information.
I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason without being penalised or disadvantaged in any way.

Name of Participant	Date	Signature

Name of Researcher taking consent	Date	Signature

Sleep&Pain_ConsentForm_Students_v.1 26/11/14

2: CPM Experiment 1 – Participant Information Sheet

Study Info – Experiment 23

We would like to invite you to take part in this study for a research project looking at the association of temporal changes and characteristics of sleep with pain response, cognitive functioning, psychological functioning and physical functioning. Joining the study is entirely voluntary and we would like you to understand why the research is being done and what it would involve. If you decide to take part, you are still free to withdraw at any time and without giving a reason.

Please note: To take part in this study, you must be fairly healthy with no known major medical or psychiatric or neurological conditions. This is because of the type of sensory testing that will be carried out to assess your pain sensitivity and pain threshold, if you have any concerns regarding this, please let me know.

Please log-on to SONA to book your timeslots. You need to book two timeslots - Part 1 and Part 2 for exactly a week apart! The password/invitation code for the study is *PANDA23*

You are allocated 2 hours to complete this research experience. You will be required to book two 30 minutes sessions a week apart to complete the tasks and can use rest of the time during the week in your own time to complete the short daily sleep & activity diaries.

The testing sessions will be carried out in the Sleep & Pain Lab (H0.102). When you come for your first session, we will describe and go through the study with you. If you agree to take part, you will sign the consent form. You will then complete some questionnaires, sensory testing will be carried out, followed by cognitive tasks on the computer, physical functioning tasks and a post-task questionnaire. After this, you will be told how to complete sleep & activity diaries for the week. Exactly a week later, you come back to the lab for the re-test session, again, you will complete some questionnaires, and sensory testing will be carried out, followed by cognitive tasks on the computer, physical functioning tasks and a post-task questionnaire.

An explanation of some of the procedures in the study.

Cognitive tasks, Diaries & Questionnaires
The cognitive tasks will be administered on a computer with clear instructions about what to do. All diaries & questionnaires will be paper-based.

Quantitative sensory testing
This will consist of sensory testing to assess your pain sensitivity and pain threshold. Specifically, we will use an instrument called an algometer to assess your Pressure Pain Threshold, this is the minimum force applied to a chosen site of your body (right forearm) till you feel the discomfort of the pressure sensation. While you are doing this, you will also be carrying out other tests. One of this is a physical task - holding a 5-6kgs weighted bag using your other arm. The other is a Cold Pressor task where you will be asked to keep your left hand in a container of water maintained at between 4 degrees Celsius until a pain sensation is first reported.

The sensory testing and physical functioning may cause some discomfort, however, these tasks have been routinely used in research and clinical settings for pain assessment. It is important to know that you can stop the procedure at any time if it gets to an unpleasant level of discomfort. We are aiming to detect your pain threshold (the point at which pain begins to be felt), NOT your pain tolerance (how much pain you are able to handle or tolerate). Any pain sensation will only be temporary so it is very important to realise that you can stop the tests as soon as you feel any discomfort or pain.

3: CPM Experiment 1 – Debrief

Experiment 23: Debrief

My research investigates the effect of sleep disturbances on pain, day-to-day functioning, health and wellbeing. Research in the field of pain and sleep has assumed a roughly reciprocal relationship between the experience of pain and the process of sleep. However, findings from recent studies are suggesting that while sleep and pain may indeed be bidirectionally linked, sleep disturbance may have stronger contributory effect on the experience of pain than the effect of pain on sleep. This current study is what is called a 'daily-process' study adapted from studies that have found sleep disturbances as a possible risk factor for onset and worsening of pain symptoms, greater sensitivity to painful stimuli and an impairment in pain processing in both healthy and clinical populations (Edwards et al., 2009; Edwards, Almeida, Klick, Haythornthwaite, & Smith, 2008; O'Brien et al., 2011; Smith, Edwards, McCann, & Haythornthwaite, 2007; Tang, Goodchild, Sanborn, Howard, & Salkovskis, 2012).

In this study, we are looking at day-to-day changes in subjective sleep, pain and mood report over the course of a week in healthy individuals and associations of these with pain response, psychological, cognitive and physical functioning. We use a week of week of sleep diary data to provide details about sleep quality and an evening diary of self-reported pain, mood and functioning. We will then examine the daily variability in these reports and how they relate to the sensory tests, cognitive tasks and physical functioning tasks you performed. We will also look at if there are any differences between poor and good sleepers.

References

Edwards, R. R., Almeida, D. M., Klick, B., Haythornthwaite, J. A., & Smith, M. T. (2008). Duration of sleep contributes to next-day pain report in the general population. *Pain*, *137*(1), 202 – 207.

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O'Brien, E. M., Waxenberg, L. B., Atchison, J. W., Gremillion, H. A, Staud, R. M., McCrae, C. S., & Robinson, M. E. (2011). Intraindividual variability in daily sleep and pain ratings among chronic pain patients: bidirectional association and the role of negative mood. *The Clinical Journal of Pain*, *27*(5), 425–433.

Smith, M. T., Edwards, R. R., McCann, U. D., & Haythornthwaite, J. A. (2007). The effects of sleep deprivation on pain inhibition and spontaneous pain in women. *Sleep*, *30*(4), 494–505.

Tang, N. K. Y., Goodchild, C. E., Sanborn, A. N., Howard, J., & Salkovskis, P. M. (2012). Deciphering the temporal link between pain and sleep in a heterogeneous chronic pain patient sample: a multilevel daily process study. *Sleep*, *35*(5), 675–687.

4: CPM Experiment 2 – Informed Consent Form

Participant ID:

CONSENT FORM

Project Title: Sleep, physical activity and pain inhibition in a healthy population

Researchers: Fatanah Ramlee & Esther Afolalu

	Please Initial
1) I confirm that I have read and understood the participant information sheet dated 5/12/15 (version 1) for the above project, which I may keep for my records and have had the opportunity to consider the information, ask questions and all questions have been answered satisfactorily.	
2) I agree to take part in the project and am willing to: *Complete study questionnaires, sleep and activity diaries, and take part in a CPM experiment.*	
3) I understand that my information will be held and processed for the following purposes: *Research findings may be published in journals, presented at conferences and shared anonymously with other researchers.* I understand that I will not be identified personally in any presentation of publication and only the research team will have access to my personal information.	
4) I understand that my data will be kept strictly confidential. However, in any situation that might put me or anyone else at risk of harm, the researcher may have to inform the appropriate authorities.	
5) I understand that my participation is totally voluntary and that I am free to withdraw at any time without giving any reason without being disadvantaged in any way.	

Name of Participant	Signature	Date
_____	_____	_____
Name of Researcher taking consent	Signature	Date
_____	_____	_____

5: CPM Experiment 2 – Participant Information Sheet

Experiment 1 & 23: Participant Information Sheet

Project Title: Sleep, physical activity and pain inhibition in a healthy population

We would like to invite you to take part in this study for a research project looking at the association between sleep, physical activity and pain inhibition. Joining the study is entirely voluntary and we would like you to understand why the research is being done and what it would involve. If you decide to take part, you are still free to withdraw at any time and without giving a reason.

Please note: To take part in this study, you must be fairly healthy with no known major medical or psychiatric or neurological conditions. This is because of the type of sensory testing that will be carried out to assess your pain sensitivity and pain threshold, if you have any concerns regarding this, please let us know.

Please log-on to SONA to book your timeslots. You need to book two timeslots - Part 1 and Part 2 for exactly a week apart! The password/invitation code for the study is *lionpanda*.

You are allocated 1 hour to complete this research experience. You will be required to book two 20 minutes sessions a week apart to complete the tasks and can use rest of the time during the week in your own time to complete the short daily sleep & activity diaries.

The testing sessions will be carried out in the Sleep & Pain Lab (H0.102). When you come for your first session, we will describe and go through the study with you. If you agree to take part, you will sign the consent form. You will then complete some questionnaires, sensory testing will be carried out, followed by a post-task questionnaire. After this, you will be told how to complete sleep & activity diaries for the week. Exactly a week later, you come back to the lab for the re-test session, again, you will complete some questionnaires, and sensory testing will be carried out, followed by a post-task questionnaire.

An explanation of some of the procedures in the study

Questionnaires & Diaries

Questionnaires will be computer-based and diaries will be paper-based.

Quantitative sensory testing

This will consist of sensory testing to assess your pain sensitivity and pain threshold. Specifically, we will use an instrument called an algometer to assess your Pressure Pain Threshold, this is the minimum force applied to a chosen site of your body (right forearm) till you feel the pain of the pressure sensation. While you are doing this, you will also be carrying out other tests. One of this is a physical task - holding a 5-6kgs weighted bag using your other arm. The other is a Cold Pressor task where you will be asked to keep your left hand in a container of water maintained at 4 degrees Celsius until a pain sensation is first reported.

The sensory testing and physical functioning may cause some discomfort, however, these tasks have been routinely used in research and clinical settings for pain assessment. It is important to know that you can stop the procedure at any time if it gets to an unpleasant level of discomfort. We are aiming to detect your pain threshold (the point at which pain begins to be felt), NOT your pain tolerance (how much pain you are able to handle or tolerate). Any pain sensation will only be temporary so it is very important to realise that you can stop the tests as soon as you feel any discomfort or pain.

For more information please contact F.Ramlee@warwick.ac.uk (Fatanah) or E.F.Afolalu@warwick.ac.uk (Esther).

CPM_PIS_v1 5/12/15

6: CPM Experiment 2 – Debrief

Experiment 1 & 23: DEBRIEFING SHEET

Project Title: Sleep, physical activity and pain inhibition in a healthy population

Poor sleep has been associated with numerous negative health outcomes and decrease quality of life. Previous studies have shown that poor sleep quality may aggravate pain, increase pain sensitivity through interfering with endogenous pain-inhibitory mechanism (e.g. conditioned pain modulation) and increasing disability and physical limitation. Although there is a general association between sleep, pain and physical activity, those associations are more complex than it seems. Different studies have used different methods to elicit conditioned pain modulation (CPM) response in healthy and clinical participants. The procedure used to elicit CPM response requires standardization and identification of factors that could affect CPM response. It is also possible that cognitive distraction could potentially influence the validity and reliability of CPM response. Hence the proposed study aims to further investigate association between sleep, engagement in physical activity, and CPM response. The study also examines the test-retest stability and reliability of two different conditioning stimuli used to elicit CPM and examine the effect of distraction stimuli on CPM response. Finally, the study examines factors (sleep quality, sleep disruption, chronotype and pain catastrophizing) that may influence variations in CPM response.

If you have any concern about your participation, please feel free to contact us via email F.Ramlee@warwick.ac.uk / E.F.Afolalu@warwick.ac.uk. Alternatively, you could contact our supervisor, Dr. Nicole K. Y. Tang n.tang@warwick.ac.uk. Thank you for your participation in the study.

References

Hermans, L., Van Oosterwijck, J., Goubert, D., Goudman, L., Crombez, G., Calders, P., & Meeus, M. (2015). Inventory of Personal Factors Influencing Conditioned Pain Modulation in Healthy People: A Systematic Literature Review. *Pain Practice*.

Moont, R., Pud, D., Sprecher, E., Sharvit, G., & Yarnitsky, D. (2010). 'Pain inhibits pain'mechanisms: Is pain modulation simply due to distraction?. *Pain*, *150*(1), 113-120.

Smith, M., Edwards, R., & McCann, U. (2007). The effects of sleep de-privation on pain inhibition and spontaneous pain in women. *Sleep*, *30*(4), 494-505.

7: CPM Experiment 1 and 2 – Screening Form

Project Title: Sleep, physical activity and pain inhibition in a healthy population

PARTICIPANT SCREENING FORM

Name:

Participant ID:

Please tick (☑) any of the following information that is applicable to your current situation:

	Aged between **18 and 65**
	English speaking
	Shift worker with irregular sleep pattern
	Sleeping problems or **sleep disorders** (e.g., insomnia, sleep apnoea, restless leg syndrome/periodic limb movement syndrome, narcolepsy)
	Acute pain as a result of injury, surgery etc.
	Presence of any malignant or non-malignant **pain condition** present for at least 6 months or more (arthritis, chronic back pain, fibromyalgia etc.)
	Presence of any debilitating or life threatening **medical condition** (e.g. cancer, HIV, dementia etc.)
	Diagnosis of learning disability, history of **psychiatric illness** or recurrent history of a psychotic disorder
	Pregnant or breastfeeding
	Receiving psychological **therapy/treatments** for pain/insomnia or enrolled in drug trials
	History of cardiovascular disorder/**heart disease**
	History of **fainting or seizure**
	History of **frostbite**
	History of **Reynaud's** phenomenon (hands gets white then blue on exposure to cold, then red on warming.
	Open cut/sore/fracture on arm/hand

8: CPM Experiment 1 and 2 – Questionnaire Pack

Sleep Diary (On waking)

Please complete the following item upon waking in the morning (within 30 minutes of your wake up time).

Today's date	Wed 20/1/16							
1. What time did you get into bed?	10:15pm							
2. What time did you try to go to sleep?	11:30pm							
3. How long did it take you to fall asleep?	55 min.							
4. How many times did you wake up, not counting your final awakening?	3 times							
5. In total, how long did these awakenings last?	1 hour 10 min.							
6. What time was your final awakening?	6:35am							
7. What time did you get out of bed for the day?	7:20am							
8. How would you rate the quality of your sleep? 0 (very poor) ---------- 10 (very good)	6							
9. Comments (if applicable)	I have a cold							

You may use the guidelines below to clarify what is being asked for each item of the Sleep Diary

1) *What time did you get into bed?* Write the time that you got into bed. This may not be the time that you began "trying" to fall asleep.
2) *What time did you try to go to sleep?* Record the time that you began "trying" to fall asleep.
3) *How long did it take you to fall asleep?* Beginning at the time you wrote in question 2, how long did it take you to fall asleep.
4) *How many times did you wake up, not counting your final awakening?* How many times did you wake up between the time you first fell asleep and your final awakening.
5) *In total, how long did these awakenings last?* What was the total time you were awake between the time you first feel asleep and your final awakening. For example, if you woke 3 times for 20 minutes, 35 minutes, and 15 minutes, add them all up (20+35+15=70 or 1hr and 10min).
6) *What time was your final awakening?* Record the last time you woke up in the morning.
7) *What time did you get out of the bed for the day?* What time did you get out of the bed with no further attempt at sleeping? This may be different from your final awakening time (e.g. you may have woken up 6:35 am but did not get out of bed to start your day until 7:20 a.m.)
8) *How would you rate the quality of your sleep?* "Sleep quality" is your sense whether your sleep was poor or good on a scale of 0 to 10: 0 is very poor and 10 is very good.
9) *Comments* If you have anything that you would like to say that is relevant to your sleep feel free to write it here

Project Title: **Sleep, physical activity and pain inhibition in a healthy population**

Please try your best to complete all sections. There are no rights or wrong answers. Do not spend too much time on each item or statement.

Demographic

1. Age :
2. Date of birth :
3. Gender : ( ) Male ( ) Female ( ) Choose not to disclose
4. Weight : _____ kg *or* _____ pounds *or* _____ stone
5. Height : _____ cm *or* _____ feet _____ inches
6. Ethnic origins :
   ( ) White
   ( ) White Irish
   ( ) Asian or Asian British: Chinese
   ( ) Asian or Asian British: Indian
   ( ) Asian or Asian British: Pakistani
   ( ) Asian or Asian British: Asian other
   ( ) Black or Black British
   ( ) British Mixed
   ( ) Other: _____
   ( ) Choose not to disclose
7. Do you smoke? :
   ( ) Yes; _____ cigarettes per day
   ( ) Quit; When did you stop smoking? _____
   ( ) No
   ( ) Choose not to disclose
8. Do you drink? :
   ( ) Yes; typical alcohol consumption in a week:
   _____ units (pint of regular beer/lager/cider)
   _____ units (glass of wine)
   _____ units (single measure of spirits)
   ( ) No
   ( ) Choose not to disclose
9. Do you have chronic pain? :
   ( ) Yes
   ( ) No
10. Any other illnesses? : (Please state)

PSQI

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...	**Not during the past month**	**Less than once a week**	**Once or twice a week**	**Three or more times a week**
a. Cannot get to sleep within 30 minutes.				
b. Wake up in the middle of the night or early morning.				
c. Have to get up to use the bathroom				
d. Cannot breathe comfortably				
e. Cough or snore badly				
f. Feel too cold				
g. Feel too hot				
h. Had bad dreams				
i. Have pain				
j. Other reason(s), please describe:				
	Very good	**Fairly good**	**Fairly bad**	**Very bad**
6. During the past month, how would you rate your sleep quality overall?				

	Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
7. During the past month, how often have you taken medicine (prescribed or "over the counter") to help you sleep?				
8. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?				
	No problem at all	**Only a very slight problem**	**Somewhat of a problem**	**A very big problem**
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 bed partner or roommate	**Partner / roommate in other room**	**Partner in same room, but not same bed**	**Partner in same bed**
10. Do you have a bed partner or roommate?				
If you have a room mate or bed partner, ask him/her how often in the past month you have had:	**Not during the past month**	**Less than once a week**	**Once or twice a week**	**Three or more times a week**
a. Loud snoring				
b. Long pauses between breaths while asleep				
c. Legs twitching or jerking while you sleep				
d. Episodes of disorientation or confusion during sleep				
e. Other restlessness while you sleep; please describe:				

MEQ

Please select the answer that best describes you by circling the point value that best indicates how you have felt in recent weeks (i.e. in the past month).

1. *Approximately* what time would you get up if you were entirely free to plan for your day?
   [5] 5.00am – 6.30am (0500-0600h)
   [4] 6.30am – 7.45am (0630-0745h)
   [3] 7.45am – 9.45am (0745-0945h)
   [2] 9.45am – 11.00am (0945-1100)
   [1] 11.00am – 12 noon (1100-1200h)

2. *Approximately* what time would you go to bed if you were entirely free to plan your evening?
   [5] 8.00pm – 9.00pm (2000-2100h)
   [4] 9.00pm – 10.15pm (2100-2215h)
   [3] 10.15pm – 12.30am (2215-0030h)
   [2] 12.30am – 1.45am (0030-0145h)
   [1] 1.45am – 3.00am (0145-0300h)

3. If you usually have to get up at a specific time in the morning, how much do you depend on an alarm clock?
   [4] Not at all
   [3] Slightly
   [2] Somewhat
   [1] Very much

4. How easy do you find it to get up in the morning (when you are not awakened unexpectedly)?
   [1] Very difficult
   [2] Somewhat difficult
   [3] Fairly easy
   [4] Very easy

5. How alert do you feel during the first half hour after you wake up in the morning?
   [1] Not at all alert
   [2] Slightly alert
   [3] Fairly alert
   [4] Very alert

6. How hungry do you feel during the first half hour after you wake up?
   [1] Not at all hungry
   [2] Slightly hungry
   [3] Fairly hungry
   [4] Very hungry

7. During the first half hour after you wake up in the morning, how do you feel?
   [1] Very tired
   [2] Fairly tired
   [3] Fairly refreshed
   [4] Very refreshed

8. If you had no commitments the next day, what time would you go to bed compared to your usual bedtime?
   [4] Seldom or never later
   [3] Less that 1 hour later
   [2] 1-2 hours later
   [1] More than 2 hours later

9. You have decided to do physical exercise. A friend suggests that you do this for one hour or twice a week, and the best time for him is between 7-8am (0700-0800h). Bearing in mind nothing but your own internal "clock", how do you think you would perform?
   [4] Would be in a good form
   [3] Would be in a reasonable form
   [2] Would find it difficult
   [1] Would find it very difficult

10. At *approximately* what time in the evening do you feel tired, and, as a result, in need of sleep?
    [5] 8.00pm – 9.00pm (2000-2100h)
    [4] 9.00pm – 10.15pm (2100-2215h)
    [3] 10.15pm – 12.45am (2215-0045h)
    [2] 12.45am – 2.00am (0045-0200h)
    [1] 2.00am – 3.00am (0200-0300h)

11. You want to be at your peak performance for a test that you know is going to be mentally exhausting and will last two hours. You are entirely free to plan your day. Considering only your "internal clock", which one of the four testing times would you choose?
    [6] 8.00am – 10.00am (0800-1000h)
    [4] 11.00am – 1.00pm (1100-1300h)
    [2] 3.00pm – 5.00pm (1500-1700h)
    [0] 7.00pm – 9.00pm (1900-2100h)

12. If you got into bed at 11pm (2300h), how tired would you be?
    [0] Not at all tired
    [2] A little tired
    [3] Fairly tired
    [5] Very tired

13 For some reason you have gone to bed several hours later than usual, but there is no need to get up at any particular time the next morning. Which one of the following are you most likely to do?
[4] Will wake up at usual time, but will not fall back asleep
[3] Will wake up at usual time and will doze off thereafter
[2] Will wake up at usual time, but will fall asleep again
[1] Will not wake up until later than usual

14 One night you have to remain awake between 4-6am (0400-0600h) in order to carry out a night watch. You have no time commitments the next day. Which one of the alternatives would suit you best?
[1] Would not go to bed until the watch is over
[2] Would take a nap before and sleep after
[3] Would take a good sleep before and nap after
[4] Would sleep only before the watch

15. You have two hours of hard physical work. You are entirely free to plan your day. Considering only your internal "clock", which of the following times would you choose?
[4] 8.00am – 10.00am (0800-1000h)
[3] 11.00am – 1.00pm (1100-1300h)
[2] 3.00pm – 5.00pm (1500-1700h)
[1] 7.00pm – 9.00pm (1900-2100h)

16. You have decided to do physical exercise. A friend suggests that you do this for one hour twice a week. The best time for her is between 10-11pm (2200-2300h). Bearing in mind only your internal "clock", how well do you think you would perform?
[1] Would be in good form
[2] Would be in reasonable form
[3] Would find it difficult
[4] Would find it very difficult

17. Suppose you can choose your own work hours. Assume that you work a five-hour day (including breaks), your job is interesting, and you are paid based on your performance. At approximately what time would you choose to begin?
[5] 5 hours starting between 4.00-8.00am (0500-0800h)
[4] 5 hours starting between 8.00-9.00am (0800-0900h)
[3] 5 hours starting between 9.00am-2.00pm (0900-1400h)
[2] 5 hours starting between 2.00-5.00pm (1400-1700h)
[1] 5 hours starting between 5.00pm-4.00am (1700-0400h)

18. At approximately what time of day do you usually feel your best?
[5] 5.00-8.00am (0500-0800h)
[4] 8.00-10.00am (0800-1000h)
[3] 10.00am-5.00pm (1000-1700h)
[2] 5.00-10.00pm (1700-2200)
[1] 10.00pm-5.00am (2200-0500h)

19. One hears about "morning types" and "evening types". Which one of these types do you consider yourself to be?
[6] Definitely a morning type
[4] Rather more a morning type than an evening type
[2] Rather more an evening type than a morning type
[1] Definitely an evening type

PCS

Instructions: Everyone experiences painful situations at some point in their lives. Such experiences may include headaches, tooth pain, joint or muscle pain. People are often exposed to situations that may cause pain such as illness, injury, dental procedures or surgery. We are interested in the types of thoughts and feelings that you have when you are in pain. Listed below are thirteen statements describing different thoughts and feelings that may be associated with pain. Using the following scale, please indicate the degree to which you have these thoughts and feelings when you are experiencing pain.

When I'm in pain....

	Not at all	To a slight degree	To a moderate degree	To a great degree	All the time
1. I worry all the time about whether the pain will end	0	1	2	3	4
2. I feel I can't go on	0	1	2	3	4
3. It's terrible and I think it's never going to get any better	0	1	2	3	4
4. It's awful and I feel it overwhelms me	0	1	2	3	4
5. I feel I can't stand it anymore	0	1	2	3	4
6. I become afraid that the pain will get worse	0	1	2	3	4
7. I keep thinking of other painful events	0	1	2	3	4
8. I anxiously want the pain to go away	0	1	2	3	4
9. I can't seem to keep it out of my mind	0	1	2	3	4
10. I keep thinking about how much it hurts	0	1	2	3	4
11. I keep thinking about how badly I want the pain to stop	0	1	2	3	4
12. There's nothing I can do to reduce the intensity of the pain	0	1	2	3	4
13. I wonder whether something serious may happen	0	1	2	3	4

BPI

Please use the scale below to answer the following questions:

No pain at all — Pain as bad as you can imagine

0 1 2 3 4 5 6 7 8 9 10

1. Please rate your pain by telling me the one number that best describes your pain **at its worst in the past week**	0 1 2 3 4 5 6 7 8 9 10
2. Please rate your pain by telling me the one number that best describes your pain **at its least in the past week**	0 1 2 3 4 5 6 7 8 9 10
3. Please rate your pain by telling me the one number that best describes your pain **on the average**	0 1 2 3 4 5 6 7 8 9 10
4. Please rate your pain by telling me the one number that tells how much pain you have **right now**	0 1 2 3 4 5 6 7 8 9 10

SSS

Using the 7-point scale below pick what best represents how you are feeling right now and note the corresponding number on the chart below.

Degree of Sleepiness	Rating scale
Feeling active, vital, alert, or wide awake	1
Functioning at high levels, but not at peak; able to concentrate	2
Awake, but relaxed; responsive but not fully alert	3
Somewhat foggy, let down	4
Foggy; losing interest in remaining awake; slowed down	5
Sleepy, woozy, fighting sleep; prefer to lie down	6
No longer fighting sleep, sleep onset soon; having dream-like thoughts	7
Asleep	x

POMS2 - Adult Short

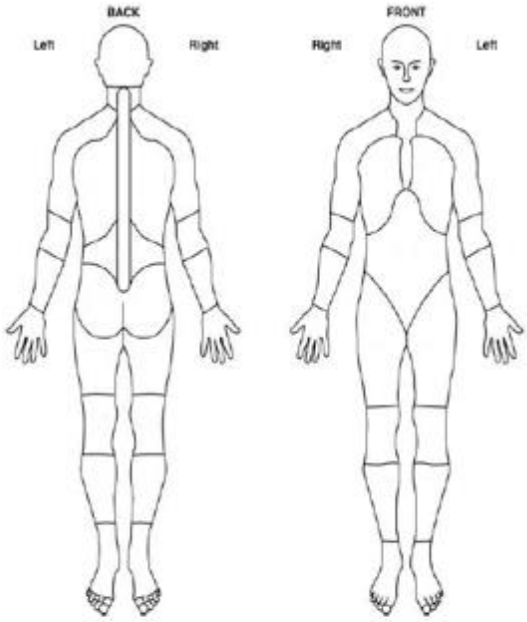
Instructions: Below is a list of words that describe feelings that people have. Please read each word carefully, then circle the number that best describes *how you are feeling right now.*

	Not at all	A little	Moderately	Quite a bit	Extremely
Friendly	0	1	2	3	4
Tense	0	1	2	3	4
Angry	0	1	2	3	4
Worn out	0	1	2	3	4
Lively	0	1	2	3	4
Confused	0	1	2	3	4
Considerate	0	1	2	3	4
Sad	0	1	2	3	4
Active	0	1	2	3	4
Grouchy	0	1	2	3	4
Energetic	0	1	2	3	4
Panicky	0	1	2	3	4
Hopeless	0	1	2	3	4
Uneasy	0	1	2	3	4
Unable to concentrate	0	1	2	3	4
Fatigued	0	1	2	3	4

	Not at all	A little	Moderately	Quite a bit	Extremely
Helpful	0	1	2	3	4
Nervous	0	1	2	3	4
Miserable	0	1	2	3	4
Muddled	0	1	2	3	4
Bitter	0	1	2	3	4
Exhausted	0	1	2	3	4
Anxious	0	1	2	3	4
Good-natured	0	1	2	3	4
Helpless	0	1	2	3	4
Weary	0	1	2	3	4
Bewildered	0	1	2	3	4
Furious	0	1	2	3	4
Trusting	0	1	2	3	4
Bad-tempered	0	1	2	3	4
Worthless	0	1	2	3	4
Vigorous	0	1	2	3	4
Uncertain about things	0	1	2	3	4
Drained	0	1	2	3	4
Enthusiastic	0	1	2	3	4

BM

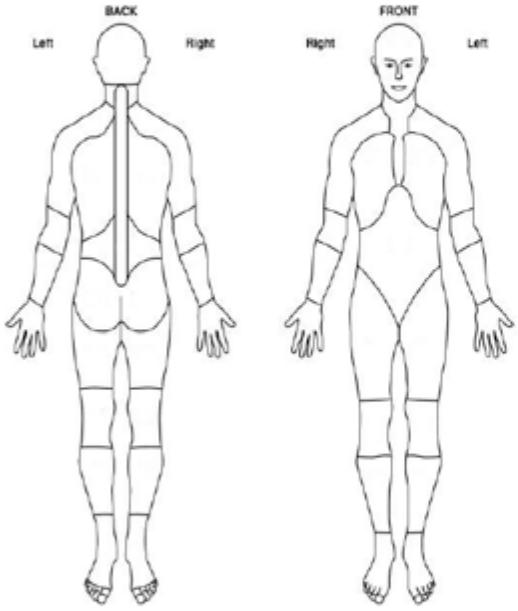
Please shade in the areas on the diagram any pain that has lasted for 1 day or longer in the past week.



Participant ID: **Part 1 / 2** **CSV** ☐

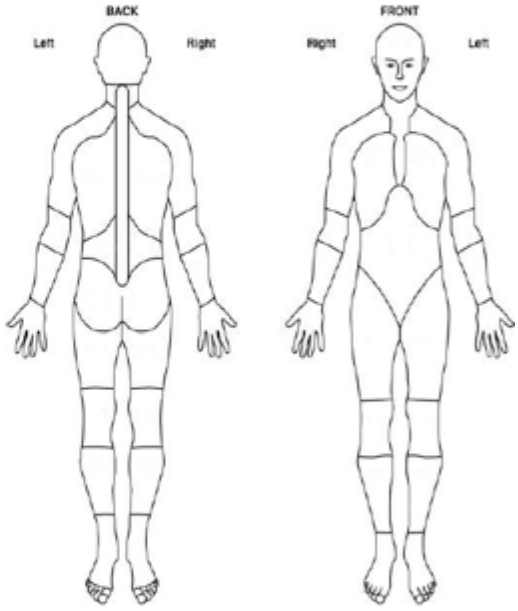
CPT – Pain Rating

No pain at all — 0 1 2 3 4 5 6 7 8 9 10 — Pain as bad as you can imagine



BHT – Pain Rating

No pain at all — 0 1 2 3 4 5 6 7 8 9 10 — Pain as bad as you can imagine



Participant ID: **Part 1 / 2** **CSV** ☐

CPT – MC

Please answer the following questions on a numerical scale rating from 0 to 10 (0 = not at all; 10 = very much).

How difficult you find the task?

0 1 2 3 4 5 6 7 8 9 10

How much attention did you pay to the task?

0 1 2 3 4 5 6 7 8 9 10

How much effort did you put into the task?

0 1 2 3 4 5 6 7 8 9 10

How much did this task distract you from the pressure pain?

BHT – MC

Please answer the following questions on a numerical scale rating from 0 to 10 (0 = not at all; 10 = very much).

How difficult you find the task?

0 1 2 3 4 5 6 7 8 9 10

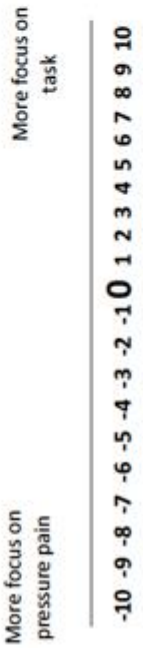
How much attention did you pay to the task?

0 1 2 3 4 5 6 7 8 9 10

How much effort did you put into the task?

0 1 2 3 4 5 6 7 8 9 10

How much did this task distract you from the pressure pain?



9: Sleep and Chronic Pain – Ethical Approvals and Authorisations

20th August 2014

Warwick
Medical School

PRIVATE
Esther Afolalu
Department of Psychology
University of Warwick
CV4 7AL

Dear Esther,

Study Title and BSREC Reference: *Sleep Disturbance and the Experience of Chronic Pain*
REGO-2014-944

Thank you for submitting your revisions to the above-named project to the University of Warwick's Biomedical and Scientific Research Ethics Sub-Committee for approval.

I am pleased to confirm that approval is granted and your study may commence.

Please keep a copy of the signed version of this letter with your study documentation.

Yours sincerely

P.P. Graham Hewitt

David Davies
Chair
Biomedical and Scientific
Research Ethics Sub-Committee

Biomedical and Scientific
Research Ethics Sub-Committee
A010 Medical School Building
Warwick Medical School,
Coventry, CV4 7AL.
Tel: 02476-151875
Email: BSREC@Warwick.ac.uk

Medical School Building
The University of Warwick
Coventry CV4 7AL United Kingdom
Tel: +44 (0)24 7657 4880
Fax: +44 (0)24 7652 8375

THE UNIVERSITY OF
WARWICK

11th May 2015

Warwick
Medical School

PRIVATE
Esther Afolalu
PhD Student
Department of Psychology
University of Warwick
CV4 7AL

Dear Esther,

Study Title and BSREC Reference: *Sleep Disturbance and the Experience of Chronic Pain* REGO-2014-944 AM01

Thank you for submitting a substantial amendment application for the above-named project to the University of Warwick's Biomedical and Scientific Research Ethics Sub-Committee.

I am pleased to confirm that the changes that you wish to make to this study have been approved.

Please keep a copy of the signed version of this letter with your study documentation.

Yours sincerely

P.P. Graham Hewitt

Professor Scott Weich
Chair
Biomedical and Scientific
Research Ethics Sub-Committee

Biomedical and Scientific
Research Ethics Sub-Committee
A010 Medical School Building
Warwick Medical School,
Coventry, CV4 7AL.
Tel: 02476-528207
Email: BSREC@warwick.ac.uk

Medical School Building
The University of Warwick
Coventry CV4 7AL United Kingdom
Tel: +44 (0)24 7657 4880
Fax: +44 (0)24 7652 8375

THE UNIVERSITY OF
WARWICK

NHS
Health Research Authority

NRES Committee East Midlands - Leicester
The Old Chapel
Royal Standard Place
Nottingham
NG1 6FS

Telephone: 0115 8839436

30 September 2014

Miss Esther F. Afolalu
Department of Psychology
University of Warwick
Coventry
CV4 7AL

Dear Miss Afolalu

Study title:	**Sleep Disturbance and The Experience of Chronic Pain**
REC reference:	**14/EM/1138**
IRAS project ID:	**160599**

Thank you for your letter of 29 September 2014, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to make a request to postpone publication, please contact the REC Assistant, Joanne Unsworth, nrescommittee.eastmidlands-leicester@nhs.net.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database within 6 weeks of recruitment of the first participant (for medical device studies, within the timeline determined by the current registration and publication trees).

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non clinical trials this is not currently mandatory.

If a sponsor wishes to contest the need for registration they should contact Catherine Blewett (catherineblewett@nhs.net), the HRA does not, however, expect exceptions to be made. Guidance on where to register is provided within IRAS.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Copies of advertisement materials for research participants [Recruitment Poster - Healthy Volunteers]	v.1	30 July 2014
Copies of advertisement materials for research participants [Recruitment Poster - Chronic Pain Patients]		30 July 2014
Covering letter on headed paper [Cover Letter]		06 August 2014
Evidence of Sponsor insurance or indemnity (non NHS Sponsors		24 September 2014

only) [Evidence of University of Warwick Insurance]		
GP/consultant information sheets or letters [GP Diagnosis Confirmation Letter]	v.1	19 August 2014
IRAS Checklist XML [Checklist_19082014]		19 August 2014
IRAS Checklist XML [Checklist_29092014]		29 September 2014
Letters of invitation to participant [Invitation Email to Database Members]	1	30 July 2014
Non-validated questionnaire [Screening Questionnaire]		27 June 2014
Non-validated questionnaire [Post-Task Questionnaire]		27 June 2014
Non-validated questionnaire [Demographics & Pain History Questionnaire]		27 June 2014
Non-validated questionnaire [Pain Diary]		27 June 2014
Other [REC form Bibliography]	v.1	27 June 2014
Other [Email advice from statistician]		30 June 2014
Other [Amendments-Resubmission Cover Letter]		
Participant consent form [Consent Form GP-Chronic Pain Patients]	v1	24 September 2014
Participant consent form [Consent Form Healthy Volunteers]	1.1	30 July 2014
Participant consent form [Consent Form Chronic Pain Patients]	v1.2	24 September 2014
Participant information sheet (PIS) [Participant Information Sheet]	v2	24 September 2014
REC Application Form [REC_Form_14082014]		14 August 2014
Research protocol or project proposal [Sleep and Chronic Pain Protocol]	v3	24 September 2014
Summary CV for Chief Investigator (CI) [Chief Investigator/Student CV]	v.1	01 July 2014
Summary CV for supervisor (student research) [Dr Nicole Tang CV]		23 June 2014
Summary, synopsis or diagram (flowchart) of protocol in non technical language [Study Schedule]	v.2	26 June 2014
Validated questionnaire [Pre-Sleep Arousal Scale]		
Validated questionnaire [Anxiety & Preoccupation about Sleep Questionnaire]		
Validated questionnaire [Brief Pain Inventory & McGill Pain Questionnaire]		
Validated questionnaire [Penn State Worry Questionnaire]		
Validated questionnaire [Medication Quantification Scale]		
Validated questionnaire [Pain Catastrophizing Scale]		
Validated questionnaire [Stanford Sleepiness Scale]		
Validated questionnaire [Beck Depression Inventory]		
Validated questionnaire [Pittsburgh Sleep Quality Index]		
Validated questionnaire [Profile of Mood States - Short Form]		
Validated questionnaire [Consensus Sleep Diary]		
Validated questionnaire [Pain Vigilance & Awareness Questionnaire]		
Validated questionnaire [Dysfunctional Belief About Sleep]		
Validated questionnaire [State Trait Anxiety Inventory]		

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research

Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website:
http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

HRA Training

We are pleased to welcome researchers and R&D staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

14/EM/1138	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project.

Yours sincerely

pp.

Professor Geoff Dickens
Chair

Email:nrescommittee.eastmidlands-leicester@nhs.net

Copy to: *Mrs Jane Prewett*

NHS
Health Research Authority

NRES Committee East Midlands - Leicester
The Old Chapel
Royal Standard Place
Nottingham
NG1 6FS
Tel: 01158839390

26 August 2015

Miss Esther F Afolalu
PhD Researcher
University of Warwick
Department of Psychology
University of Warwick
Coventry
CV4 7AL

Dear Miss Afolalu

Study title: **Sleep Disturbance and The Experience of Chronic Pain**
REC reference: **14/EM/1138**
Amendment number: **Substantial amendment 31.07.15**
Amendment date: **31 July 2015**
IRAS project ID: **160599**

The above amendment was reviewed on 21 August 2015 by the Sub-Committee in correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Notice of Substantial Amendment (non-CTIMP)		31 July 2015
Other [Summary of amendment]		28 July 2015
Other [Participant screening form - tracked changes]	2	11 May 2015
Participant information sheet (PIS) [PIS - tracked changes]	2.1	28 April 2015
Research protocol or project proposal [Protocol - tracked changes]	2.1	28 April 2015

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

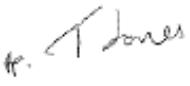
Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

14/EM/1138:	**Please quote this number on all correspondence**

Yours sincerely



Mr Ken Willis
Chair

E-mail: nrescommittee.eastmidlands-leicester@nhs.net

Enclosures: *List of names and professions of members who took part in the review*

Copy to:
Mrs Jane Prewett

NRES Committee East Midlands - Leicester

Attendance at Sub-Committee of the REC meeting on 21 August 2015

Committee Members:

Name	*Profession*	*Present*	*Notes*
Mr John Baker		Yes	
Mr Murthy Nyasavajjala	Specialist Registrar - General Surgery	Yes	
Mr Ken Willis	Medical Devices Manager - Retired	Yes	

Also in attendance:

Name	*Position (or reason for attending)*
Mr Tad Jones	REC Assistant

University Hospitals Coventry and Warwickshire NHS Trust

Research, Development & Innovation Department
University Hospitals Coventry & Warwickshire NHS Trust
1st Floor Rotunda, (Opposite Cardiology)
University Hospital
Clifford Bridge Road
Coventry
CV2 2DX

Commercial enquiries: 02476 964995
Governance/Non-commercial enquiries: 02476 966195
Innovation & Communication enquiries: 02476 964748
Research Funding & Grant enquiries: 02476 964958
Email: RD&I@uhcw.nhs.uk

20/08/2015

Miss Esther Afolalu
Flat E, 30
Heath Terrace,
Leamington Spa
CV32 5NA

Dear Esther,

Study Title: Sleep Disturbance and the Experience of Chronic Pain
R&D no: EA148014

Thank you for submitting the above study for consideration by the Research Development and Innovation Office. I am pleased to inform you that your study has been approved.

Approved Documents:
The documents approved for use in this study are listed at the end of this letter

Conditions of Approval:

- Should you wish to make any changes to the documents listed above, you must obtain R,D&I approval prior to use.
- Notification of any serious breaches of GCP or the trial protocol must be reported to the RD&I Department and a DATIX Clinical Adverse Event form completed within 24 hours of any suspected breach being identified and confirmed.

Sponsorship & Indemnity:
Your research sponsorship & Indemnity is provided by the University of Warwick

Standard Operating Procedures
Current versions of all RD&I SOPs are available to view on the Trust intranet as follows:
http://webapps/intranet/departments/research_and_development/SOP's.asp

Your project may be subject to ad hoc audit by our department to ensure these standards are being met.

University Hospitals Coventry and Warwickshire NHS Trust

May I take this opportunity to remind you that, as a researcher, you must ensure that your research is conducted in a way that protects the dignity, rights, safety and well-being of participants. Trust RD&I Approval assumes that you have read and understand the Research Governance Framework and accept that your responsibilities as a researcher are to comply with it, the Data Protection and Health & Safety Acts.

The Trust wishes you every success with your project.

Yours sincerely

NEmbury

Natassia Embury
RD&I Business Manager

Documents Approved for this study:

Document	Version	Date
Copies of advertisement materials for research participants [Recruitment Poster - Healthy Volunteers]	1	30/07/2014
Copies of advertisement materials for research participants [Recruitment Poster - Chronic Pain Patients]		30/07/2014
GP/consultant information sheets or letters [GP Diagnosis Confirmation Letter]	1	19/08/2014
Letters of invitation to participant [Invitation Email to Database Members]	1	30/07/2014
Non-validated questionnaire [Screening Questionnaire]		27/062014
Non-validated questionnaire [Post-Task Questionnaire]		27/062014
Non-validated questionnaire [Demographics & Pain History Questionnaire]		27/062014
Non-validated questionnaire [Pain Diary]		27/06/2014
Participant consent form [Consent Form GP-Chronic Pain Patients]	1	24/09/2014
Participant consent form [Consent Form Healthy Volunteers]	1.1	30/07/2014
Participant consent form [Consent Form Chronic Pain Patients]	1.2	24/09/2014
Participant information sheet (PIS) [Participant Information Sheet]	v2	24/09/2014
Research protocol or project proposal [Sleep and Chronic Pain Protocol]	v3	24/09/2014
Validated questionnaire [Pre-Sleep Arousal Scale]		
Validated questionnaire [Anxiety & Preoccupation about Sleep Questionnaire]		
Validated questionnaire [Brief Pain Inventory & McGill Pain Questionnaire]		
Validated questionnaire [Penn State Worry Questionnaire]		
Validated questionnaire [Medication Quantification Scale]		
Validated questionnaire [Pain Catastrophizing Scale]		
Validated questionnaire [Stanford Sleepiness Scale]		
Validated questionnaire [Beck Depression Inventory]		
Validated questionnaire [Pittsburgh Sleep Quality Index]		
Validated questionnaire [Profile of Mood States - Short Form]		
Validated questionnaire [Consensus Sleep Diary]		
Validated questionnaire [Pain Vigilance & Awareness Questionnaire]		
Validated questionnaire [Dysfunctional Belief About Sleep]		
Validated questionnaire [State Trait Anxiety Inventory]		

University Hospitals Coventry and Warwickshire NHS Trust

Research, Development & Innovation Department
University Hospitals Coventry & Warwickshire NHS Trust
1st Floor Rotunda, (Opposite Cardiology)
University Hospital
Clifford Bridge Road
Coventry
CV2 2DX

Commercial enquiries: 02476 964995
Governance/Non-commercial enquiries: 02476 966195
Innovation & Communication enquiries: 02476 964748
Research Funding & Grant enquires: 02476 964958
Email: RD&I@uhcw.nhs.uk

24 September 2015

Miss Esther Afolalu
PhD Researcher
University of Warwick
Department of Psychology
Coventry,
CV4 7AL

Dear Esther,

Short Title: Sleep disturbance and the experience of chronic pain
R&D Reference: EA148041
Amendment No: 1
Amendment date: 31st July 2015

Following review of substantial amendment 1 for the above study, University Hospitals Coventry & Warwickshire NHS Trust confirms that there is no objection to this amendment and it may be immediately implemented at this site under the existing NHS permission.

Documents approved are:

Document	Version	Date
Other [Participant screening form - tracked changes]	2	11 May 2015
Participant information sheet (PIS) [PIS - tracked changes]	2	28 April 2015
Research protocol or project proposal [Protocol - tracked changes	2	28 April 2015

You are reminded that the agreed protocol must be followed at all times and any further amendments must be submitted to the RD&I Department.

Thank you for keeping R,D&I informed.

Yours sincerely

Sonia Kandola
Research Governance Specialist

Certificate of Attendance

This is to certify that

Esther Afolalu

has attended

An Introduction to Good Clinical Practice

Signature

QA Support Officer

Warwick Medical School
CLINICAL TRIALS UNIT

12 August 2015

Date

University of Warwick
Genetic Modification and Biosafety Committee

Record of Committee Assessment

Project Approval to Proceed

Project Reference	**Project 142**		
Project Title	Sleep Disturbance and The Experience of Chronic Pain		
Principal Investigator	Dr Nicole Tang / Esther F. Afolalu	☎	50556
Institution / Dept	Department of Psychology	**e-mail**	N.Tang@warwick.ac.uk
Project to investigate sleep disturbance due to chronic pain involving human volunteers and analysis of blood samples.			
Biological agents, vector & inserts, hosts, materials:			
No biological agents involved. Human volunteers. Blood samples for cytokine analysis.			
Risks to Human Health or other species:			
Risk to human health or other species is low to effectively zero.			
Environmental risks:			
Risk to environment is effectively zero.			
Control measures: security, containment facilities and practices, emergency protocols, including waste management, transport			
Facilities are apropriate for the procedures described. Appropriate disinfection procedures are in place. MTA and Authority to Export Human Samples forms to be used for transport of blood samples to University College Coventry. Waste management procedures are appropriate (clinical and sharps waste). Candidates with known risk of BBV (Hep B, Hep C and HIV/AIDS will not be recruited.			
Other considerations: notification, licence, training and competence			
HTA approved, work involves materials of human origin. No other notifications necessary. Staff are trained and competent in venepuncture and have undergone HTA training. Venepuncture training log and HTA training certificate on file. No work with GM, animal or plant pathogens.			
Committee decision: activity class, containment level			
The project is assessed as Activity Class 1 and assigned a University low hazard level. The project as described is Approved to Proceed.			
Signature	**Ron Croy BSA on behalf of the Chair of GMBSC**	**Date**	**28th November 2014**

Appendix 2

THE UNIVERSITY OF WARWICK

Authority to Export Human Samples

To be completed by the Lead Investigator or Person Responsible undertaking the export or transfer of human samples from the University and submitted to the Designated Individual

Name: Esther Afolalu	Title: PhD Researcher
Contact details: E-mail: e.f.afolalu@warwick.ac.uk Telephone: 024 765 23158	Department: Psychology
Research Project Title: Sleep Disturbance and The Experience of Chronic Pain	
Ethical Approval Number: BSREC REGO-2014-944 / AM BSC Project 142 / MTA Ref 46969	
Destination organisation	University Hospitals Coventry & Warwickshire NHS Trust
Address/country of destination organisation	University Hospital 'UHCW' Clifford Bridge Road Coventry, CV2 2DX
Type of sample (e.g. urine)	Blood Samples
Quantity of samples (e.g. 100 x 2ml tubes)	2 x 5mls tubes per participant.
Under what conditions will the samples be transported? (e.g. refrigerated container)	Transported in a sealed box.
Proposed date of export?	Ongoing April 2015 – January 2018
Fate of samples following project completion: Return, transfer to another organisation, retain, dispose in accordance with the terms of the MTA	Dispose in accordance with the terms of the MTA

I confirm that the information above is accurate and complete and that the Sample Register will be updated following the transfer/export of the human samples.

Signature of Lead Investigator....[signature].................... Date...27/4/15

I authorise transfer/export of these human samples:

Signature of Designated Individual.......J. L. Davey.................... Date.28-4-2015

CERTIFICATE OF ATTENDANCE

This certificate is presented to

Esther Afolalu

For attending

Session 1 of the Warwick Human Tissue Information Series

"Research using human samples - Knowing your responsibilities"

Topics covered included:

- **Human Tissue Act 2004**
- **Relevant material & Scheduled purposes**
- **Consent & Ownership**
- **Ethical approval**
- **Storage of samples and access**

On: Wednesday 10th September 2014
At: Warwick Medical School, Gibbet Hill

Signed: J. Davey

Name: **Professor John Davey**
Designated Individual for HTA Licence

THE UNIVERSITY OF WARWICK

MRC Medical Research Council

This is to certify that

Esther Afolalu

completed the following e-learning with an assessment (England, Wales and Northern Ireland) score of

100%

Research and human tissue legislation

Overview of Human Tissue Act and Human Tissue (England, Wales and Northern Ireland) Act

When the Acts apply

What constitutes best practice

Top tips to support compliance

Where to find help

September 16, 2014

MRC Regulatory Support Centre

Working with Human Samples
Registration of individual researchers

University of Warwick

The University of Warwick maintains a register of all researchers working with human samples. Registration requires the researcher to undertake training appropriate to their research needs and to maintain a training programme that demonstrates they are competent to perform duties appropriate to their role in each research project. The responsibility for ongoing personal development rests with the individual researcher.

Declaration of Registration
I believe that I have received adequate information, instruction and training to be able to carry out my work with human tissue safely and in accordance with the Human Tissue Act (2004) and the University's Standard Operating Procedures. I will at all times follow the appropriate instructions I have been given and adopt safe working practices.

I have read/attended and understood the following documents/presentations:

- HTA Code of Practice 1 – Consent
- HTA Code of Practice 9 – Research
- Briefing Session 1 (Knowing your Responsibilities)
- MRC e-learning module (www.rsclearn.mrc.ac.uk)

In the event of any situation arising where I am not sure about the appropriate action to take I will seek advice before proceeding. Where appropriate, I will bring to the attention of my supervisor and/or Lead Investigator for the research project any concerns that I have in relation to my work with human samples. If I still have concerns, or where I am Lead Investigator or Person Responsible, I will notify the Designated Individual (or their named representative).

Name: Esther Afolalu

Signed: Afolalu Date: 16 Sept 2014

Lead Investigator or Person Responsible (where applicable)
I confirm that I accept overall responsibility for the involvement of the above named researcher on research projects involving human samples that I am custodian for.

Name: Esther Afolalu

Signed: Afolalu Date: 16 Sept 2014.

Confirmation of Registration
I confirm that the above named researcher is registered for working with human samples at the University of Warwick.

Name: John Davey (Designated Individual, HTA Licence #12297)

Signed: J. Davey Date: 17 SEPTEMBER 2014

All researchers working with human samples are required to update their skills at least every 3 years. This registration will be due for renewal on SEPTEMBER 2017

This is to certify that

Esther F Afolalu

has been awarded

3 Credits at Level Three

on a course entitled

Phlebotomy Skills

provided by

Phlebotomy Training Services Ltd

Credit/s Awarded

Unit Title	Unit Code	Credit(s)	Level
Understanding and Applying Phlebotomy Skills and Techniques	PD2/3/NE/010	3	Three

These units are quality assured by ONE Awards and are not in the Qualifications and Credit Framework (QCF)

Learner ID: 20101001
Award Date: 03 Sep 2015
Certificate No: 5567864

David Hall
CHAIR
One Awards

10: Sleep and Chronic Pain – Informed Consent Form

THE UNIVERSITY OF WARWICK

Participant identification number:

CONSENT FORM

Project Title: Sleep Disturbances and the Experience of Chronic Pain

Name of Researcher: Esther Afolalu

	Please Initial
I confirm that I have read and understood the participant information sheet dated 28/04/15 (version 2.1) for the above project which I may keep for my records and have had the opportunity to ask any questions I may have.	
I agree to take part in the above study and am willing to: *Complete study questionnaires, carry out the pain testing, physical functioning tasks, cognitive testing, blood sampling, and overnight sleep assessment.*	
I agree for my blood samples to be taken and analysed as part of this study. *I have read and understood the Donor Information Sheet and signed the Donor Consent Form*	
I understand that as part of the sleep assessment it is necessary that I be videotaped as I sleep. I understand that any video footage will only be accessible to the research team and I confirm that I am happy for this to be carried out.	
I agree that my General Practitioner may be contacted if necessary to confirm my diagnosis of a chronic pain condition.	
I understand that my information will be held and processed for the following purposes: *Research findings may be published in journals, presented at conferences and shared anonymously with other researchers.* I understand that I will not be identified personally in any presentation of publication and only the research team will have access to my personal information.	
I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason without being penalised or disadvantaged in any way.	
I agree for my information to be kept so that I can be contacted for future similar studies.	
I would like to be sent a copy of the study results summary when available.	

Name of Participant	Date	Signature
_____	_____	_____
Name of Researcher taking consent	Date	Signature
_____	_____	_____

P.T.O

THE UNIVERSITY OF WARWICK

Donor Information Sheet

Donation of blood for research is voluntary and you should not be placed under any pressure to donate. You do not have to agree to give a blood sample nor explain if you choose not to, refusal will have no disadvantage to you in any way. You will be given an explanation of what your blood will be used for before it is taken. Any personal information provided by you in connection with the donation will be held in confidence

For reasons of safety, you should not donate if you:

- **Know you are, or think you might be infected with Hepatitis B, Hepatitis C or HIV (the AIDS virus)**
- **Have, or have had, a sexual partner who is infected with hepatitis or HIV**
- **Are feeling unwell at the moment**
- **Are anaemic or receiving treatment for anaemia or iron deficiency**
- **Are, or may be, pregnant**

DONOR CONSENT FORM

Please Initial

I freely consent to donating blood sample for use by: **Esther Afolalu** for the project – **Sleep Disturbances and the Experience of Chronic Pain**		
I do not fall into any of the categories of individual who should not donate blood as detailed above and I understand it is my responsibility to inform the study researchers if any of these circumstances change.		
I have been informed of the following:		
The quantity of blood to be taken	10mls in total.	
The frequency of blood donations	5mls once daily over a period of two days	
The use that will be made of the sample	To detect markers of inflammation in the blood	
Donor Signature:	Date:	
Signature of person taking blood:	Date:	
Name and contact details of person taking blood: Esther Afolalu, Department of Psychology, University of Warwick, Coventry, CV4 7AL, United Kingdom. *Tel: (024) 765 23158. E-mail: e.f.afolalu@warwick.ac.uk*		

11: Sleep and Chronic Pain – Participant Information Sheet

THE UNIVERSITY OF
WARWICK

PARTICIPANT INFORMATION SHEET

Study Title – Sleep Disturbance and the Experience of Chronic Pain

PhD Researcher – Esther Afolalu *(BSc Nursing Science, MSc Psychology)*
PhD Student – Department of Psychology
Academic Supervisor – Dr Nicole Tang *(D.Phil, C.Psychol)*
Assistant Professor – Department of Psychology

We would like to invite you to take part in this research study looking at sleep disturbances and its effect on the experience of chronic pain. Joining the study is entirely voluntary - before you decide, we would like you to understand why the research is being done and what it would involve. Please feel free to talk to others about the study if you wish. One of our team will also go through this information sheet with you to help you decide whether or not you would like to take part and answer any questions you may have. The first part of the Participant Information Sheet tells you the purpose of the study and what will happen to you if you take part. Part Two gives you more detailed information about the conduct of the study. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part. This is your copy of this information sheet to keep for future reference. Thank you for reading this.

What is the purpose of the study?

Chronic pain is a debilitating health problem and sleep impairment is one of the most common complaints in individuals suffering from chronic pain. Recent studies are suggesting that sleep disturbance may have stronger contributory effect on the experience and maintenance of chronic pain than the effect of pain on sleep. To date, the direct effect of sleep disturbances on pain has mostly been investigated in experiments using healthy volunteers. Generalisability of their findings to treatment seeking chronic pain patients has yet to be established. In order to understand and address the fundamental role of sleep in chronic pain, the first step is gaining an insight into how sleep is disturbed and shaped in this population.

Hence, the primary aim of the research is to address this gap by first identifying the characteristics of sleep disturbance in two chronic pain conditions (namely fibromyalgia and chronic back pain) compared with healthy populations. A secondary aim of the research will be to explore the associations of these characteristics with subsequent pain responses, physical, cognitive and psychological functioning.

The study will be carried out at the Sleep & Pain Laboratory at the University of Warwick where you will undergo two overnight sleep assessments and two daytime session testing of pain, psychological, cognitive and physical functioning.

Why have I been invited?

We are inviting volunteers both healthy and with chronic pain to help us better understand the pattern and effects of sleep disturbances in individuals with chronic pain. You are been recruited as a part of one of three groups – chronic pain patients with fibromyalgia, chronic back pain patients, or healthy individual with no chronic pain condition.

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part, we will describe the study and go through this information sheet with you. If you agree to take part we will ask you to sign a consent form. If you decide to take part, you are still free to withdraw at any time and without giving a reason. We would like to assure you that your withdrawal from this study will not jeopardise your opportunity to take part in future study or affect your standard hospital care in any way (if applicable).

What will happen to me if I take part?

ASSESSMENT

- If you fulfil our inclusion and exclusion criteria and have signed the consent form, we will then carry out an assessment session. This session will involve you completing a range of questionnaires to assess your sleeping, pain and psychological history. This will also be a chance for you to visit the sleep lab. The laboratory session (see page. 4 for schedule) will also be explained to you and you will be given an overview and a chance to practice some of the tasks you will be performing during this session.

- After the assessment visit, you will be asked to complete a week of sleep and pain diary immediately prior to the laboratory session. You will also be given a device called an actiwatch to wear for this week. An actiwatch is a wristwatch like device used that detects movements and is used to assess activity and sleep patterns. We are doing this to help us gain a record of your baseline sleeping and waking times and information about your sleep, daily pain & medication use.

- You will be given instructions for wearing the actiwatch and completing the diaries at the assessment visit. We will make sure to send you helpful reminders so that you know what you need to do for the different sessions.

LABORATORY SESSION

The laboratory session will be carried out in the Sleep & Pain Laboratory in the Department of Psychology at the University of Warwick. You will be resident in the laboratory for two overnights sleep assessment and two mornings of procedures and assessments. (*See below for a schedule*)

RECRUITMENT AND SCREENING SCHEDULE *(Volunteers Version)*

Recruitment and eligibility check.
Inclusion and exclusion criteria checklist.

FIBROMYALGIA	CHRONIC BACK PAIN	HEALTHY CONTROLS

Informed Consent	**Assessment Session**	Screening Interview Complete Questionnaires Overview and Practice of Tasks Instructions for laboratory session Instructions for actiwatch, sleep, and pain diary. 
Baseline Week (7 days till lab session)	Complete Sleep Diary upon waking. Complete pain diary in the evening before sleeping. Wear actiwatch continually, press marker upon sleeping, overnight awakenings and waking.	

Note: Bed time & wake time for lab session will be determined based on the sleep information provide during assessment session

LAB SESSION SCHEDULE *(Volunteers Version)*

NIGHT 1	***2 hours prior to bedtime*** – Arrive at lab. Check sleep and pain diary and actiwatch. Attach electrodes and sensors.			***10 mins before sleep*** Questionnaires 	Overnight sleep assessment. 
DAY 1	Wake  Remove Electrodes ***10 mins after wake*** Questionnaires 	***30mins after wake*** • Sensory testing 	***Approx. 1hour*** Shower 	***Approx. 1 hour*** Questionnaires  Cognitive Tasks  Physical functioning tasks 	**Day Leave**  • No strenuous exercise • No naps • No excessive caffeine • No alcohol
NIGHT 2	***2 hours prior to bedtime*** Return to lab Attach electrodes and sensors			***10 mins before sleep*** Questionnaires 	Overnight sleep assessment. 
DAY 2	Wake  Remove Electrodes ***10 mins after wake*** Questionnaires 	***30mins after wake*** • Blood Sampling  • Sensory testing 	***Approx. 1hour*** Shower 	***Approx. 1 hour*** Questionnaires  Cognitive Tasks  Physical functioning tasks 	End of study & debrief. 

What will I have to do?

This will give you an explanation of some of the procedures in the study.

OVERNIGHT SLEEP ASSESSMENT - POLYSOMNOGRAPHY (PSG)

- An overnight sleep assessment involves applying polysomnography (PSG) to monitor a range of physiological functions during sleep; this includes brain activities, heart rate, breathing, eye movements and leg movements. It is the gold standard of sleep measurement.

- For this study, we are interested in using PSG to obtain some information about the quality and structure of your sleep. We are looking for crucial information to help us understand the kind of sleep disturbance experienced by people with chronic pain.

- PSG involves attaching sensors to your scalp and body and this will take about an hour. The sensor sites will be treated with a mild abrasive cream on a cotton-bud and the sensors will be attached via a paste that is a glue-like conducive adhesive and/or medical tape. This is to make sure that we are getting good quality signals from the sensors during the recording. None of these monitoring devices is painful. They are all designed to be as comfortable as possible. The sensors may feel strange on your skin at first. However, most people get used to them very quickly.

- Sleep recording will be carried out in a sound attenuated, light and temperature controlled room with a comfortable bedroom-like atmosphere. The first night will be for screening and adaptation to the new sleeping environment and will not be included in the analysis. You will be monitored continuously for duration of time similar to your normal sleep schedule as determined by the average of habitual bedtimes and waketimes recorded and collected during assessment.

- The bedroom in the lab is fitted with an infrared video camera and the researcher will be able to monitor your sleep from the adjacent room. Any video footage recorded will only be accessible to the study researchers and no other third parties, and you will not in any way identified from it.

- You will be able to communicate with the researcher in the control room through the intercom system at anytime and if you require any help or assistance or need to be disconnected in order to get up to use the toilet.

BLOOD SAMPLING

You will also be asked to have your blood samples taken and analysed as part of the study. Blood samples will be taken at the Sleep & Pain Lab at the Department of Psychology, University of Warwick. Blood samples will be obtained through venepuncture. Venepuncture is the process of using a small needle to obtain blood samples through the vein, usually near the elbow into a blood collection tube. We will

be taking a total of around 10mls of blood from you. The researcher has a nursing background and has had training and clinical experience in venepuncture. The procedure will be carried out according to the NHS clinical practice, health and safety and infection control guidelines. The collected blood samples will be stored in the Sleep & Pain lab until transferred to the tissue bank of the biochemistry lab at the University Hospital Coventry & Warwickshire where they will be stored until they are analysed at the end of the study to detect markers of inflammation in the blood.

QUANTITATIVE SENSORY TESTING

This will consist of sensory testing to assess your pain sensitivity and pain threshold. Specifically, we will use an instrument called an algometer to assess your Pressure Pain Threshold, this is the minimum force applied to a chosen side of your body till you feel the pressure sensation. While you are doing this, you will be also be doing one of two tasks - carrying out a physical task - holding a 5-6kgs weighted bag or carrying out a cold pressor task which will involve you putting your hands in a bath of cold water maintained at 4 degrees Celsius.

You have full control over when to stop any of the tests before or as soon as you start to feel any pain or discomfort.

PHYSICAL FUNCTIONING TASKS
This will consist of simple 5 minutes walking, 1 minute sit-to-stand and 1 minute climbing stairs tasks.

COGNITIVE TASKS & QUESTIONNAIRES
The cognitive tasks will be administered on the computer with clear instructions about what to do. All questionnaires will be paper-based.

What are the possible disadvantages and risks of taking part?

- This is quite an intensive study requiring time, effort and commitment. You will be required to spend two nights in an unfamiliar environment, undergo a sleep study and complete tasks and questionnaires. To minimise discomfort, the sleep lab at the University of Warwick has been specifically designed with participant comfort in mind. The rooms are nicely decorated like a hotel room to make participants feel relaxed and comfortable. There is also a range of facilities and amenities available on the university campus. The researchers will be in an adjacent room to the sleep lab to monitor you overnight. In the event of any medical emergency, health and safety protocols will be followed in accordance with the University of Warwick's security office guidelines and regulations. They are available to provide around the clock emergency assistance and appropriate medical assistance as required.

- The physical functioning and pain threshold testing may cause some discomfort, however, these tasks have been routinely used in a clinical setting for pain threshold assessment. It is important to know that you can stop the procedure at any time if it gets to an unpleasant level of discomfort and you will be advised to

do only as much as you are able to do and can stop at any time. If a medical issue arises, arrangements will be made for medical assistance as appropriate.

- You will be asked to give blood samples. Whereas this may cause some burden, it is no more than chronic pain patients would be exposed to as part of their routine hospital care. It is also considerably less blood than a healthy person would give during a routine blood donation session for example. The samples required for the study are solely for the benefit of expanding knowledge in this area. The procedure for taking blood is relatively safe and will be carried out according to the NHS clinical practice, health and safety and infection control guidelines. If you feel unwell during the procedure, arrangements will be made for medical assistance as appropriate.

- The administration of the cognitive tasks and questionnaires may also create some burden but the testing schedule has been designed with sufficient number of breaks between procedures. Also, the assessment questionnaires can be completed at your own pace. You are also allowed to have a considerable lengthy daybreak during the lab session. Consequently, the majority of the time spent at the lab is limited to the overnight sleep assessment and the other study procedures which all occur in the morning.

What are the possible benefits for taking part?

There are no direct benefits, however, you may learn more about your sleep patterns and any disturbances by participating in this study - we will give you a short report summary of your sleep in the form of a hypnogram – this is short graph obtained from the sleep recording. It is a pictorial representation of sleep stages through the night and will give you a brief interpretation and description of your sleep pattern overnight. When all the data has been collected and analysed, if you are interested in receiving more information regarding the results of the study, we can provide you with a written result summary written in lay terminology.

There may also be some benefits in the future for others with chronic pain conditions as a consequence of discovery through research. On the whole, sleep is emerging as a very important and key aspect of the chronic pain condition; however, sleep is not currently routinely considered as a therapeutic target in chronic pain management. Proactive management of sleep disturbance would be beneficial to those individuals whose sleep quality may put them at greater risk for developing chronic pain conditions.

Involvement of the General Practitioner

Your GP will not be specifically informed of your participation in this study unless you wish to inform him/her yourself. However, if you are recruited as part of the group with chronic pain, with your permission we may need to contact your GP to confirm your diagnosis of a chronic pain condition.

What will happen to the blood samples I give?

If you consent to have your blood taken and analysed for the study, the samples required for the study are solely for the benefit of expanding knowledge in this area. We would like more information about the role of certain inflammatory markers in relation

to sleep and pain. Blood samples collected for the purpose of the research will be frozen immediately and analysed at the end of the study period. Handling and storage of your blood samples will follow the Medical Research Council, Good Clinical Practice & Code of Good Health & Safety Practice. Samples will be kept securely in the tissue bank of biochemistry lab at the University Hospital Coventry & Warwickshire until the end of the study when they will be analysed. No genetic testing will be carried out on your sample.

Expenses and payments

We are grateful for your contribution to this research but we also appreciate that cannot sufficiently reimburse your time and commitment with sufficient monetary value. You will be given £10 gift vouchers as a small token of appreciation. You will also be given a summary description of your overnight sleep pattern. In addition, we might be able to provide you with a Warwick meal voucher if you are staying on campus in between the two nights of sleep recording and reimburse you the travel expenses directly incurred by your participation of the study. There are also free disabled parking spaces available for blue-badge holders.

PART 2
What will happen if I don't want to carry on with the study?

You will be given sufficient time to address all the information about the study and make an informed decision. You will be able to make a free choice and can choose to opt out of any of the procedure or withdraw from the study at any time without giving reason. You also have the choice to decline the use of any or all of your data that has already been collected. In addition, if you withdraw from the study, we will destroy all your identifiable blood samples.

Will my information be kept confidential?

Participation in the study will be kept strictly confidential. Your personal data will be stored in locked filing cabinets in a locked research office accessed only by the research team. Electronic data will be stored on university computers with restricted access, which will be encrypted, and password protected. Each participant admitted in the study will be anonymised and given a unique identification code, which will be used to identify your data. The link between your name and unique numerical identifiers will be stored on a password-protected encrypted university computer. You will never be identified personally in any presentation or publication. As per the University of Warwick's Research Code of Conduct, data will be retained intact in paper or electronic format as appropriate, normally for a period of at least 10 years from the date of any publication, which is based upon it.

What will happen to the results of this study?

When the results of the study are known they may be published in academic journals, presented at conferences etc. When the findings are reported or presented, you will not be referred to in a way that could reveal your identity.

Who is organising and funding the study?

The study is been carried out as an educational fulfilment of a PhD degree funded by a postgraduate research scholarship awarded to the researcher by the Department of Psychology, University of Warwick.

Who has reviewed this study?

All research carried out is looked at by an independent group of people called a research ethics committee to protect your interest.
This study has been reviewed and given approval by the Biomedical and Scientific Research Ethics Sub-Committee (BSREC) at the University of Warwick. (Ref. No: REGO-2014-944 / AM01)
This study has been reviewed and given favourable opinion by NHS Leicester Research Ethics Committee. (Ref. No: 14/EM/1138)

What if something goes wrong?

If you have a concern about any aspect of the study, you should speak to the researcher who will do their best to answer your questions. If you remain unhappy, you can also contact the academic supervisor for this project. If you have any further complaints relating to a study about the research staff, conduct etc. and wish to complain formally, please contact the Director of Delivery Assurance, details as below –

Registrar's Office / Ms. Jo Horsburgh, Deputy Registrar, University of Warwick, Research Support Services, University House, Kirby Corner Road, Coventry, CV4 8UW. Email: complaints@warwick.ac.uk | n.lynch@warwick.ac.uk Telephone: 024 7652 2785. Fax: 024 7652 4751

Further information and contact details.

For more general information about the Sleep & Pain Lab, facilities and what we do, please visit our website
http://www2.warwick.ac.uk/fac/sci/psych/research/lifespan/sleeplab/
For more specific information and concerns about the study please contact with the researcher or academic supervisor:

Researcher
Esther F. Afolalu
Department of Psychology
University of Warwick
Coventry, CV4 7AL
Phone: +44 (0) 24 765 23158
E-mail: e.f.afolalu@warwick.ac.uk

Academic Supervisor
Dr. Nicole K. Y. Tang
Department of Psychology
University of Warwick
Coventry, CV4 7AL.
Phone: +44 (0)24 761 50556
Email: n.tang@warwick.ac.uk

What Really Happens When You Sleep?

Help us with our research and discover what goes on when you're sleeping.

We are *recruiting* ***GOOD AND POOR SLEEPERS & PEOPLE WITH OR WITHOUT CHRONIC PAIN*** *to take part in future research.*

WHAT'S INVOLVED?

Studies will take place at the **Sleep & Pain Lab - Department of Psychology, University of Warwick** and would include:

- Overnight sleep assessments
- Some testing sessions (e.g. questionnaires, cognitive tasks, physical functioning tasks etc.)
- Short periods of self-monitoring at home

WARWICK
THE UNIVERSITY OF WARWICK

FOR MORE INFORMATION

- **CONTACT THE LAB**
  Esther – e.f.afolalu@warwick.ac.uk
  Fatanah – f.ramlee@warwick.ac.uk
- **VISIT THE LAB WEBSITE**
  http://goo.gl/bMPuIx
- **READ ABOUT A NIGHT IN THE LAB**
  http://goo.gl/dfybcx
- **REGISTER INTEREST HERE**
  http://goo.gl/daxgmw

RETURN ADDRESS
SLEEP & PAIN LAB
DEPARTMENT OF PSYCHOLOGY
UNIVERSITY OF WARWICK
Coventry, CV4 7AL

REGISTERING INTEREST

First Name:
Surname:
Age:
Gender:
Contact phone number:
Email address:
How would you describe yourself? ☐ I am a good/normal sleeper ☐ I am a poor sleeper/insomniac
Do you have persistent problems sleeping? ☐ Yes ☐ No
Do you have chronic pain (persistent pain for 6 months or longer)? ☐ Yes ☐ No
Comments and Questions?

12: Sleep and Chronic Pain – Debrief

THE UNIVERSITY OF WARWICK

SLEEP DISTURBANCE AND THE EXPERIENCE OF CHRONIC PAIN

Chronic pain is a major health problem and sleep impairment is one of the most common complaints in individuals with chronic pain. Recent studies are suggesting that sleep disturbance may have stronger contributory effect on the experience and maintenance of chronic pain than the effect of pain on sleep. To date, the direct effect of sleep disturbances on pain has mostly been investigated in experiments using healthy volunteers. Generalisability of their findings to treatment seeking clinical chronic pain patients has yet to be established. In order to understand and address the fundamental role of sleep in chronic pain, the first step is gaining an insight into how sleep is disturbed and shaped in this population.

Hence, the primary aim of the research is to address this gap by first identifying the characteristics of sleep disturbance in two chronic pain conditions (namely fibromyalgia and chronic back pain) compared with healthy populations. A secondary aim of the research will be to explore the associations of these characteristics with subsequent pain responses, physical, cognitive and psychological functioning.

Overnight sleep assessment data will be used to explore patterns of sleep disturbances. The sensory tests were to determine your body's pain inhibition response and the physical tasks to assess your level of activity. The cognitive tasks were to assess your vigilance and decision making and the questionnaires were used to get a picture of your overall psychological functioning.

When the overnight sleep data has been analysed, we will send you a short report summary of your sleep and this will give you a brief interpretation and description of your sleep pattern overnight. When all the study data has been collected and analysed, if you are interested in receiving more information regarding the results of the study, we can also provide you with a written result summary written in lay terminology.

Thank you again for your participation!

In you have any questions or concerns about the study, please contact the researcher -

Esther F. Afolalu
Department of Psychology
University of Warwick
Coventry, CV4 7AL
United Kingdom
Tel: Lab - 024 765 28294
Office - 024 765 23158
E-mail: e.f.afolalu@warwick.ac.uk

13: Sleep and Chronic Pain – Screening Form

THE UNIVERSITY OF WARWICK

PARTICIPANT SCREENING FORM

Participant's name : _____

Participant's telephone : _____ D.OB/Age: _____

Participant's address : _____

_____

Postcode : _____ Gender: _____

Participant's email : _____

GP's Name : _____

GP's Address : _____

_____

Postcode : _____

GP's Telephone : _____

Please tick (☑) any of the following information that is applicable to your current situation:

	Aged between **18 and 65**
	English speaking
	Shift worker with irregular sleep pattern
	Sleeping problems or **sleep disorders** (e.g., insomnia, sleep apnoea, restless leg syndrome/periodic limb movement syndrome, narcolepsy)
	Medical diagnosis of **chronic back pain** present for more than 6 months.
	Medical diagnosis of **fibromyalgia** present for more than 6 months.
	Acute pain as a result of injury, surgery etc.
	Presence of any malignant or non-malignant **pain condition** present for at least 6 months or more (arthritis, chronic back pain, fibromyalgia etc.)
	Presence of any debilitating or life threatening **medical condition** (e.g. cancer, HIV, dementia etc.)
	Diagnosis of learning disability, history of **psychiatric illness** or recurrent history of a psychotic disorder
	Presence of any illness that could affect **ability to donate blood** (anaemia or receiving treatment for anaemia or iron deficiency, Hepatitis B, Hepatitis C, HIV/AIDS)
	Pregnant or breastfeeding
	Receiving psychological **therapy/treatments** for pain/insomnia or enrolled in drug trials
	History of cardiovascular disorder/**heart disease**
	History of **fainting or seizure**
	History of **frostbite**
	History of **Reynaud's** phenomenon (hands gets white then blue on exposure to cold, then red on warming.
	Open cut/sore/fracture on arm/hand

14: Sleep and Chronic Pain – Questionnaire Pack

Consensus Sleep Diary-Core ID/Name

Today's date	Sample Wed 4/5/11	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
1. What time did you get into bed?	10:15pm							
2. What time did you try to go to sleep	11:30pm							
3. How long did it take you to fall asleep?	55 min.							
4. How many times did you wake up, not counting your final awakening?	3 times							
5. In total, how long did these awakenings last?	1 hour 10 min.							
6. What time was your final awakening	6:35am							
7. What time did you get out of bed for the day?	7:20am							
8. How would you rate the quality of your sleep?	☐Very poor ☐Poor ☑ Fair ☐Good ☐Very good	☐Very poor ☐Poor ☐Fair ☐Good ☐Very good	☐Very poor ☐Poor ☐Fair ☐Good ☐Very good	☐Very poor ☐Poor ☐Fair ☐Good ☐Very good	☐Very poor ☐Poor ☐Fair ☐Good ☐Very good	☐Very poor ☐Poor ☐Fair ☐Good ☐Very good	☐Very poor ☐Poor ☐Fair ☐Good ☐Very good	☐Very poor ☐Poor ☐Fair ☐Good ☐Very good
9. Comments (if applicable)	I have a cold							

General Instructions for the CSD

What is a sleep diary? A sleep diary is designed to gather information about your daily sleep pattern.

How often and when do I fill out the sleep diary? It is necessary for you to complete your sleep diary **every day.** If possible, the sleep diary should be completed within one hour of getting out of bed in the morning.

What should I do if I miss a day? If you forget to fill in the diary or are unable to finish it, leave the diary blank for that day.

What if something unusual affects my sleep or how I feel in the daytime? If your sleep or daytime functioning is affected by some unusual event (such as an illness, or an emergency) you may make brief notes on your diary.

What do the words "bed and "day" mean on the diary? This diary can be used for people who are awake or asleep at unusual times. In the sleep diary, the word "day" is the time when you choose or are required to be awake. The term "bed" means the place where you usually sleep.

Will answering these questions about my sleep keep me awake? This is usually a problem. You should not worry about giving exact times, and you should not watch the clock. Just give your best estimate.

Item instructions

Use the guide below to clarify what is being asked for each item of the Sleep Diary

Date: Write the day and date of the morning you are filling out the diary.

1. *What time did you get into bed?* Write the time that you got into bed. This may not be the time that you began "trying" to fall asleep.
2. *What time did you try to go to sleep?* Record the time that you began "trying" to fall asleep.
3. *How long did it take you to fall asleep?* Beginning at the time you wrote in question 2, how long did it take you to fall asleep.
4. *How many times did you wake up, not counting your final awakening?* How many times did you wake up between the time you first fell asleep and your final awakening.
5. *In total, how long did these awakenings last?* What was the total time you were awake between the time you first feel asleep and your final awakening. For example, if you woke 3 times for 20 minutes, 35 minutes, and 15 minutes, add them all up (20+35+15=70 or 1hr and 10min).
6. *What time was your final awakening?* Record the last time you woke up in the morning.
7. *What time did you get out of the bed for the day?* What time did you get out of the bed with no further attempt at sleeping? This may be different from your final awakening time (e.g. you may have woken up 6:35 am but did not get out of bed to start your day until 7:20 a.m.)
8. *How would you rate the quality of your sleep?* "Sleep quality" is your sense whether your sleep was good or poor.
9. *Comments* If you have anything that you would like to say that is relevant to your sleep feel free to write it here.

EVENING DIARY

This pain is designed to help you create a record of your daily level of functioning. This diary can contain 7 days of information: please complete one column of the diary a day. Fill out the diary in the evening just before settling to sleep.

DIARY - EVENING	E.g. 25/8	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
How physically active have you been today? 0----------10 Not at all active Very active	4							
Rate your level of functioning today? 0----------10 Very poor Very well	6							
How would you rate your mood today? 0----------10 Very bad Very good	7							
What was the average level of pain today? 0----------10 No pain at all A lot of pain	5							
What is the level of pain right now? 0----------10 No pain at all A lot of pain	6							
If you have taken pain medication today, please write down the name and dosage.	Tramadol 50mg							
If you have taken sleep medication today, please write down the name and dosage.	Temazepam 20mg							

ACTIWATCH

- The watch is to be worn on the non-dominant wrist continually day & night during the week except when bathing, shower, swimming or coming into any contact with water-based activity.

- Press the event marker twice:
  - At bedtime: (When you switch off the lights)
  - On waking (Final awakening in the morning)

SLEEP DIARY

- The **Sleep Diary** contains 9 items asking about your experience of sleep. Information about seven nights (one week) can be recorded on one form.
- Please complete one column of the diary each morning, within 30 minutes after you wake up.

EVENING DIARY

- The **evening diary** contains items that ask you to rate your daily functioning on a numerical scale 0-10 (e.g. activity, mood, pain etc.) and about any pain or sleep medications you've taken for the day.
- Please complete on column of the diary in the evening just before settling to sleep.

Day 1 ↓ Day 7	***Wake:*** (within 30mins) ➢ Press event marker  ➢ Fill in Sleep Diary 	***Bedtime:*** ➢ Fill in Evening Dairy  ➢ Press the event marker 

Bring actiwatch & diaries with you to the lab session the evening of Day 7!

DEMOGRAPHICS & PAIN HISTORY **Participant ID:**

1. **Age** :
2. **Gender** : ( ) Male ( ) Female
3. **Weight** : _____ kg *or* _____ pounds *or* _____ stone
4. **Height** : _____ cm *or* _____ feet _____ inches
5. **Ethnic origins** : ( ) White
   ( ) White Irish
   ( ) Asian or Asian British: Chinese
   ( ) Asian or Asian British: Indian
   ( ) Asian or Asian British: Pakistani
   ( ) Asian or Asian British: Asian other
   ( ) Black or Black British
   ( ) British Mixed
   ( ) Other: _____
6. **Current relationship status** : ( ) Single ( ) Living with partner
   ( ) Married ( ) Separating
   ( ) Divorced ( ) Widowed
   ( )Other: _____
7. **Current employment status** : ( ) Paid work ( ) Unpaid work
   ( ) Studying ( ) On sick leave
   ( ) Unemployed ( ) Retired
   ( ) Medically retired ( ) Other: _____
8. **Highest education qualification** : ( ) No formal education ( ) Primary
   ( ) Secondary ( ) Diploma
   ( ) Degree ( ) Postgraduate
   ( ) Other: _____
9. **Do you smoke?** : ( ) Yes; _____ cigarettes per day
   ( ) Quit; When did you stop smoking? _____
   ( ) No
10. **Do you drink? If yes – tick typical alcohol consumption in a week** : ( ) Yes; _____ units (pint of regular beer/lager/cider)
    _____ units (glass of wine)
    _____ units (single measure of spirits)
    ( ) No
11. **Which hand do you use to do the majority of your everyday activities?** ( ) Right hand
    ( ) Left hand
    ( ) Either hand
12. **Do you have chronic pain?** : ( ) Yes
    ( ) No
13. **If yes to No.12 - Have you ever had any of these treatments for your pain** ( ) Medication ( ) Surgery
    ( ) Physiotherapy ( ) Hydrotherapy
    ( ) Acupuncture ( ) Exercise
    ( ) Massage ( ) TENS
    ( ) Injection ( ) Self-help
    ( ) Support group ( ) Psychological treatment
    ( ) Other: _____

14. Which of the above treatments you are currently taking? : _____

_____

15. What is the pain like? : ( ) Constant
( ) Recurrent
( ) Intermittent: comes and goes
( ) Seasonal

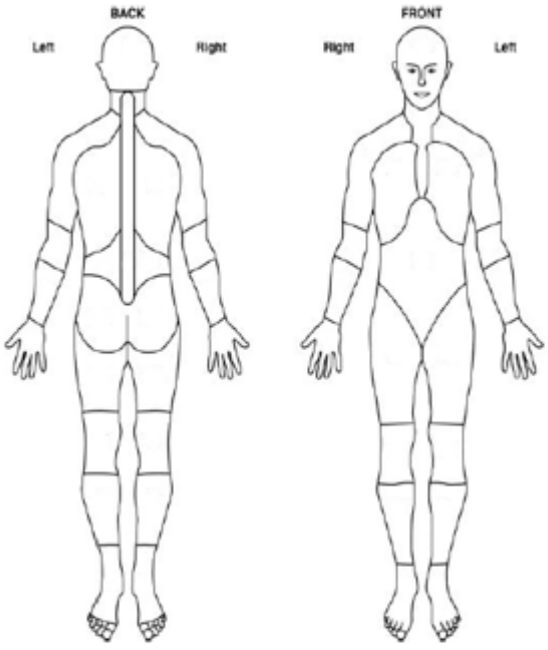
16. Have you been giving a formal diagnosis? : ( ) Yes; please specify _____
( ) No

17. How long have you been having pain? : _____ year(s) _____ month(s)

18. Any other illnesses? : (Please state)
_____

BODY MANIKINS

Shade in the diagram any pain that has lasted for 1 day or longer in the last week.



Anxiety & Preoccupation about Sleep Questionnaire (APSQ)

On the scales provided below, please rate each of the following statements for how true they are for you during the past month.

1. I worry about the amount of sleep I am going to get every night
   1 2 3 4 5 6 7 8 9 10
   Not true Very true

2. I worry about how the amount of sleep I had last night is going to affect my day time performance
   1 2 3 4 5 6 7 8 9 10
   Not true Very true

3. I worry about how the amount of sleep I get is going to afflict my health
   1 2 3 4 5 6 7 8 9 10
   Not true Very true

4. I worry about how much the amount of sleep I get will weaken my social ability
   1 2 3 4 5 6 7 8 9 10
   Not true Very true

5. I worry about how much the amount of sleep I get will shake my mood
   1 2 3 4 5 6 7 8 9 10
   Not true Very true

6. I worry about my loss of control over sleep
   1 2 3 4 5 6 7 8 9 10
   Not true Very true

7. I worry about my ability to stay awake and alert during the day
   1 2 3 4 5 6 7 8 9 10
   Not true Very true

8. I put great effort into trying to rectify my sleep problems
   1 2 3 4 5 6 7 8 9 10
   Not true Very true

9. My failure to rectify my sleep problems troubles me a lot
   1 2 3 4 5 6 7 8 9 10
   Not true Very true

10. My worry about sleep is persistent
    1 2 3 4 5 6 7 8 9 10
    Not true Very true

Reference: Tang, N.K.Y., & Harvey, A.G. (2004). Correcting distorted perception of sleep in insomnia: A novel behavioural experiment? Behaviour Research and Therapy, 42(1), 27-39.

Beck's Depression Inventory (BDI-II)

Participant ID:

Instructions: This questionnaire consists of 21 groups of statements. Please read each group of statements carefully, and then pick out the one statement in each group that best describes the way you have been feeling during the past two weeks, including today. Circle the number beside the statement you have picked. If several statements in the group seem to apply equally well, circle the highest number for that group. Be sure that you do not choose more than one statement for any group, including Item 16 (Changes in Sleeping Pattern) or Item 18 (Changes in Appetite).

1. Sadness

0 I do not feel sad.
1 I feel sad much of the time
2 I am sad all the time
3 I am so sad or unhappy that I can't stand it.

2. Pessimism

0 I am not discouraged about my future.
1 I feel more discouraged about my future than I used to be.
2 I do not expect things to work out for me
3 I feel my future is hopeless and will only get worse

3. Past Failure

0 I do not feel like a failure.
1 I have failed more than I should have.
2 As I look back I see a lot of failures.
3 I feel my future is hopeless and will only get worse.

4. Loss of Pleasure

0 I get as much pleasure as I ever did from the things I enjoy.
1 I don't enjoy things as much as I used to.
2 I get very little pleasure from the things I used to enjoy.
3 I can't get any pleasure from the things I used to enjoy.

5. Guilty Feelings

0 I don't feel particularly guilty
1 I feel guilty over many things I have done or should have done
2 I feel quite guilty most of the time.
3 I feel guilty all of the time.

6. Punishment Feelings

0 I don't feel I am being punished.
1 I feel I may be punished.
2 I expect to be punished.
3 I feel I am being punished.

7. Self-Dislike

0 I feel the same about myself as ever.
1 I have lost confidence in myself.
2 I am disappointed in myself.
3 I dislike myself.

8. Self-Criticalness

0 I don't criticise or blame myself more than usual.
1 I am more critical of myself than I used to be.
2 I criticise myself for all of my faults.
3 I blame myself for everything bad that happens.

9. Suicidal Thoughts or Wishes

0 I don't have any thoughts of killing myself.
1 I have thoughts of killing myself, but I would not carry them out.
2 I would like to kill myself.
3 I would kill myself if I had the chance.

10. Crying

0 I don't cry anymore than I used to.
1 I cry more now than I used to.
2 I cry over every little thing.
3 I feel like crying, but I can't.

11. Agitation

0 I am no more restless or wound up than usual.
1 I feel more restless or wound up than usual.
2 I am so restless or agitated that it's hard to stay still.
3 I am so restless or agitated that I have to keep moving or doing something.

12. Loss of Interest

0 I have not lost interest in other people or activities.
1 I am less interested in other people or things than before.
2 I have lost most of my interest in other people or things.
3 It's hard to get interested in anything.

13. Indecisiveness

0 I make decisions about as well as I ever.
1 I find it more difficult to make decisions than usual.
2 I have much greater difficulty in making decision than I used to.
3 I have trouble making any decisions.

14. Worthlessness

0 I do not feel I am worthless.
1 I don't consider myself as worthwhile and useful as I used to.
2 I feel more worthless as compared to other people.
3 I feel utterly worthless.

15. Loss of Energy

0 I have as much energy as ever.
1 I have less energy than I used to have.
2 I don't have enough energy to do very much.
3 I don't have enough energy to do anything.

16. Changes in Sleeping Pattern

0 I have not experienced any change in my sleeping pattern.
1a I sleep somewhat more than usual.
1b I sleep somewhat less than usual.
2a I sleep a lot more than usual.
2b I sleep a lot less than usual.
3a I sleep most of the day.
3b I wake up 1-2hours early and can't get back to sleep.

17. Irritability

0 I am no more irritable than usual.
1 I am more irritable than usual.
2 I am much more irritable than usual.
3 I am irritable all the time.

18. Changes in Appetite

0 I have not experienced any change in my appetite.
1a My appetite is somewhat less than usual.
1b My appetite is somewhat greater than usual.
2a My appetite is much less than before
2b My appetite is much greater than usual.
3a I have no appetite at all.
3b I crave food all the time.

19. Concentration Difficulty

0 I can concentrate as well as ever.
1 I can't concentrate as well as usual.
2 It's hard to keep my mind on anything for very long.
3 I find I can't concentrate on anything.

20. Tiredness or Fatigue

0 I am no more tired or fatigues than usual.
1 I get more tired or fatigued more easily than usual.
2 I am too tired or fatigued to do a lot of the thing I used to do.
3 I am too tired or fatigued to do most of the things I used to do.

21. Loss of Interest in Sex

0 I have not noticed any recent change in my interest in sex.
1 I am less interested in sex than I used to be.
2 I am much less interested in sex now.
3 I have lost interest in sex completely.

BRIEF PAIN INVENTORY

"Imagine a scale from 0 to 10, with 0 as "No pain at all" and 10 as "Pain as bad as you can imagine". Please use this scale and circle the number to answer the following items:

No pain at all — 0 1 2 3 4 5 6 7 8 9 10 — Pain as bad as you can imagine

1. Please rate your pain by telling me the one number that best describes your pain **at its worst in the last 24 hours**	0	1	2	3	4	5	6	7	8	9	10
2. Please rate your pain by telling me the one number that best describes your pain **at its least in the last 24 hours**	0	1	2	3	4	5	6	7	8	9	10
3. Please rate your pain by telling me the one number that best describes your pain **on the average**	0	1	2	3	4	5	6	7	8	9	10
4. Please rate your pain by telling me the one number that tells how much pain you have **right now**	0	1	2	3	4	5	6	7	8	9	10

Imagine a scale that has 0 as "does not interfere" and 10 as "completely interfere". Please use this scale to answer the following items by circling the number that best describes how, during the past week, your pain has interfered with different aspects of your life:

Does not interfere — 0 1 2 3 4 5 6 7 8 9 10 — Completely interfere

5. General activity	0	1	2	3	4	5	6	7	8	9	10
6. Mood	0	1	2	3	4	5	6	7	8	9	10
7. Walking ability	0	1	2	3	4	5	6	7	8	9	10
8. Normal work (including bot work outside the home and housework)	0	1	2	3	4	5	6	7	8	9	10
9. Relationship with other people	0	1	2	3	4	5	6	7	8	9	10
10. Sleep	0	1	2	3	4	5	6	7	8	9	10
11. Enjoyment with life	0	1	2	3	4	5	6	7	8	9	10

DBAS

Several statements reflecting people's belief and attitudes about sleep are listed below. Please indicate to what extent you personally disagree or agree with each statement. There is no right or wrong answer. For each statement, circle the number that corresponds to your own personal belief. Please respond to all items even though some may not apply to your own situation directly.

Strongly Disagree 0 1 2 3 4 5 6 7 8 9 10 Strongly Agree	
1. I need 8 hours sleep to feel refreshed and function well during the day.	0 1 2 3 4 5 6 7 8 9 10
2. When I don't get proper amount of sleep on a given night, I need to catch up on the next day by napping or on the next night by sleeping longer.	0 1 2 3 4 5 6 7 8 9 10
3. I am concerned that chronic insomnia may have serious consequences on my physical health.	0 1 2 3 4 5 6 7 8 9 10
4. I am worried that I may lose control over my abilities to sleep.	0 1 2 3 4 5 6 7 8 9 10
5. After a poor night's sleep, I know that it will interfere with my daily activities on the next day.	0 1 2 3 4 5 6 7 8 9 10
6. In order to be alert and function well during the day, I believe I would be better off taking a sleeping pill rather than having a poor night's sleep.	0 1 2 3 4 5 6 7 8 9 10
7. When I feel irritable, depressed or anxious during the day, it is mostly because I did not sleep well the night before.	0 1 2 3 4 5 6 7 8 9 10
8. When I sleep poorly on one night, I know it will disturb my sleep schedule for the whole week.	0 1 2 3 4 5 6 7 8 9 10
9. Without an adequate night's sleep, I can hardly function the next day.	0 1 2 3 4 5 6 7 8 9 10
10. I can't ever predict whether I'll have a good or poor night's sleep	0 1 2 3 4 5 6 7 8 9 10
11. I have little ability to manage the negative consequences of disturbed sleep	0 1 2 3 4 5 6 7 8 9 10
12. When I feel tired, have no energy, or just seem not function well during the day, it is generally because I did not sleep well the night before	0 1 2 3 4 5 6 7 8 9 10
13. I believe insomnia is essentially the result of a chemical imbalance	0 1 2 3 4 5 6 7 8 9 10
14. I feel insomnia is running my ability to enjoy life and prevents me from doing what I want	0 1 2 3 4 5 6 7 8 9 10
15. Medication is probably the only solution to sleep problem	0 1 2 3 4 5 6 7 8 9 10
16. I avoid or cancel obligations (social, family) after a poor night's sleep	0 1 2 3 4 5 6 7 8 9 10

Medication Quantification Scale – III (MQS-III)

Patient to complete		Clinician to complete				
Drug	**Dosage (mg/day)**	**Detrimental Weight**		**Dosage Level**		**MQS Score**
			X		=	
			X		=	
			X		=	
			X		=	
			X		=	
			X		=	
			X		=	
			X		=	
			X		=	
			X		=	
			X		=	

PAIN CATASTROPHISING SCALE (PCS)

Participant ID:

Instructions: Everyone experiences painful situations at some point in their lives. Such experiences may include headaches, tooth pain, joint or muscle pain. People are often exposed to situations that may cause pain such as illness, injury, dental procedures or surgery. We are interested in the types of thoughts and feelings that you have when you are in pain. Listed below are thirteen statements describing different thoughts and feelings that may be associated with pain. Using the following scale, please indicate the degree to which you have these thoughts and feelings when you are experiencing pain.

When I'm in pain....

	Not at all	To a slight degree	To a moderate degree	To a great degree	All the time
1. I worry all the time about whether the pain will end	0	1	2	3	4
2. I feel I can't go on	0	1	2	3	4
3. It's terrible and I think it's never going to get any better	0	1	2	3	4
4. It's awful and I feel it overwhelms me	0	1	2	3	4
5. I feel I can't stand it anymore	0	1	2	3	4
6. I become afraid that the pain will get worse	0	1	2	3	4
7. I keep thinking of other painful events	0	1	2	3	4
8. I anxiously want the pain to go away	0	1	2	3	4
9. I can't seem to keep it out of my mind	0	1	2	3	4
10. I keep thinking about how much it hurts	0	1	2	3	4
11. I keep thinking about how badly I want the pain to stop	0	1	2	3	4
12. There's nothing I can do to reduce the intensity of the pain	0	1	2	3	4
13. I wonder whether something serious may happen	0	1	2	3	4

Profile of Mood States (POMS2 – Adult Short)

Instructions: Below is a list of words that describe feelings that people have. Please read each word carefully, then circle the number that best describes *how you have been feeling during the past week, including today OR how you are feeling right now.*

	Not at all	A little	Moderately	Quite a bit	Extremely
Friendly	0	1	2	3	4
Tense	0	1	2	3	4
Angry	0	1	2	3	4
Worn out	0	1	2	3	4
Lively	0	1	2	3	4
Confused	0	1	2	3	4
Considerate	0	1	2	3	4
Sad	0	1	2	3	4
Active	0	1	2	3	4
Grouchy	0	1	2	3	4
Energetic	0	1	2	3	4
Panicky	0	1	2	3	4
Hopeless	0	1	2	3	4
Uneasy	0	1	2	3	4
Unable to concentrate	0	1	2	3	4
Fatigued	0	1	2	3	4

	Not at all	A little	Moderately	Quite a bit	Extremely
Helpful	0	1	2	3	4
Nervous	0	1	2	3	4
Miserable	0	1	2	3	4
Muddled	0	1	2	3	4
Bitter	0	1	2	3	4
Exhausted	0	1	2	3	4
Anxious	0	1	2	3	4
Good-natured	0	1	2	3	4
Helpless	0	1	2	3	4
Weary	0	1	2	3	4
Bewildered	0	1	2	3	4
Furious	0	1	2	3	4
Trusting	0	1	2	3	4
Bad-tempered	0	1	2	3	4
Worthless	0	1	2	3	4
Vigorous	0	1	2	3	4
Uncertain about things	0	1	2	3	4
Drained	0	1	2	3	4
Enthusiastic	0	1	2	3	4

Pre-Sleep Arousal Scale

Please describe how intensely you generally experience each of these symptoms as you attempt to fall asleep in your own bedroom.

	Not at all	Slightly	Moderately	A lot	Extremely
PHYSIOLOGICAL/SOMATIC					
1. Heart racing, pounding, or beating irregularly.	1	2	3	4	5
2. A jittery, nervous feeling in your body.	1	2	3	4	5
3. Shortness of breath or laboured breathing.	1	2	3	4	5
4. A tight, tense feeling in your muscles.	1	2	3	4	5
5. Cold feeling in your hands, feet or your body	1	2	3	4	5
6. Have stomach upset (knot or nervous feeling, heartburn, nausea, etc.	1	2	3	4	5
7. Perspiration in the palms of your hands or other parts of your body.	1	2	3	4	5
8. Dry feeling in your mouth or throat	1	2	3	4	5
COGNITIVE					
9. Worry about falling asleep.	1	2	3	4	5
10. Review or ponder events of the day.	1	2	3	4	5
11. Depressing or anxious thoughts.	1	2	3	4	5
12. Worry about problems other than sleep.	1	2	3	4	5
13. Being mentally alert, active.	1	2	3	4	5
14. Can't shut off your thoughts.	1	2	3	4	5
15. Thoughts keep racing through your head.	1	2	3	4	5
16. Being distracted by sounds, noise in the environment, (e.g., ticking of the clock, house noises, traffic).	1	2	3	4	5

Pittsburgh Sleep Quality Index (PSQI)

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…	**Not during the past month**	**Less than once a week**	**Once or twice a week**	**Three or more times a week**
a. Cannot get to sleep within 30 minutes.				
b. Wake up in the middle of the night or early morning.				
c. Have to get up to use the bathroom				
d. Cannot breathe comfortably				
e. Cough or snore badly				
f. Feel too cold				
g. Feel too hot				
h. Had bad dreams				
i. Have pain				
j. Other reason(s), please describe:				

	Very good	**Fairly good**	**Fairly bad**	**Very bad**
6. During the past month, how would you rate your sleep quality overall?				
	Not during the past month	**Less than once a week**	**Once or twice a week**	**Three or more times a week**
7. During the past month, how often have you taken medicine (prescribed or "over the counter") to help you sleep?				
8. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?				
	No problem at all	**Only a very slight problem**	**Somewhat of a problem**	**A very big problem**
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 bed partner or roommate	**Partner / roommate in other room**	**Partner in same room, but not same bed**	**Partner in same bed**
10. Do you have a bed partner or roommate?				
If you have a room mate or bed partner, ask him/her how often in the past month you have had:	**Not during the past month**	**Less than once a week**	**Once or twice a week**	**Three or more times a week**
a. Loud snoring				
b. Long pauses between breaths while asleep				
c. Legs twitching or jerking while you sleep				
d. Episodes of disorientation or confusion during sleep				
e. Other restlessness while you sleep; please describe:				

Penn State Worry Questionnaire (PSWQ)

Instructions: Rate each of the following statements on a scale of 1 ("not at all typical of me") to 5 ("very typical of me").

Not at all typical of me 1 2 3 4 5 Very typical of me	
1. If I do not have enough time to do everything, I do not worry about it.	1 2 3 4 5
2. My worries overwhelm me.	1 2 3 4 5
3. I do not tend to worry about things.	1 2 3 4 5
4. Many situations make me worry	1 2 3 4 5
5. I know I should not worry about things, but I just cannot help it.	1 2 3 4 5
6. When I am under pressure I worry a lot.	1 2 3 4 5
7. I am always worrying about something.	1 2 3 4 5
8. I find it easy to dismiss worrisome thoughts.	1 2 3 4 5
9. As soon as I finish one task, I start to worry about everything else I have to do.	1 2 3 4 5
10. I never worry about anything.	1 2 3 4 5
11. When there is nothing more I can do about a concern, I do not worry about it any more.	1 2 3 4 5
12. I have been a worrier all my life.	1 2 3 4 5
13. I notice that I have been worrying about things.	1 2 3 4 5
14. Once I start worrying, I cannot stop.	1 2 3 4 5
15. I worry all the time.	1 2 3 4 5
16. I worry about projects until they are all done.	1 2 3 4 5

PVAQ

Consider your behaviour over the last 2 weeks and indicate how frequently, on a scale from 0 (never) to 5 (always), each of these items was a true description of you.

Never — Always 0 1 2 3 4 5	
1. I am very sensitive to pain.	0 1 2 3 4 5
2. I am aware of sudden or temporary changes in pain.	0 1 2 3 4 5
3. I am quick to notice changes in pain intensity.	0 1 2 3 4 5
4. I am quick to notice effects of medication on pain.	0 1 2 3 4 5
5. I am quick to notice changes in location or extent of pain.	0 1 2 3 4 5
6. I focus on sensations of pain.	0 1 2 3 4 5
7. I notice pain even if I am busy with another activity.	0 1 2 3 4 5
8. I find it easy to ignore pain,	0 1 2 3 4 5
9. I know immediately when pain starts or increases.	0 1 2 3 4 5
10. When I do something that increases pain, the first thing I do is check to see how much pain was increased.	0 1 2 3 4 5
11. I know immediately when pain decreases.	0 1 2 3 4 5
12. I seem to be more conscious of pain than others.	0 1 2 3 4 5
13. I pay close attention to pain.	0 1 2 3 4 5
14. I keep track of my pain level.	0 1 2 3 4 5
15. I become preoccupied with pain.	0 1 2 3 4 5
16. I do not dwell on pain.	0 1 2 3 4 5

STATE-TRAIT ANXIETY INVENTORY FOR ADULTS
(STAI – FORM Y1 & Y2)

Participants ID:

Directions: A number of statements which people have used to describe themselves are given below. Read each statement and then circle the appropriate number to the right of the statement to indicate ***how you feel right now, that is, at this moment***. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe your present feelings best.

	Not at all	Somewhat	Moderately so	Very much so
1. I feel calm	1	2	3	4
2. I feel secure	1	2	3	4
3. I feel tense	1	2	3	4
4. I feel strained	1	2	3	4
5. I feel at ease	1	2	3	4
6. I feel upset	1	2	3	4
7. I am presently worrying over possible misfortunes	1	2	3	4
8. I feel satisfied	1	2	3	4
9. I feel frightened	1	2	3	4
10. I feel comfortable	1	2	3	4
11. I feel self-confident	1	2	3	4
12. I feel nervous	1	2	3	4
13. I am jittery	1	2	3	4
14. I feel indecisive	1	2	3	4
15. I am relaxed	1	2	3	4
16. I feel content	1	2	3	4
17. I am worried	1	2	3	4
18. I feel confused	1	2	3	4
19. I feel steady	1	2	3	4
20. I feel pleasant	1	2	3	4

Directions: A number of statements which people have used to describe themselves are given below. Read each statement and then circle the appropriate number to the right of the statement to indicate ***how you generally feel***. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe how you generally feel.

	Almost Never	Sometimes	Often	Almost Always
21. I feel pleasant	1	2	3	4
22. I feel nervous and restless	1	2	3	4
23. I feel satisfied with myself	1	2	3	4
24. I wish I could be as happy as others seem to be	1	2	3	4
25. I feel like a failure	1	2	3	4
26. I feel rested	1	2	3	4
27. I am "calm, cool, and collected"	1	2	3	4
28. I feel that difficulties are piling up so that I cannot overcome them	1	2	3	4
29. I worry too much over something that really doesn't matter	1	2	3	4
30. I am happy	1	2	3	4
31. I have disturbing thoughts	1	2	3	4
32. I lack self-confidence	1	2	3	4
33. I feel secure	1	2	3	4
34. I make decisions easily	1	2	3	4
35. I feel inadequate	1	2	3	4
36. I am content	1	2	3	4
37. Some unimportant thought runs through my mind and bothers me	1	2	3	4
38. I take disappointments so keenly that I can't put them out of my mind	1	2	3	4
39. I am a steady person	1	2	3	4
40. I get in a state of tension or turmoil as I think over my recent concerns and interests.	1	2	3	4

The Stanford Sleepiness Scale (SSS)

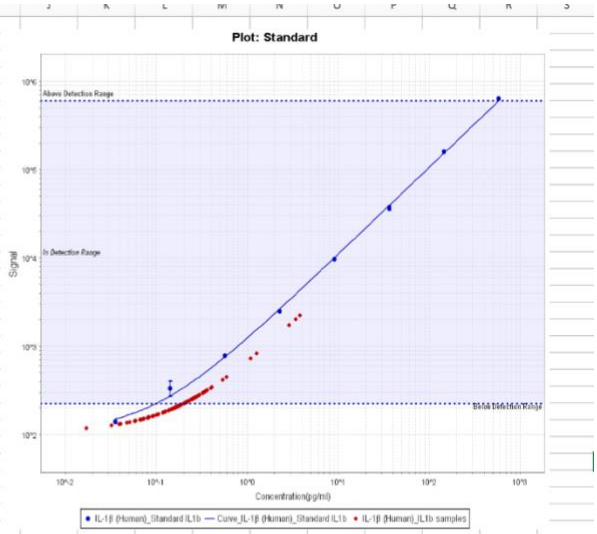
Using the 7-point scale below pick what best represents how you are feeling right now and note the corresponding number on the chart below.

Degree of Sleepiness	Scale Rating
Feeling active, vital, alert, or wide awake	1
Functioning at high levels, but not at peak; able to concentrate	2
Awake, but relaxed; responsive but not fully alert	3
Somewhat foggy, let down	4
Foggy; losing interest in remaining awake; slowed down	5
Sleepy, woozy, fighting sleep; prefer to lie down	6
No longer fighting sleep, sleep onset soon; having dream-like thoughts	7
Asleep	X

15: Sleep and Chronic Pain – Cytokines Inter/Intra-Assay Coefficients of Variability

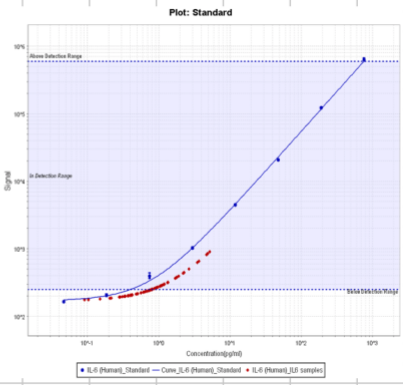
Interleukin-1beta (IL-β) Inter and Intra Assay Coefficients of Variability (CV)

IL1b samples: IL-1β (Human)								
Sample	Well	Signal	Mean	CV	Calc. Conce	Calc. Conc.	Calc. Conc. CV	
SCP 4	A03	178	163	13.01424	0.119555	0.09379	38.8492	
SCP 4	A04	148	163	13.01424	0.068026	0.09379	38.8492	
SCP 6	B04	151	170	15.43537	0.07316	0.104984	42.86938	
SCP 6	B03	188	170	15.43537	0.136807	0.104984	42.86938	
SCP 7	C04	197	217	12.73772	0.15236	0.186171	25.68379	
SCP 7	C03	236	217	12.73772	0.219982	0.186171	25.68379	
SCP 8	D03	161	147	13.99734	0.090307	0.065526	53.48316	
SCP 8	D04	132	147	13.99734	0.040745	0.065526	53.48316	
SCP 11	E04	214	213	0.998268	0.181795	0.179195	2.05168	
SCP 11	E03	211	213	0.998268	0.176595	0.179195	2.05168	
SCP 12	F04	136	171	28.61605	0.047547	0.106875	78.50532	
SCP 12	F03	205	171	28.61605	0.166203	0.106875	78.50532	
SCP 13	G04	156	177	16.7788	0.081727	0.117908	43.39644	
SCP 13	G03	198	177	16.7788	0.154089	0.117908	43.39644	
SCP 14	H03	181	156	22.66368	0.124727	0.081887	73.9862	
SCP 14	H04	131	156	22.66368	0.039047	0.081887	73.9862	
SCP 15	A05	97	112	18.94036	0	0.016132	141.4214	
SCP 15	A06	127	112	18.94036	0.032265	0.016132	141.4214	
SCP 17	B06	143	143	0.496215	0.059481	0.058627	2.058848	
SCP 17	B05	142	143	0.496215	0.057774	0.058627	2.058848	
SCP 18	C06	156	124	36.49583	0.081727	0.040864	141.4214	
SCP 18	C05	92	124	36.49583	0	0.040864	141.4214	
SCP 19	D06	155	137	19.167	0.080013	0.048549	91.65406	
SCP 19	D05	118	137	19.167	0.017085	0.048549	91.65406	
SCP 20	E06	147	170	19.13348	0.066315	0.10588	52.84557	
SCP 20	E05	193	170	19.13348	0.145445	0.10588	52.84557	
SCP 21	F05	201	207	4.09917	0.159279	0.16967	8.660914	
SCP 21	F06	213	207	4.09917	0.180061	0.16967	8.660914	
SCP 22	G05	182	196	9.765669	0.126452	0.149791	22.03486	
SCP 22	G06	209	196	9.765669	0.17313	0.149791	22.03486	
SCP 24	H06	170	180	7.484696	0.105777	0.122156	18.96163	
SCP 24	H05	189	180	7.484696	0.138534	0.122156	18.96163	
SCP 25	A07	448	1343	94.22823	0.591312	2.192833	103.2862	
SCP 25	A08	2237	1343	94.22823	3.794355	2.192833	103.2862	
SCP 26	B07	150	144	5.892557	0.071448	0.0612	23.67979	
SCP 26	B08	138	144	5.892557	0.050953	0.0612	23.67979	



Iinterleukin-6 (IL-6) Inter and Intra Assay Coefficients of Variability (CV)

IL6 samples: IL-6 (Human)							
Sample	Well	Signal	Mean	CV	Calc. Conce	Calc. Conc.	Calc. Conc. CV
SCP 4	A04	149	163	11.74885	0	0.051636	141.4214
SCP 4	A03	176	163	11.74885	0.103271	0.051636	141.4214
SCP 6	B04	242	260	9.790709	0.738441	0.887318	23.72815
SCP 6	B03	278	260	9.790709	1.036195	0.887318	23.72815
SCP 7	C04	166	182	12.43265	0	0.169476	141.4214
SCP 7	C03	198	182	12.43265	0.338952	0.169476	141.4214
SCP 8	D04	142	172	24.32612	0	0.184123	141.4214
SCP 8	D03	201	172	24.32612	0.368246	0.184123	141.4214
SCP 11	E03	180	183	1.937279	0.150343	0.178003	21.97534
SCP 11	E04	185	183	1.937279	0.205663	0.178003	21.97534
SCP 12	F04	267	258	5.217487	0.947087	0.868242	12.84245
SCP 12	F03	248	258	5.217487	0.789397	0.868242	12.84245
SCP 13	G04	231	217	9.471638	0.643296	0.510606	36.75085
SCP 13	G03	202	217	9.471638	0.377916	0.510606	36.75085
SCP 14	H04	195	181	11.36072	0.309191	0.154595	141.4214
SCP 14	H03	166	181	11.36072	0	0.154595	141.4214
SCP 15	A06	186	150	34.52762	0.216385	0.108192	141.4214
SCP 15	A05	113	150	34.52762	0	0.108192	141.4214
SCP 17	B06	501	468	10.13394	2.658198	2.427412	13.44561
SCP 17	B05	434	468	10.13394	2.196626	2.427412	13.44561
SCP 18	C05	216	226	5.957884	0.509188	0.59368	20.12685
SCP 18	C06	235	226	5.957884	0.678171	0.59368	20.12685
SCP 19	D05	248	249	0.28455	0.789397	0.793614	0.751465
SCP 19	D06	249	249	0.28455	0.797831	0.793614	0.751465
SCP 20	E05	163	185	16.81767	0	0.212812	141.4214
SCP 20	E06	207	185	16.81767	0.425625	0.212812	141.4214
SCP 21	F05	227	258	16.99249	0.608074	0.866004	42.12082
SCP 21	F06	289	258	16.99249	1.123934	0.866004	42.12082
SCP 22	G05	298	290	4.152268	1.194804	1.127529	8.438102
SCP 22	G06	281	290	4.152268	1.060253	1.127529	8.438102
SCP 24	H05	241	243	1.163962	0.729887	0.746941	3.228982
SCP 24	H06	245	243	1.163962	0.763996	0.746941	3.228982
SCP 25	A08	118	130	12.55865	0	0	NaN
SCP 25	A07	141	130	12.55865	0	0	NaN
SCP 26	B07	241	246	2.874418	0.729887	0.772269	7.761159
SCP 26	B08	251	246	2.874418	0.814651	0.772269	7.761159



Tumour necrosis factor-alpha (TNF-α) Inter and Intra Assay Coefficients of Variability (CV)

	A	B	C	D	E	F	G	H
1	TNFa samples: TNF-α (Human)							
2	Sample	Well	Signal	Mean	CV	Calc. Conce	Calc. Conc.	Calc. Conc. CV
3	SCP 4	A04	384	410	8.968184	1.534007	1.701945	13.95467
4	SCP 4	A03	436	410	8.968184	1.869884	1.701945	13.95467
5	SCP 6	B03	377	401	8.298132	1.488613	1.640591	13.10071
6	SCP 6	B04	424	401	8.298132	1.792569	1.640591	13.10071
7	SCP 7	C04	309	333	10.19253	1.044938	1.201796	18.45827
8	SCP 7	C03	357	333	10.19253	1.358654	1.201796	18.45827
9	SCP 8	D04	299	314	6.54102	0.979206	1.074329	12.52169
10	SCP 8	D03	328	314	6.54102	1.169452	1.074329	12.52169
11	SCP 11	E03	438	440	0.642824	1.882759	1.89563	0.960208
12	SCP 11	E04	442	440	0.642824	1.908501	1.89563	0.960208
13	SCP 12	F04	618	567	12.72044	3.031374	2.707068	16.94222
14	SCP 12	F03	516	567	12.72044	2.382763	2.707068	16.94222
15	SCP 13	G03	376	366	4.06272	1.482125	1.41388	6.826052
16	SCP 13	G04	355	366	4.06272	1.345636	1.41388	6.826052
17	SCP 14	H03	326	373	17.65394	1.156367	1.458345	29.2839
18	SCP 14	H04	419	373	17.65394	1.760322	1.458345	29.2839
19	SCP 15	A06	353	354	0.20003	1.332613	1.335869	0.344688
20	SCP 15	A05	354	354	0.20003	1.339125	1.335869	0.344688
21	SCP 17	B05	375	409	11.59759	1.475635	1.692068	18.08923
22	SCP 17	B06	442	409	11.59759	1.908501	1.692068	18.08923
23	SCP 18	C06	381	384	1.104854	1.514558	1.534003	1.792617
24	SCP 18	C05	387	384	1.104854	1.553447	1.534003	1.792617
25	SCP 19	D06	336	332	1.703872	1.221743	1.195597	3.092588
26	SCP 19	D05	328	332	1.703872	1.169452	1.195597	3.092588
27	SCP 20	E06	342	327	6.713724	1.260911	1.159489	12.37025
28	SCP 20	E05	311	327	6.713724	1.058068	1.159489	12.37025
29	SCP 21	F06	502	526	6.452685	2.293303	2.446431	8.851907
30	SCP 21	F05	550	526	6.452685	2.599559	2.446431	8.851907
31	SCP 22	G06	496	493	1.005025	2.254927	2.232527	1.418934
32	SCP 22	G05	489	493	1.005025	2.210128	2.232527	1.418934
33	SCP 24	H05	364	389	8.918464	1.404186	1.562892	14.36084
34	SCP 24	H06	413	389	8.918464	1.721598	1.562892	14.36084
35	SCP 25	A07	367	370	0.956843	1.423684	1.439922	1.594855
36	SCP 25	A08	372	370	0.956843	1.456161	1.439922	1.594855
37	SCP 26	B08	494	497	0.85365	2.24213	2.261322	1.200223
38	SCP 26	B07	500	497	0.85365	2.280513	2.261322	1.200223