Sleep in later life
A population-based approach

Julia F. van den Berg

2008

The research presented in this thesis was conducted at the Department of Epidemiology & Biostatistics, Erasmus Medical Center, Rotterdam, The Netherlands.

The Rotterdam Study is supported by the Erasmus Medical Center and Erasmus University Rotterdam, the Netherlands Organization for Scientific Research (NWO), the Netherlands Organization for Health Research and Development (ZonMw), the Research Institute for Diseases in the Elderly (RIDE), the Ministry of Education, Culture and Science, the Ministry of Health, Welfare and Sports, the European Commission (DG XII), and the Municipality of Rotterdam. Additional funding for the work presented in this thesis was provided by ZonMw grant 4200.0019.

The contributions of the participants , general practitioners and pharmacists of the Ommoord district to the Rotterdam Study are gratefully acknowledged.

Financial support for the publication of this thesis was kindly provided by the Department of Epidemiology of the Erasmus MC, the Parnassia Bavo Groep, The Dutch Society for Sleep-Wake Research (NSWO), and Servier Nederland Farma B.V.

Cover design: Joris van den Ende, Amsterdam
Lay-out and printing: Optima Grafische Communicatie, Rotterdam

ISBN: 978-90-8559-422-2

Sleep in Later Life. A Population-based Approach

Slaap op hogere leeftijd. Een onderzoek in de algemene bevolking

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de rector magnificus

prof.dr. S.W.J. Lamberts

en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op
donderdag 4 december 2008 om 11.00 uur

door

Julia Fabienne van den Berg

geboren te Hoofddorp

PROMOTIECOMMISSIE

Promotor:

Prof.dr. A. Hofman

Overige leden:

Prof.dr. J.C.M. Witteman
Prof.dr. G.T.J. van der Horst
Prof.dr. E. Van Cauter

Copromotor(en):

Dr. H.W. Tiemeier
Dr. A. Knuistingh Neven

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Introduction

INTRODUCTION

Why do we sleep? How much sleep do we need? What happens if we do not sleep as much as we need, or indeed if we sleep too much?

These questions have intrigued researchers for decades. Studies in rats have shown that sleep deprivation causes several physical changes, including increased food intake, weight loss, increased energy expenditure, decreased body temperature, and, after approximately two weeks, death. Although the significance of this syndrome for the function of sleep is not entirely clear, the main mechanism eventually leading to death appears to be that the rat's brain loses the power to regulate body temperature.[1]

The dramatic physical effects of sleep deprivation in rats and other small mammals have not been demonstrated in humans. Experiments in humans showed that the most prominent effects of prolonged sleep deprivation are apparent in the executive functions of the frontal lobe of the brain, including decreased vigilance, concentration, and reaction speed. Sleep deprivation also affects mood and increases irritability, and in some people, it may cause distorted perception and even hallucinations.[2] In addition, laboratory studies have shown that sleep restriction also leads to an altered glucose metabolism and to lower circulating levels of leptin and higher levels of ghrelin. Leptin is a hormone that decreases appetite, while ghrelin stimulates it; therefore, the hormonal changes that result from sleep deprivation cause an upregulation of appetite.[3] In addition to these experiments, epidemiological studies have shown that the amount of sleep a person usually obtains may have long-term effects on their health. In 1964, Hammond investigated a large number of health-related variables and their associations with mortality in a study of 1,064,004 persons.[4] Self-reported sleep duration was one of the variables recorded; Hammond reported that men sleeping about 7 hours per night had lower death rates than men who slept either more or less than this. This finding has often been replicated afterwards, although the precise mechanism, or mechanisms, behind this U-shaped association of habitual sleep duration with mortality is still under investigation.

The objective of this thesis was twofold. Firstly, its aim was to investigate methods of assessing habitual sleep in population-based studies. Its second aim was to gain insight into the relationship of sleep duration with both cardiovascular risk factors and psychiatric disorders. The research described in this thesis was conducted within the setting of the Rotterdam Study, a large prospective cohort study of community-dwelling inhabitants of a district of Rotterdam, aged 55 and over. The Rotterdam Study has been designed to investigate the occurrence of chronic diseases in the elderly, and the risk factors associated with these diseases.

Measuring habitual sleep patterns on a population level is not straightforward. In large studies, mostly self-report measures of sleep parameters are used, varying from one question in a telephone survey to elaborate sleep diaries. However, self-reported measures of sleep can be distorted by matters of perception. Particularly in insomniacs, misperception

of sleep duration is common.[5] This becomes clear when self-report measures are compared with objective measurements. The most accurate method to distinguish sleep from waking is polysomnography. This is an invasive and time-consuming method; and therefore is not feasible in large studies. An alternative method is actigraphy, a method that infers sleep and wakefulness from the presence or absence of arm movement. Actigraphy is not without its own shortcomings, but it is a reasonable alternative for polysomnography in large studies. In part I of this thesis, the focus is on the methodological problems associated with measuring sleep patterns in a population-based study. In chapter 1, a study is described in which we compared actigraphy with sleep diaries. We assessed sleep duration with both methods, and calculated the level of disagreement between the two. Moreover, we studied a number of characteristics of the participants that were related to this disagreement. In chapter 2, another type of differences is discussed: sleep parameters in men are compared with sleep parameters in women. Again, both actigraphic and self-report measures are used.

In an effort to explain the U-shaped association between sleep duration and mortality, recent epidemiological studies have focused on the relationship between sleep duration and cardiovascular disease. Cardiovascular disease is the leading cause of death for adult men and women in developed countries.[6] Obesity is a major cardiovascular risk factor. Since a link between sleep and appetite has been established in laboratory experiments, epidemiological investigations of the association between sleep duration and obesity are a matter of course. Part II of the thesis is devoted to the relationships between sleep and cardiovascular risk factors. Firstly, in chapter 3, a study on the association of sleep duration with obesity is described. Chapter 4 concentrates on the possible relationship of sleep duration with hypertension. Sleep duration and other sleep parameters are studied in relation to cholesterol levels in chapter 5.

Part III of this thesis consists of one chapter, chapter 6, in which sleep duration and other sleep parameters are examined in persons with depression and anxiety disorders. Disturbed sleep, which often results in a shorter than average sleep duration, is an important feature of several psychiatric disorders. This implies that the study of sleep and health must take this into account, and may even need to record symptoms of e.g. depression that do not exceed the threshold above which a full-blown disorder can be diagnosed. To conclude, in chapter 7, the main findings, and suggestions for further research, are discussed in the context of current knowledge.

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Part I.

Measuring sleep. Methodology and gender differences

Chapter 1.

Disagreement between subjective and actigraphic measures of sleep duration

SUMMARY

Sleep duration is an important concept in epidemiological studies. It characterizes a night's sleep or a person's sleep pattern, and is associated with numerous health outcomes. In most large studies, sleep duration is assessed with questionnaires or sleep diaries. As an alternative, actigraphy may be used, as it objectively measures sleep parameters and is feasible in large studies. However, actigraphy and sleep diaries may not measure exactly the same phenomenon. Our study aims to determine disagreement between actigraphic and diary estimates of sleep duration, and to investigate possible determinants of this disagreement. This investigation was embedded in the population-based Rotterdam Study. The study population consisted of 969 community-dwelling participants aged 57 to 97 years. Participants wore an actigraph and kept a sleep diary for, on average, six consecutive nights. Both measures were used to determine Total Sleep Time (TST). In 34 % of the participants, the estimated TST in the sleep diaries deviated more than 1 h from actigraphically measured TST. The level of disagreement between diary and actigraphic measures decreased with subjective and actigraphic measures of sleep quality, and increased with male gender, poor cognitive function, and functional disability. Actigraphically measured poor sleep was often accompanied by longer subjective estimates of TST, whereas subjectively poor sleepers tended to report shorter TST in their diaries than was measured with actigraphy. We recommend, whenever possible, to use multiple measures of sleep duration, to perform analyses with both, and to examine the consistency of the results over assessment methods.

INTRODUCTION

Sleep duration is a core concept in sleep medicine and sleep research, and in epidemiological studies. Total sleep time (TST) is one of the most important parameters used to characterize a night's sleep or a person's sleep pattern. Recent research has consistently demonstrated that sleep duration can have important effects on health. Observational studies have found that both reduced sleep and prolonged sleep are associated with an increased risk for mortality.[1-3] The mechanisms behind this U-shaped association are as yet unclear, and several possible pathways have been investigated recently.[4-7] However, in population-based epidemiological studies, data on average sleep duration are typically obtained by subjective measures only. It has been assumed that diary data better represent actual times spent asleep than retrospective questionnaire data[8]; however, diary data are still subject to the influence of perception. As perceived sleep duration may differ from objectively measured sleep duration under the influence of personal characteristics, such as cognitive deficits, the use of only self-report measures may introduce bias.

Since polysomnography is an expensive and intrusive approach, and its ecological validity is sometimes questionable,[9] other objective assessment methods are needed in large studies. Actigraphy is a method that infers wakefulness and sleep from the presence or absence of arm movement. In normal sleepers, agreement coefficients between polysomnography and actigraphy of 0.90 and above have been reported.[10] However, although actigraphy is objective and devoid of the subjective biases that influence sleep diary estimation, it is not without its own shortcomings with regard to sleep time estimation. The accuracy of actigraphy to detect sleep and wakefulness, when compared with polysomnography, depended on sleep efficiency in older adults with primary insomnia.[11] However, actigraphy data were more accurate than sleep diary data when compared with polysomnography in insomniacs.[9]

A number of factors may influence the measurement or perception of sleep duration. Vanable et al.[12] compared subjective estimations of sleep duration to polysomnographic measures in a study of patients with different subtypes of insomnia. Depending on insomnia subtype, sleep quality and current psychopathology, patients underestimated or overestimated TST.

Sleep medication may also influence sleep time perception. Depression has been studied previously as determinant of discrepancies between subjective and objective measures of sleep duration, but the results are contradictory, both with regard to the level and the direction of disagreement.[13-15] Impaired cognitive function may decrease the accuracy of sleep time perceptions as cognitive functions, such as memory and executive function, are involved in the estimation of time.[16, 17] Several studies of subjective and objective sleep measures have been performed in patients with chronic illnesses, e.g. chronic fatigue syndrome,[18] Parkinson's disease,[19] cystic fibrosis,[20] and fibromyalgia.[21] All of these studies suggested that

congruence between subjective and objective measures of sleep is different in patients than in healthy controls.

To our knowledge, disagreement between actigraphic and self-report measures of sleep duration has not been investigated in a large normal population. The aim of the current study was to describe this disagreement in a large community-dwelling population of elderly persons, and to examine sleep parameters, sleep medication use, depressive symptoms, cognitive function and physical health as possible determinants of this disagreement.

METHODS

Study population

This study is part of the Rotterdam Study, a prospective population-based cohort study that started in 1990. Its overall aim is to investigate the incidence of, and risk factors for chronic disabling diseases. A more detailed description of the Rotterdam Study and the collection of data has been given elsewhere.[22] The Medical Ethics Committee of the Erasmus University Rotterdam approved the Rotterdam Study and written informed consent was obtained from all participants.

In 2000, the study population was extended with a second cohort of people aged 55 years and over. From May 2004 to December 2005, these participants underwent their second examination, consisting of a home interview and two visits to the research center. From December 2004 onward, 1515 persons were asked to participate in the actigraphy study, 1076 (71.0%) of whom agreed. In this study, we only included subjects who contributed at least 3 valid nights of actigraphy. A night's data were considered invalid if the actigraph malfunctioned, if the participant discontinued wearing of the actigraph, if diary estimates of TST were missing, or if discrepancies of more than 1 h existed between the actigraphy and sleep diary measures of bed time or get up time, indicating that the participant did not carefully follow the instructions. A total of 969 subjects fulfilled the criterion of 3 valid nights; 107 were excluded. Together they contributed 6004 valid nights: on average 6.2 (SD: 1.1) nights per participant.

Actigraphy and sleep diary

We used the Actiwatch model AW4 (Cambridge Neurotechnology Ltd), an actigraph that can be worn like a watch and is equipped with an event marker button. Participants were instructed to wear the actigraph over a period of five to seven consecutive days and nights, on the non-dominant wrist, while continuing their normal activities and sleep-wake rhythms in their home environment. During the actigraphy study period, participants kept a sleep diary, in which they indicated, among other things, their estimated TST of the night before. Participants were asked to press the event marker button on the actigraph each night when

they began trying to fall asleep and again when they got out of bed each morning. To calculate sleep parameters from the raw actigraphy data, we used the Actiwatch algorithm that has been validated against polysomnography by Kushida et al.[23] With this algorithm, a score is calculated for each 30-s epoch, taking into account the weighted value of previous and following epochs. We used a threshold of 20 to distinguish sleep from waking, as this high sensitivity setting yielded the best agreement with polysomnography with regard to TST in Kushida et al.'s validation study.[23]

We applied the following rules to the data:

- Bed time and get up time were derived from the event marker buttons, and if these data were not present for a certain night, we derived them from the sleep diary, to determine Sleep Start and Sleep End.
- Sleep Start was defined using the first immobile period of at least 10 min after bed time with no more than one 30-s epoch of movement. The midpoint of that period was classified as Sleep Start.
- To define Sleep End, we identified the last period of at least 10 minutes of immobility before get up time that had no more than one epoch of movement. The last epoch of this period was classified as Sleep End.
- TST is the time between Sleep Start and Sleep End, minus the time classified as awake by the algorithm.
- Sleep onset latency (SOL) is the time between bed time and Sleep Start.
- Sleep efficiency is 100% * TST / the time between bed time and get up time.

The definitions of Sleep Start and Sleep End were derived from the Actiwatch manual and are equal to those used by the Actiwatch software.[24]

Assessment of other determinants

Subjective sleep quality was assessed with the Pittsburgh Sleep Quality Index (PSQI).[25] The PSQI is a self-rating questionnaire which measures sleep quality and disturbance retrospectively over a 1-month period, resulting in a global score between 0 and 21, with higher scores indicating poorer sleep quality. The use of sleep medication was defined as at least one night of reported sleep medication use in the sleep diary. Depressive symptoms were assessed with the Center for Epidemiologic Studies Depression scale.[26] The CES-D is a self-report scale with 20 items, with a maximum score of 60. Scores of 16 or greater on the CES-D are traditionally interpreted as suggestive of clinically significant depression.[27] Cognitive function was assessed using the Mini Mental State Examination.[28] Scores on this test range from 0 to 30, with higher scores indicating a better cognitive performance. We used the Stanford Health Assessment Questionnaire[29] to evaluate functional disability, a subjective measure of physical health with emphasis on the ability to perform daily activities in five different domains. Larger scores on this questionnaire represent more disability. All questionnaires were administered

as part of the home interview. Persons who reported having visited a general practitioner or other clinician with complaints of joint pain were classified as having joint pain.

Statistical analysis

There are several possible ways to handle the concept '(dis)agreement between two measurement methods' in statistical analyses. For example, a number of studies used a correlation coefficient to describe the agreement between self-reported and objectively measured sleep duration.[15, 30, 31] However, a correlation coefficient is not sufficiently informative with regard to agreement, since a correlation is only a measure of the extent to which two variables are linearly related, regardless of their measurement scales.[32]

As a consequence, strong disagreement can still be present in spite of a high correlation between self-reported and measured sleep duration. Moreover, if averages over three to seven nights are used, as we did in our study, a correlation coefficient is even less informative. A final reason why the use of correlation coefficients may overestimate the level of agreement is that it fails to take into account the chance agreement due to the high base rate of sleep during the night.[33]

We devised two separate measures of disagreement between subjective and actigraphic sleep duration. First, the 'level of disagreement', expressed as the average of the absolute differences between night-by-night diary estimates of TST and actigraphically measured TST. Second, the 'direction of disagreement', expressed as the average of the normal differences. The 'direction of disagreement' signals whether an individual has a tendency to over- or underestimate TST in his diary when compared with the actigraphically measured TST: positive differences indicate that diary estimates are higher than actigraphic parameters, whereas negative differences reflect lower subjective than actigraphic values. This measure, the average of the normal differences, is not suitable as a general indicator of the level of disagreement, as positive and negative differences cancel out when the average is taken, hence the use of absolute differences for this purpose.

First, we examined the association of categories of actigraphic TST with categories of disagreement (diary < actigraphy, accordance, diary > actigraphy), with Pearson's chi-squared test.

Next, we studied whether age, gender, TST, bed time, get up time, sleep onset latency, sleep efficiency, subjective sleep quality, the use of sleep medication, depressive symptoms, cognitive function, functional disability and joint pain were determinants of disagreement. We included these determinants in two multiple linear regression analyses, with the level of disagreement (absolute differences) and the direction of disagreement (differences) between self-reported and actigraphic TST as dependent variables.

We adjusted all analyses for the covariates age, gender, actigraphic TST, depressive symptoms, cognitive function, functional disability and joint pain. We did not adjust for the other

sleep parameters because of potential multicollinearity and over-adjustment. All analyses were performed with SPSS version 11.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Table 1 shows the characteristics of the study population. The 969 participants of the study had a mean age of 68.5 years (SD: 6.9) and had a mean TST, as measured with actigraphy, of 6:31 h (SD: 0:50). On average, diary-assessed TST was 0:23 h (SD: 1:04) longer than actigraphically measured TST. This average difference was statistically significant at the $p < 0.001$ level (paired samples *t*-test).

A non-response analysis showed that those who visited the research centre but refused to participate in the actigraphy study (N = 439), were on average 2.5 years older than responders ($p < 0.001$) and were more likely to be female (32.2 % versus 25.1 %, $p = 0.002$). Refusal to participate was neither associated with average TST, as derived from the PSQI, nor with global PSQI score, but was often related to the unattractive appearance of the actigraph. Absence of the event marker signal at bed time or get up time was associated with cognitive function: those with > 2 missings had a 0.4 points lower MMSE score than those with ≤ 2 missings ($p = 0.02$).

Table 1. Characteristics of the study population, N = 969

Characteristic	Mean (SD) / N (%)
Age, years	68.5 (6.9)
Gender, female, N (%)	506 (52.2)
Actigraphic TST, h:min	6:31 (0:50)
Diary TST, h:min	6:54 (0:57)
Difference between Actigraphic and Diary TST, h:min	0:23 (1:04)
Actigraphic Bed Time, h:min	11:51 PM (0:49)
Actigraphic Get Up Time, h:min	8:10 AM (0:46)
Actigraphic Sleep Onset Latency, h:min	0:21 (0:14)
Actigraphic Sleep efficiency (%)	78.4 (7.4)
Subjective sleep quality, PSQI score	3.6 (3.5)
Use of sleep medication (≥ 1 night), N (%)	101 (10.4)
Depressive symptoms, CES-D score	5.0 (6.6)
Cognitive function (MMSE)	27.7 (2.1)
Functional disability, HAQ score	1.41 (0.47)
Joint pain, N (%)	412 (42.5)

Data are presented as mean (SD), unless indicated otherwise.
TST: Total Sleep Time, PSQI: Pittsburgh Sleep Quality Index, CES-D: Center for Epidemiologic Studies Depression scale, MMSE: Mini Mental State Examination, HAQ: Health Assessment Questionnaire

Table 2 shows the mean diary TST per category of actigraphically measured TST. It also shows the frequency of negative differences, accordance, and positive differences between diary and actigraphic TST. One third (34%) of the participants reported in their diaries an average TST that differed more than 1 h from their average actigraphically measured TST. Table 2 also shows that diary estimates were more often higher than actigraphy estimates of TST. In addition, it clearly shows that discrepancies were related to the actigraphically measured TST itself ($p < 0.001$). A particularly striking result is that the majority of participants who slept less than 5 h per night according to actigraphy, estimated a markedly longer TST: their average self-reported TST was more than 6 h. The best agreement between the two measurement methods was found in the category of those who slept 7-8 h per night as measured with actigraphy.

Table 2. Mean diary TST, and frequency of positive and negative differences, per category of actigraphically measured TST, N = 969

Actigraphic TST, h	N	Mean Diary TST (SD), h:min	Diary < Actigraphy[1], N (%)	Accordance[2], N (%)	Diary > Actigraphy[3], N (%)
Total	969	6:54 (0:57)	82 (9)	638 (66)	249 (26)
<5	45	6:16 (0:57)	0 (0)	14 (31)	31 (69)
5- <6	204	6:33 (0:56)	4 (2)	105 (52)	95 (47)
6- <7	446	6:52 (0:53	30 (7)	313 (70)	103 (23)
7- <8	237	7:14 (0:50)	36 (15)	184 (78)	17 (7)
8 - >	37	7:45 (1:19)	12 (32)	22 (60)	3 (8)
			Pearson's $\chi^2 = 179.069$, df = 8, $p < 0.001$		

[1]average difference between diary and actigraphic TST of < -1 hour per night
[2] average difference between diary and actigraphic TST between -1 and +1 hour per night
[3] average difference between diary and actigraphic TST of > 1 hour per night
TST: Total sleep time

Table 3 shows the results of the regression analyses with the level of disagreement, i.e. the average absolute differences between actigraphic and diary TST, as the dependent variable. A poorer sleep quality was consistently associated with larger absolute differences, i.e. a higher level of disagreement between the two methods. This was true for all measures of sleep quality in our study. Average absolute differences decreased with 13.3 min h^{-1} of actigraphic TST (95% CI: 10.7 to 16.0), increased with 24.3 min (95% CI: 14.6 to 33.9) per hour of SOL, and decreased with 2.60 (95% CI: 2.23 to 2.96) min per percent of sleep efficiency (all *p*-values < 0.001). A poorer subjective sleep quality (PSQI) also increased the level of disagreement between diary and actigraphic measures of TST ($\beta = 0.72$ (0.02 to 1.42)), as did the use of sleep medication ($\beta = 8.52$ (1.13 to 15.9)).

Table 3. Determinants of level of disagreement of TST estimates, N = 969

Characteristic	Absolute difference of TST Diary – actigraphy (min)		
	β	95% CI	*p*-value
Age	-0.15	-0.50, 0.20	0.41
Gender (female)	-5.13	-9.70, -0.56	0.03
Actigraphic TST (h)	-13.3	-16.0, -10.7	< 0.001
Actigraphic Bed Time (h)	-3.28	-6.37, -0.20	0.04
Actigraphic Get Up Time (h)	11.8	8.85, 14.7	<0.001
Actigraphic SOL (h)	24.3	14.6, 33.9	< 0.001
Actigraphic Sleep efficiency (%)	-2.60	-2.96, -2.23	< 0.001
Subjective sleep quality (PSQI)	0.72	0.02, 1.42	0.04
Use of sleep medication (≥ 1 night)	8.52	1.13, 15.9	0.02
Depressive symptoms (CES-D)	0.13	-0.23, 0.49	0.49
Cognitive function (MMSE)	-2.03	-3.14, -0.91	< 0.001
Functional disability (HAQ)	7.90	2.21, 13.6	0.007
Joint pain (yes/no)	-2.10	-6.81, 2.61	0.38

Multivariate linear regression analyses. All were adjusted for age, gender, actigraphic TST, depressive symptoms, cognitive function, functional disability and joint pain.
TST: Total Sleep Time, SOL: Sleep Onset Latency, PSQI: Pittsburgh Sleep Quality Index, CES-D: Center for Epidemiologic Studies Depression scale, MMSE: Mini Mental State Examination, HAQ: Health Assessment Questionnaire.

An earlier bed time, later get up time, poor cognitive function, male gender and functional disability were also associated with a higher level of disagreement. All associations were adjusted for actigraphic TST and all other covariates except sleep parameters.

Determinants of the direction of disagreement are shown in Table 4. The normal arithmetic difference between self-reported and actigraphically measured TST was the dependent variable in these regression analyses. A negative difference, and thus also a negative regression coefficient, means that the diary estimate of TST was on average lower than the actigraphic TST.

Actigraphic measures of poor sleep quality, i.e. shorter TST, lower sleep efficiency and longer SOL, were all associated with positive differences, i.e. diary estimates of TST were higher than actigraphic estimates. However, participants with poor perceived sleep quality (PSQI) and those who used sleep medication showed shorter diary estimates of TST than their actigraphic measures.

Relative to non-depressed participants, those with depressive symptoms reported a lower TST than was actigraphically measured. A later get up time, poor cognitive functioning, male gender and a higher age were associated with positive differences, i.e. higher diary than actigraphy estimates.

Table 4. Determinants of direction of disagreement between subjective and actigraphic TST, N = 969

Characteristic	Difference of TST Diary – actigraphy (min)		
	β	95% CI	*p*-value
Age	-0.98	-1.50, -0.46	< 0.001
Gender (female)	-18.6	-25.5, -11.8	< 0.001
Actigraphic TST (h)	-32.2	-36.2, -28.2	< 0.001
Actigraphic Bed Time (h)	2.41	-2.35, 7.22	0.32
Actigraphic Get Up Time (h)	16.1	11.5, 20.7	< 0.001
Actigraphic SOL (h)	35.6	20.7, 50.6	< 0.001
Actigraphic Sleep efficiency (%)	-2.37	-2.79, -1.77	< 0.001
Subjective sleep quality (PSQI)	-7.12	-8.12, -6.13	< 0.001
Use of sleep medication (≥ 1 night)	-15.8	-27.2, -4.37	0.007
Depressive symptoms (CES-D)	-0.83	-1.36, -0.29	0.003
Cognitive function (MMSE)	-3.30	-4.96, -1.64	< 0.001
Functional disability (HAQ)	3.27	-5.26, 11.8	0.45
Joint pain (yes/no)	-2.22	-9.28, 4.85	0.54

Multivariate linear regression analyses. All were adjusted for age, gender, actigraphic TST, depressive symptoms, cognitive function, functional disability and joint pain.
TST: Total Sleep Time; SOL: Sleep Onset Latency; PSQI: Pittsburgh Sleep Quality Index; CES-D: Center for Epidemiologic Studies Depression scale; MMSE: Mini Mental State Examination, HAQ: Health Assessment Questionnaire.

DISCUSSION

In this population-based study of 969 community-dwelling elderly, we found that 34 % of participants did not estimate their sleep duration in a diary within a range of 1 h from their actigraphically measured TST. Poor sleep quality as measured by actigraphic and subjective measures was consistently associated with a high level of disagreement between assessment methods, albeit in opposite directions. Poor actigraphically measured sleep quality was often accompanied by longer subjective estimates of TST, whereas subjectively poor sleepers tended to report shorter TST in their diaries than was measured with actigraphy. Gender, age, bed time, get up time, depressive symptoms, cognitive function and functional disability were also associated with either level or direction of disagreement between subjective and actigraphic measures of TST, whereas joint pain was not.

Before we discuss our findings, some methodological comments have to be made. Actigraphy is not the gold standard for distinguishing sleep from waking. The results of the study may differ with different actigraphy devices or algorithms. The Actiwatch algorithm has only been validated in a study of sleep disordered patients[23]; the appropriateness of this algorithm in a normal population has not been tested. Unfortunately, within the limitations of the Rotterdam Study setting, we were not able to compare actigraphy and diary to polysomnography in a subsample. Agreement between actigraphy and polysomnography is high

in normal sleepers,[10, 34] but can be lower in persons with poor sleep quality,[11] as these persons tend to lie in bed motionless, but awake, for long time periods. In these participants, the actigraphy algorithm will overestimate sleep duration, compared with polysomnography. If these participants accurately estimate their true sleep duration in their sleep diaries, they would be misclassified as persons with negative differences between diary and actigraphic assessment of TST in our study. However, in our study, positive differences were much more common than negative differences: the average diary TST of the study population was longer than the average actigraphically measured TST. This is in accordance with previous literature; in the CARDIA study, mean self-reported sleep duration was on average almost an hour longer than actigraphically measured duration.[35] Tryon[36] noted that sleep scoring based on polysomnography is not a fully reliable process either. There are substantial variations between and within scorers, and actigraphy cannot be expected to be more accurate than the scored polysomnography itself. Another interesting point he makes is that sleep onset is a gradual rather than a discrete process, and that this may result in discrepancies between polysomnographic, actigraphic and perceived sleep parameters, as all of the three measures are sensitive to different phases of the sleep-onset process.[36] With these considerations in mind, multiple authors, including the American Academy of Sleep Medicine's Standards of Practice Committee, view actigraphy as a reliable method for assessing sleep-wake patterns in adults.[9, 34, 36-38]

Our study has several strengths. Numerous studies investigated assessment methods of sleep parameters in small, and often clinical, samples.[11, 15, 30, 39, 40] However, for research questions related to aetiology and prevalence, it is important to know how such measurement instruments behave in a normal population. To our knowledge, this is the first large population-based study on this subject. Moreover, our 969 participants contributed on average six nights each. This is important as, especially in insomniacs, night-to-night variability of the accuracy of perception, as well as variability of sleep parameters, can be large.[40, 41] By calculating averages over multiple nights, and by studying absolute differences, we took that variability into account. As all measurements were taken in the home environment, distortions of the normal sleep pattern, or of the perception of sleep, as a consequence of the laboratory setting, did not occur in our study.

Insomniacs, as a group, show a greater propensity than normal sleepers to underestimate TST.[40, 42] However, some studies identified a subgroup of insomniacs who substantially overestimated their sleep duration.[43, 44] Others suggest that insomniacs' sleep time perceptions are widely distributed across a broad continuum, ranging between gross underestimates and remarkable overestimates of actual sleep times, and that the accuracy and nature of sleep time perceptions may relate to the underlying type of sleep pathology.[12, 45, 46] Moreover, recent papers have suggested that the degree of departure between diary and polysomnography estimates of sleep time relates to high frequency activity in the EEG during NREM sleep.[47, 48] One implication of such findings is that such discrepancies do not reflect "misperception"

at all but rather convey some aspect of poor sleep quality that is not reflected by polysomnography sleep time, nor, most probably, by actigraphy. All these views taken together, it is probable that a poor subjective sleep quality, even when not fulfilling clinical criteria for insomnia, can somehow distort the assessment of sleep duration. Our study showed that, in a normal elderly population, persons with poor subjective sleep quality consistently tend to report shorter sleep durations than were actigraphically measured, whereas persons without sleep complaints generally report longer sleep durations. These results may reflect underestimation of sleep duration in those with sleep disturbance as well as overestimation of sleep duration by actigraphy, or both, in this subgroup. The 'underestimation' of sleep by the diary in persons with a high actigraphic sleep efficiency, which correlates with long actigraphic TST and short SOL, can be partly explained statistically. In these persons, substantial overestimation of TST is unlikely, as the maximum TST in the diary is limited by the time spent in bed.

The literature investigating the relationship between objective and subjective sleep parameters in depressed patients is limited and the results are inconsistent. Rotenberg et al.[13] found that depressed and healthy subjects had an almost identical percentage of correct estimations of sleep duration, compared with polysomnography. However, if the estimations were incorrect, the degree of misperception was larger in depressed patients than in healthy subjects. Armitage et al.[14] reported that subjects with major depressive disorders were more accurate in their estimations of TST and time in bed than normal controls. Tsuchiyama et al.[15] noted that some depressed patients underestimated sleep duration, while others overestimated sleep duration, but they did not compare the estimations with those of normal controls. In our study, the level of disagreement was not different in participants with or without depressive symptoms. However, in depressed participants, diary estimations of TST were on average shorter than actigraphic estimations, whereas non-depressed participants on average judged their TST to be longer than was actigraphically measured. There are two possible explanations for this phenomenon. First, depressed persons may estimate differently than non-depressed persons. This could be due to a pessimistic estimate of their TST, or it could be due to less overestimation, thus a more realistic estimate of TST compared with non-depressed persons. Second, depressed persons may have a different sleep pattern. They may have longer episodes of lying in bed still while awake than non-depressed persons, as a result of which actigraphic estimations of sleep duration in depressed persons are overestimations of the 'true' sleep duration. Either way, depressive symptoms would introduce considerable bias in population-based studies of sleep duration.

In view of the high prevalence of cognitive impairment in elderly persons, this phenomenon could also introduce substantial bias in studies of elderly persons. A poor cognitive function substantially increased disagreement between the two methods. The most likely explanation for this phenomenon is that both subjective measures and actigraphy are problematic in those with poor cognitive function. Perception in itself can be distorted, memory and calculation problems can interfere with accurate estimation of sleep time, and in an actigraphy

study, adequate use of the event marker buttons to signal bed time and get up time may be hampered, as happened in our study. Nevertheless, it is informative for future research that poor cognitive function results in substantially longer self-reported sleep durations than the sleep duration as measured with actigraphy.

Physical health is an important determinant of sleep quality, and possibly also of sleep perception. In a study of monozygotic twins who were discordant for chronic fatigue syndrome, chronic fatigue syndrome patients had worse subjective sleep than their co-twins despite little objective data supporting this discrepancy, suggesting they suffered from an element of paradoxical insomnia.[18] Happe et al.[19] stated that healthy elderly persons may better estimate their sleep than patients with chronic diseases, as subjective and objective sleep duration and sleep efficiency correlated in a control group, but not in a group of patients with Parkinson's disease. In our study, functional disability was associated with more disagreement between the two assessment methods, but not in any particular direction. Joint pain was not associated with any of the measures of disagreement.

The substantial discrepancies between self-reported and actigraphic sleep duration have important implications for epidemiological studies of consequences or correlates of sleep duration. Many studies of sleep duration use 1-h categories, e.g. 5-6, 6-7 h, etc. A difference of an hour or more between two assessment methods, occurring in 34% of persons in our normal study population, would thus result in allocation to different categories with another assessment method. This misclassification is not random, and depends on age, gender, subjective sleep quality, the use of sleep medication, depressive symptoms, poor cognitive function and functional disability. As these determinants are likely to be associated with many medical outcome measures, this phenomenon may bias the results of the study. Relying on one measure of sleep duration is more likely to cause spurious associations or obscure true associations. We recommend, whenever possible, to use multiple measures of sleep duration, to perform analyses with both, and to examine the consistency of the results over assessment methods.

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Chapter 2.

Gender differences in subjective and actigraphic sleep measures

SUMMARY

Objective: To investigate and explain gender differences in subjective and actigraphic sleep parameters in community-dwelling elderly persons.
Design: Cross-sectional study.
Setting: The study was embedded in the Rotterdam Study, a population-based study.
Participants: 956 participants aged 59-97.
Measurements and Results: Participants wore an actigraph and kept a sleep diary for on average six consecutive nights. Subjective sleep quality was assessed with the Pittsburgh Sleep Quality Index. Age-adjusted gender differences in sleep parameters were assessed with ANCOVAs. Women reported shorter total sleep time, and less favorable sleep onset latency, sleep efficiency and global sleep quality than men. When assessed with actigraphy, however, women were found to have longer and less fragmented sleep than men; only actigraphic sleep onset latency did not differ between men and women. Gender differences in self-reported sleep parameters were partly explained by depressive symptoms and sleep medication use, which are both more common in women and related to poor self-reported sleep quality. The shorter actigraphically measured sleep duration in men was partly explained by their higher alcohol consumption. However, none of the gender differences in self-reported or actigraphic sleep measures could be fully explained by adjustment for multiple covariates.
Conclusions: In an elderly population, women consistently report shorter and poorer sleep than men if assessed by diary or interview. In contrast, actigraphic sleep measures show either no gender differences or poorer sleep in men. These discrepancies are partly explained by covariates such as depressive symptoms and alcohol consumption.

INTRODUCTION

Epidemiologic studies have consistently shown that women have more sleep-related complaints and a higher risk of insomnia than men.[1-5] Zhang et al.[4] stated that the trend of female predisposition for insomnia was consistent across numerous studies and progressive across age. These gender differences are also pervasive in neuropsychiatric disorders such as depression, that are strongly related to disturbed sleep.[6] Explaining gender differences in sleep parameters might shed light on the etiology of sleep complaints.

However, when sleep parameters such as sleep duration are taken into account, findings are less consistent: some authors found that women reported longer total sleep time (TST) than men,[1, 3, 7] while others found no substantial gender differences in self-reported TST.[2, 8] Gender is not only related to self-report measures of sleep and sleep quality, but it is also an important determinant of objectively measured sleep parameters. Redline et al.[9] noted that gender explained the largest proportion of the variance in each sleep architecture measure they investigated. A meta-analysis of 65 studies that investigated sleep in convenience samples of healthy participants with objective measurement methods showed that women had a modestly longer TST but also a longer sleep onset latency (SOL) than men, and there was no difference in sleep efficiency (SE).[10]

Studies that investigated gender differences in objectively measured sleep parameters are rarely community-based. As a result of recruitment methods and inclusion criteria, study populations often represent a limited range of demographic and comorbid conditions, and the results may not be representative of the population. In addition, the use of polysomnography has some limitations; although it is the gold standard for distinguishing sleep from waking, the sensors attached to the participant may affect his or her usual bedtime, sleep latency and sleep hours, even when it is home based.[11] Therefore, the ecological validity of polysomnography studies is debatable.[12] Moreover, little effort is generally made in these studies to explain the differences, as commonly only few covariates are measured. One exception is a large community-based actigraphy study by Lauderdale et al.[11] They found longer sleep durations and a higher sleep efficiency in women than in men. However, their study did not include elderly persons, they did not investigate the effect of psychiatric disorders or sleep medication, and they did not present data of self-report measures.

We investigated gender differences in self-reported and objectively measured sleep parameters in a large study of community-dwelling elderly persons. In this study, we used wrist actigraphy, which is relatively unobtrusive and enabled the participants to stay in their natural environment and adhere to their normal sleep habits. Our study also examined the extent to which the observed gender differences in sleep patterns were attributable to a range of demographic, health- and sleep-related variables, as this is still poorly understood. We hypothesize that gender differences in sleep parameters are partly explained by differences in mental health, as depression and anxiety disorders are consistently found to be

more common in women and these disorders are strongly related to sleep disturbance.[6, 13-15] Demographic variables such as socioeconomic status, as well as physical health, have also been linked to subjective and objective sleep parameters[7, 11, 14, 16, 17]; these variables may also account for a share of the gender differences in sleep parameters. Another possibility is that the difference may be due to artifacts arising from measurement issues. In the present study, we thus relied on self-report as well as actigraphic measures.

METHODS

Study population

This study is embedded in the Rotterdam Study, a population-based cohort study aimed at assessing the occurrence of and risk factors for chronic diseases in the elderly.[18] In 1990, all of the inhabitants of a district of Rotterdam aged 55 years and over were invited. In 2000, the study population was extended with a second cohort of people aged 55 years and over. From May 2004 to December 2005, these participants underwent their second examination, consisting of a home interview and two visits to the research centre. From December 2004 onward, 1515 persons were asked to participate in the actigraphy study, 1076 (71.0%) of whom agreed. In the present study, we only included subjects who contributed at least 2 valid nights of actigraphy, at least 2 valid nights of diary data, and a valid score on the Pittsburgh Sleep Quality Index (PSQI).[19] A total of 956 subjects fulfilled these criteria. Together they contributed 5895 valid nights: on average 6.2 (SD = 1.1) nights per participant. The Medical Ethics Committee of the Erasmus University Rotterdam approved the Rotterdam Study and written informed consent was obtained from all of the participants.

Assessment of sleep parameters

Participants were instructed to wear an actigraph (Actiwatch model AW4, Cambridge Neurotechnology Ltd) over a period of five to seven consecutive days and nights. During the actigraphy study period, participants kept a sleep diary, in which they indicated, among other things, their estimated Total Sleep Time (TST) and Sleep Onset Latency (SOL) of the night before. Sleep Efficiency (SE) was defined as 100% * TST divided by the time spent in bed. The procedure and the algorithms that were used to calculate sleep parameters from the raw actigraphy data were based on the Actiwatch manual[20] and have been described in more detail previously.[21] Subjective sleep quality was assessed with the PSQI.[19] The PSQI is a self-rating questionnaire which measures sleep quality and disturbance retrospectively over a 1-month period, resulting in a global score between 0 and 21, with higher scores indicating poorer sleep quality.

Assessment of covariates

Age, marital status (married/other), educational attainment (low / intermediate / high), employment (paid job for ≥ 20 h per week), smoking, bereavement and joint pain were assessed in the home interview. Weight and height were measured and body mass index (BMI) was calculated. Sleep medication use, coffee and alcohol consumption during the study period were ascertained with the sleep diary. To operationalize the occurrence of probable sleep apnea, two questions from the Pittsburgh Sleep Quality Index were used. In line with Fogelholm et al.,[22] sleep apnea was considered probable in persons who reported 1) loud snoring at least 2 nights a week, with at least occasional respiratory pauses, or 2) respiratory pauses during sleep with a frequency of at least 1-2 nights weekly. Depressive symptoms were assessed with the Center for Epidemiologic Studies Depression scale.[23] The CES-D is a self-report scale with 20 items, with a maximum score of 60. Scores of 16 or greater on the CES-D are interpreted as suggestive of clinically significant depression. Cognitive function was assessed using the Mini Mental State Examination (MMSE).[24] Scores on this test range from 0 to 30, with higher scores indicating a better cognitive performance. We used a slightly adapted Munich version of the Composite International Diagnostic Interview (M-CIDI)[25] to assess the presence of anxiety disorders. The Stanford Health Assessment Questionnaire (HAQ)[26] was used to evaluate functional disability, a subjective measure of physical health with emphasis on the ability to perform daily activities in five different domains. Larger scores on this questionnaire represent more disability. All of the questionnaires were administered as part of the home interview.

Statistical analysis

We performed analyses of covariance to investigate gender differences in objective and subjective sleep parameters. All of the analyses were adjusted for age, as we were not interested in gender differences of sleep parameters that are due to the different age distribution between men and women. Three multivariate models were tested separately: one model with age and marital status, one model with age, employment and educational attainment, and one with age, sleep medication use, probable sleep apnea, depressive symptoms, functional disability and alcohol consumption. Finally, a fully adjusted model was tested which included all of the covariates above. Coffee consumption, anxiety disorders, joint pain, smoking, bereavement, cognitive function and BMI were also tested, but adjustment for these variables did not change any of the estimated gender differences by ≥ 10%, compared to the age-adjusted model. Means were imputed for missing values for alcohol consumption (N = 48), depressive symptoms (N = 3) and functional disability (N = 1). As educational attainment was missing for 23 participants, and probable sleep apnea for 219 participants, 'missing' categories were added for these variables. The high number of missing values for probable sleep apnea was due to the fact that a substantial proportion of participants slept alone in a bedroom and

were therefore not aware of their snoring or respiratory pauses. All of the analyses were performed with SPSS version 11.0 (SPSS Inc., Chicago, IL).

RESULTS

Table 1 presents the characteristics of the study population. The participants were on average 68.4 ± 6.8 years old (range 59 - 97) and 52.3 % were female. Of the total study population, 74.7 % were married and 6.3 % were employed. The average self-reported TST was 6.89 h ± 0.97, and the average actigraphically measured TST was 6.53 h ± 0.83.

Table 2 shows that women reported less and poorer sleep than men on all of the subjective measures. Women reported a 0.22 h (= 13.2 min) shorter TST, a 10.1 min longer SOL, and a 4.2 % lower SE than men. In addition, they had a 2 points higher global PSQI score. However, when measured with actigraphy, women slept 0.25 h (= 15 min) longer than men, had a

Table 1. Characteristics of the study population, N = 956

Characteristic	Men, N = 460	Women, N = 496	*p*-value[1]
Age, y, mean (SD)	68.3 (6.7)	68.4 (7.0)	0.88
Marital status (married), N (%)	397 (86.3)	317 (63.9)	< 0.001
Educational attainment			< 0.001
low, N (%)	63 (14.0)	124 (25.6)	
intermediate, N (%)	282 (62.8)	313 (64.7)	
high, N (%)	104 (23.2)	47 (9.7)	
Employment (paid job for ≥ 20 h per week), N (%)	47 (10.2)	13 (2.6)	< 0.001
Sleep medication use, at least 1 night, N (%)	28 (6.1)	74 (14.9)	< 0.001
Probable sleep apnea			< 0.001
yes, N (%)	81 (17.6)	14 (2.8)	
no, N (%)	304 (66.1)	338 (68.1)	
missing, N (%)	75 (16.3)	144 (29.0)	
Depressive symptoms, CES-D score, mean (SD)	4.0 (6.0)	5.9 (6.9)	< 0.001
Functional disability, HAQ score, mean (SD)	1.3 (0.4)	1.5 (0.5)	< 0.001
Alcohol, mean no. of drinks per day, mean (SD)	1.0 (1.1)	0.5 (0.8)	< 0.001
Coffee, mean no. of drinks per day, mean (SD)	1.1 (0.9)	0.9 (0.8)	< 0.001
Anxiety disorder, N (%)	19 (4.2)	56 (11.8)	< 0.001
Joint pain, N (%)	156 (33.9)	251 (50.6)	< 0.001
Smoking, N (%)	77 (16.7)	69 (13.9)	0.23
Bereavement, N (%)	57 (12.4)	117 (23.7)	< 0.001
Cognitive function, MMSE score, mean (SD)	27.9 (1.7)	27.8 (1.9)	0.59
Body mass index, kg/m^2, mean (SD)	27.7 (3.5)	28.1 (4.4)	0.14

Note: Except for probable sleep apnea, all of the percentages refer to the cases with information on this variable (valid percentage).

[1] Student's t-test for continuous variables, chi-squared test for categorical variables

CES-D: Center for Epidemiologic Studies Depression scale, HAQ: Health Assessment Questionnaire, MMSE: Mini Mental State Examination

Table 2. Gender differences in subjective and actigraphic sleep measures, N = 956

	Model 1: age-adjusted				Model 5: fully adjusted*			
	Men	Women	Sex difference		Men	Women	Sex difference	
	Estimated Mean	Estimated Mean	Male - female (95% CI)	*p*-value	Estimated Mean	Estimated Mean	Male - female (95% CI)	*p*-value
Subjective sleep parameters								
Diary TST (h)	7.01	6.79	0.22 (0.10, 0.35)	< 0.001	6.98	6.82	0.16 (0.02, 0.30)	0.03
Diary SOL (min)	20.1	30.2	-10.1 (-12.9, -7.3)	< 0.001	22.4	28.1	-5.7 (-8.8, -2.6)	< 0.001
Diary SE (%)	85.4	81.3	4.2 (2.9, 5.5)	< 0.001	84.5	82.1	2.4 (0.9, 3.9)	0.001
Global PSQI score	2.6	4.6	-2.0 (-2.5, -1.6)	< 0.001	2.98	4.26	-1.3 (-1.7, -0.8)	< 0.001
Objective sleep parameters								
Actigraphic TST (h)	6.40	6.65	-0.25 (-0.36, -0.15)	< 0.001	6.42	6.63	-0.21 (-0.33, -0.09)	0.001
Actigraphic SOL (min)	20.8	22.5	-1.6 (-3.4, 0.2)	0.08	21.9	21.5	0.4 (-1.7, 2.4)	0.73
Actigraphic SE (%)	77.8	79.0	-1.2 (-2.1, -0.2)	0.01	77.6	79.2	-1.6 (-2.6, -0.5)	0.004
Fragmentation index	7.2	6.0	1.2 (0.8, 1.5)	< 0.001	7.3	6.0	1.3 (0.9, 1.7)	< 0.001

Each row represents a single ANCOVA analysis.

*Adjusted for age, marital status, employment, educational attainment, sleep medication use, probable sleep apnea, depressive symptoms, functional disability and alcohol consumption.

TST: Total Sleep Time, SOL: Sleep Onset Latency, SE: Sleep Efficiency, PSQI: Pittsburgh Sleep Quality Index

Table 3. Explaining gender differences in subjective and actigraphic sleep parameters, N = 956

	Gender difference: Male - female (95% CI)				
	Model 1: age-adjusted	Model 2: marital status	Model 3: education and employment	Model 4: physical and mental health	Model 5: fully adjusted
Subjective sleep parameters					
Diary TST (h)	0.22 (0.10, 0.35)***	0.18 (0.05, 0.31)**	0.26 (0.14, 0.39)***	0.14 (0.01, 0.28)*	0.16 (0.02, 0.30)*
Diary SOL (min)	-10.1 (-12.9, -7.3)***	-9.7 (-12.6, -6.8)***	-10.3 (-13.1, -7.4)***	-5.8 (-8.7, -2.8)***	-5.7 (-8.8, -2.6)***
Diary SE (%)	4.2 (2.9, 5.5)***	3.8 (2.5, 5.2) ***	4.2 (2.9, 5.6)***	2.6 (1.2, 4.0)***	2.4 (0.9, 3.9)**
Global PSQI score	-2.0 (-2.5, -1.6)***	-2.0 (-2.4, -1.5)***	-2.0 (-2.4, -1.5)***	-1.3 (-1.7, -0.8)***	-1.3 (-1.7, -0.8)***
Objective sleep parameters					
Actigraphic TST (h)	-0.25 (-0.36, -0.15)***	-0.29 (-0.40, -0.18)***	-0.22 (-0.32, -0.11)***	-0.23 (-0.34, -0.11)***	-0.21 (-0.33, -0.09)**
Actigraphic SOL (min)	-1.6 (-3.4, 0.2)	-1.0 (-2.8, 0.9)	-1.6 (-3.4, 0.3)	-0.1 (-2.0, 1.9)	0.4 (-1.7, 2.4)
Actigraphic SE (%)	-1.2 (-2.1, -0.2)*	-1.4 (-2.4, -0.5)**	-1.1 (-2.0, -0.1)*	-1.5 (-2.5, -4.6)**	-1.6 (-2.6, -0.5)**
Fragmentation index	1.2 (0.8, 1.5)***	1.2 (0.8, 1.5)***	1.2 (0.8, 1.5)***	1.3 (0.9, 1.6)***	1.3 (0.9, 1.7)***

Each row represents a single ANCOVA analysis.
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$
Model 1: age-adjusted
Model 2: adjusted for age and marital status
Model 3: adjusted for age, educational attainment and employment
Model 4: adjusted for age, sleep medication use, probable sleep apnea, depressive symptoms, functional disability and alcohol consumption
Model 5: Adjusted for age, marital status, educational attainment, employment, sleep medication use, probable sleep apnea, depressive symptoms, functional disability and alcohol consumption
TST: Total Sleep Time, SOL: Sleep Onset Latency, SE: Sleep Efficiency, PSQI: Pittsburgh Sleep Quality Index

1.2 % higher SE and a lower fragmentation index, indicating less fragmented sleep. Only actigraphically measured SOL did not differ significantly between men and women.

All of the differences, in self-reported as well as actigraphic measures, remained significant after adjustment for age, marital status, employment, educational attainment, sleep medication use, probable sleep apnea, depressive symptoms, functional disability and alcohol consumption (Table 2). However, the gender differences in self-reported sleep parameters were substantially attenuated after this adjustment. Table 2 also shows that the average discrepancy between self-reported and actigraphic TST is larger in men (7.01 - 6.40 = 0.61 h) than in women (6.79 - 6.65 = 0.14 h).

Table 3 presents three additional models with subsets of covariates, to clarify the effect of each of the adjustments. A substantial proportion of the gender differences in self-reported sleep parameters was explained by adjustment for physical and mental health. This was mainly due to adjustment for depressive symptoms and the use of sleep medication. Both were more common in women, and were associated with shorter self-reported TST and poorer self-reported sleep quality (higher SOL, lower SE and higher PSQI score). Marital status also explained the differences between men and women in some degree. Men were more often married than women, and being married was related to more and better sleep. Adjustment for education and employment did not explain gender differences in self-reported measures, but in contrast, it increased gender differences in self-reported TST by from 0.22 h to 0.26 h (i.e. by 2.4 min). Men were more often employed than women, and employment was associated with reporting shorter TST.

With regard to actigraphic measures, alcohol consumption was the strongest explanatory factor for the gender differences that we found. Adjustment for only alcohol consumption reduced the shorter actigraphic TST in men by 2.6 min (from -0.25 (95% CI -0.36 to -0.15) to -0.21 (-0.32, -0.11), in comparison to the age-adjusted model. Men consumed twice as much alcohol as women and alcohol consumption was related to shorter actigraphic TST. Finally, employment status explained part of the gender difference in actigraphic TST, as men were more likely to be employed and employment was related to shorter actigraphic TST.

For actigraphic SE and fragmentation index, the gender differences were not attenuated in the multivariate-adjusted model. Rather, if anything, the differences were larger.

DISCUSSION

This study demonstrates that, in a normal elderly population, actigraphically measured sleep is better in women, while - as is well known - women report less and poorer sleep than men. The gender differences in subjective sleep parameters were attenuated after adjustment for marital status, the use of sleep medication and depressive symptoms and other covariates, but all of the differences remained significant. Gender differences in actigraphic sleep pa-

rameters were only marginally explained by adjustment for covariates, although differences in alcohol consumption accounted for a part of the gender differences in actigraphic TST and SE.

Before we discuss these findings, some methodological comments have to be made. First, a selection effect may have occurred due to nonparticipation. Women were less likely than men to participate in the actigraphy study. However, it is unlikely that this has resulted in substantial bias, because participation in the actigraphy study was neither associated with global PSQI score, nor with self-reported TST in the home interview. Second, actigraphy is not the gold standard for distinguishing sleep from waking. The results of the study may differ with different actigraphy devices or algorithms. The Actiwatch algorithm has only been validated in a study of sleep-disordered patients[27]; the appropriateness of this algorithm in a normal population has not been tested. Agreement between actigraphy and polysomnography is high in normal sleepers,[28] but can be lower in persons with poor sleep quality,[29] since these persons tend to lie in bed motionless, but awake, for long time periods. In these participants the actigraphy algorithm will overestimate sleep duration, compared to polysomnography. Nevertheless, multiple authors, including the American Academy of Sleep Medicine's Standards of Practice Committee, conclude that actigraphy is a reliable method for assessing sleep-wake patterns in adults.[12, 28, 30] Strengths of the present study include its population-based nature, its large size, the availability of multiple nights of actigraphic measurements, and assessment of numerous covariates. An important advantage of actigraphy over polysomnography is that the participants of our study were able to continue their normal sleep and activity habits, as a result of which the measured sleep parameters are probably representative of habitual sleep.

This study confirmed earlier studies that showed that self-reported sleep quality was poorer in women.[1-3, 5] The shorter self-reported TST that we found is less commonly noted in previous literature.[1, 3, 7] We also found - in line with earlier studies - that women had longer actigraphically measured sleep duration and a higher sleep efficiency than men. Lauderdale et al.[11] studied the combined effect of gender and race on sleep parameters measured with 3 nights of actigraphy in a population-based study of 669 participants, and found that mean sleep duration varied by race-gender group, ranging from 6.7 hours for White women to 5.1 hours for Black men. They very elaborately adjusted for a wide range of socio-economic, demographic and lifestyle variables. However, they did not adjust for psychiatric disorders or the use of sleep medication, which may be important in explaining (race-) gender differences in sleep. In addition, they did not show data for subjective measures, although these substantially differed from their actigraphy measurements. Longer sleep in women had been observed earlier by Jean-Louis et al.,[31] in a small population-based study with actigraphic sleep parameters. However, in this study no attempt was made to explain the differences by adjusting for covariates other than age and work status. In a meta-analysis of polysomnography studies, which are mostly performed in clinical convenience samples, Ohayon et al.

confirmed a modestly higher mean TST in women than in men, but they did not find gender differences in SE.[10]

We investigated whether the gender differences that we found were explained by demographic factors such as marital status, employment or educational attainment, by sleep-related factors such as sleep medication use and probable sleep apnea, or by depressive symptoms, functional disability or alcohol consumption. Particularly the gender differences in self-reported sleep parameters were to some extent explained by adjustment for these covariates, although none of the differences was fully accounted for. The most important covariates explaining gender differences in self-reported sleep parameters were marital status, the use of sleep medication and depressive symptoms. In our study, men were more likely to be married than women, which is to be expected at this age, and sleep medication use and depressive symptoms were more common in women. Apparently, not being married, using sleep medication and depressive symptoms are related to reporting relatively less sleep and poorer sleep quality. The relationship of marital status with self-reported sleep is not explained by bereavement-related problems, as bereavement was not related to any of the gender differences in sleep parameters. Sleep medication use is related to complaints about poor sleep and more common in women. The relationship between depressive symptoms and sleep complaints has also been described. Longitudinal studies have shown that the association of depression with poor sleep quality is bi-directional: on the one hand, depression strongly increases the risk of poor sleep quality, and on the other hand, poor sleep quality is a predictor for future depressive episodes.[13, 15, 32] Epidemiological studies estimate that complaints of poor sleep quality are observed in 40% to 90% of subjects with diagnosed depression.[32, 33] In addition, it has been suggested that women are more likely than men to express emotional distress and report somatic symptoms in general.[4, 8] This reporting bias may play a role in both the higher prevalence of self-reported depressive symptoms in women as in the poorer self-reported sleep quality. Nevertheless, depressive symptoms did not fully explain gender differences in subjective sleep parameters. This is in line with the findings of Zhang et al.[4] and Voderholzer et al.,[34] who showed that gender differences in the prevalence of insomnia persisted after the underlying psychiatric disorders had been taken into account.

Gender differences in self-reported sleep duration were increased by adjustment for educational attainment and employment. Men were more likely than women to be employed and have a higher educational level. Being employed was related to shorter self-reported TST as well as actigraphic TST, therefore adjustment for employment explained part of the shorter actigraphic TST in men, but it increased the gender difference in self-reported TST (longer TST in men). Ursin et al.[7] found that gender differences in sleep duration were smaller in persons with a higher education and family income. Work status has also been taken into account by Jean-Louis et al.[31]: in their study, it explained gender differences in the amount of exposure to light, but not in sleep parameters.

Other than employment, only alcohol consumption, which was almost twice as high in men, explained a part of the gender differences in actigraphically measured TST and SE. Alcohol affects physiological processes that occur during sleep, especially at higher doses.[35] This may be detectable by actigraphy if it also affects the frequency or intensity of movement during sleep.

Adjustment for marital status, functional disability, sleep medication use and depressive symptoms increased gender differences in actigraphic SE. This suggests that not being married, functional disability, sleep medication use and depressive symptoms, which are all more prevalent in women, are related to decreased actigraphic SE, i.e. to objectively measured poor sleep quality.

We were not able to explain all of the gender differences in sleep parameters, therefore other mechanisms must explain why women sleep longer and better than men when sleep is measured with actigraphy, and why they nevertheless report less and poorer sleep than men. We propose a few biological, psychological and methodological hypotheses that may be addressed in future research.

Women may need more sleep than men, and therefore the same amount of sleep may be satisfactory for men but not for women. This would offer a partial explanation of the gender differences in both self-reported and objective sleep measures. However, a higher self-reported sleep need in women has been demonstrated by Lindberg et al.[1] only in subjects aged 20-45, and by Broman et al.,[36] also in younger persons. In this age group, hormonal differences may underlie a higher sleep need in women. Likewise, gender differences in circadian rhythms - morningness versus eveningness - are only apparent before the age of menopause.[37] Moreover, if differences in sleep need were to explain the gender differences that we found, the question arises why women do not simply adapt their sleep times to their needs. It could be speculated that this discrepancy between sleep duration and sleep need is worse in married women, as they may adapt timing of sleep to their husbands. However, this is unlikely, as married women did not sleep worse or less than unmarried women in our study.

Both Groeger et al.[8] and Zhang et al.[4] hypothesized that the gender difference in reporting symptoms, which we discussed above, might be related to the greater bodily vigilance and awareness among women. If this is true, and if this also implies that women's perceptions of sleep are more realistic than men's, gender differences in self-reported sleep parameters may also result from an increased likelihood of overestimation of sleep, or the perception of wakefulness as sleep, in men. As can be derived from Table 2, the average discrepancy between self-reported and actigraphic TST is indeed larger in men than in women, which supports this hypothesis. However, it could be argued that the absolute values of actigraphically measured sleep parameters may differ from the "true" values of the sleep parameters. In that case, another possible explanation for the shorter self-reported TST in women arises:

women - more than men - may show a tendency to perceive sleep as wakefulness and thus underestimate their sleep duration. This phenomenon is often seen in insomniacs.[38, 39] We did not exclude persons who suffered from insomnia, which is more frequent in women.[4] However, matters of perception and reporting still do not offer an explanation for discrepancies in actigraphic sleep measures.

Finally, gender differences may also result from a methodological issue. Actigraphy measures limb movement. It is possible that there are gender differences in the relationship between sleep and movement. For example, limb movement might be more frequent or more intense in sleeping men than in sleeping women, and women might lie quietly awake more often than men. In this case, the differences in 'true' sleep may be smaller than our study indicates. Although Van Hilten et al.[40] stated that the mean duration of nocturnal immobility periods was higher in females than males, there is no indication that the validity of actigraphic measurement, i.e. the relationship between movement and sleep, differs between men and women.

To conclude, in a normal elderly population, women consistently report shorter and poorer sleep than men. When actigraphic measurements are considered, women show more and better sleep than men. In other words, gender differences in sleep parameters depend on what is measured: either perceived sleep or measured sleep. Gender differences in sleep parameters in the elderly are partly, but not fully, explained by covariates that are related to both poor sleep and gender, such as depressive symptoms and alcohol consumption. Other mechanisms underlying these discrepancies remain to be elucidated.

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Part II.

Sleep and cardiovascular risk factors

Chapter 3.

Actigraphic sleep duration and fragmentation are related to obesity in the elderly

SUMMARY

Objective: The epidemiological evidence for the association between sleep duration and obesity in the elderly is inconsistent and has not been investigated with objective measures. Furthermore, the role of sleep fragmentation in this relationship is unknown. Our aim was to investigate the association of sleep measures with body mass index (BMI) and obesity in a normal elderly population.

Design: Cross-sectional study.

Subjects: A total of 983 community-dwelling elderly (mean age 68.4 ± 6.9 years, range 57 - 97).

Measurements: Weight and height were measured, and sleep duration and sleep fragmentation were assessed with on average six nights of actigraphy.

Results: A quadratic model adequately described the association between continuous measures of sleep duration and BMI. Actigraphic sleep duration had a significant U-shaped relationship with BMI (β of quadratic term = 0.30, 95% confidence interval (CI): 0.08, 0.52). Both short sleepers (< 5 h: OR 2.76 (95% CI: 1.38, 5.49), 5 - < 6 h: OR = 1.97 (95% CI: 1.26, 3.08)) and long sleepers (> 8 h: OR = 2.93 (95% CI: 1.39, 6.16)) were more likely to be obese, compared to participants who slept 7 - < 8 h. BMI increased with 0.59 kg/m^2 per standard deviation of sleep fragmentation (95% CI: 0.34, 0.84). After adjustment for sleep fragmentation, the association between short sleep and obesity was no longer significant. Exclusion of participants with probable sleep apnea only marginally changed these associations. Self-reported habitual sleep duration was not associated with BMI or obesity.

Conclusions: Sleep duration, as measured with actigraphy, had a U-shaped-relationship with BMI and obesity in an elderly population. A highly fragmented sleep is associated with a higher BMI and a higher risk of obesity, and may explain why short sleep is related to obesity. To preclude bias that can be introduced by self-report measures of sleep duration, using multiple measures of sleep parameters is recommended in future research.

INTRODUCTION

A growing body of epidemiological evidence indicates that sleep duration is associated with elevated body mass index (BMI) and an increased prevalence of obesity. Several studies, summarized by Knutson et al. in a recent review,[1] point toward a role of particularly short sleep, or sleep deprivation, in the development of obesity, impaired glucose metabolism and diabetes risk. A number of authors reported an inverse linear relationship between sleep duration and BMI or an association between short sleep duration and obesity.[2-7] Others have reported a U-shaped association, suggesting that short as well as long sleep duration increase the risk of a high BMI.[8-10]

Most epidemiological researchers used self-reported sleep duration only. We are aware of only one study that did not rely on self-report, but used actigraphy, a method that infers wakefulness and sleep from the presence or absence of arm movement. Several authors, including the American Academy of Sleep Medicine's Standards of Practice Committee, view actigraphy as a reliable method for assessing sleep-wake patterns in adults.[11-15] Lauderdale et al.[16] collected actigraphy data over two three-day periods for 669 participants aged 38-50 years in the CARDIA Study. They demonstrated substantial discrepancies between self-reported and actigraphically measured sleep duration. This finding suggests that reliance on self-report in epidemiologic studies may result in systematic misclassification of sleep duration, which has been confirmed in the Rotterdam Study and has been extensively discussed elsewhere.[17] Interestingly, Lauderdale et al. found that actigraphically measured sleep duration was not related to weight gain in their study.[18]

Experimental and epidemiological studies that describe the effect of sleep deprivation on glucose metabolism and other physiologic parameters focus on short sleep duration, regardless of the continuity or discontinuity of sleep. Whereas most research on sleep fragmentation investigates behavioral or cognitive consequences such as daytime sleepiness, vigilance and cognitive and psychomotor performance, Ekstedt et al.[19] reported that sleep fragmentation was also associated with elevated cortisol and cholesterol levels. The role of sleep fragmentation in the relationship between sleep duration and obesity has, to our knowledge, not been described earlier. It is not clear whether a short sleep duration *per se*, or short sleep due to frequent interruptions, be it of internal or external origin, gives rise to a higher risk of obesity.

Moreover, the association between sleep parameters and obesity has not been extensively studied in elderly persons; many studies were performed in children and adolescents or young adults only. A study that included elderly participants suggested that the association disappears above a certain age.[6] Gottlieb et al.[20] found no significant differences in BMI between categories of self-reported sleep duration in the Sleep Heart Health study, of which the age distribution is similar to ours.

Our study investigates whether a linear or U-shaped association exists between sleep duration and BMI or obesity in a normal elderly population. Further, we assessed whether sleep fragmentation is related to BMI and obesity. We measured sleep duration and sleep fragmentation with multiple nights of actigraphy. To the best of our knowledge, ours is the largest study of obesity with objective actigraphy measurements of sleep so far. Almost all previous studies have relied on self-report.

METHODS

Study population

This study is embedded in the Rotterdam Study, a population-based cohort study aimed at assessing the occurrence of and risk factors for chronic diseases in the elderly.[21] In 1990, all of the inhabitants of a district of Rotterdam aged 55 years and over were invited. In 2000, the cohort was extended with a second cohort from the same district, also aged 55 years and over. Between January 2002 and December 2005, these participants underwent their second examination, consisting of a home interview and two visits to the research center. From December 2004 onward, 1515 of these persons were asked to participate in the actigraphy study, of whom 1076 (71 %) agreed. Both valid actigraphy data for at least two nights and valid data for height and weight were available for 983 of these subjects. Together they contributed 6069 valid nights (mean 6.17 ± 1.1). The Medical Ethics Committee of the Erasmus University Rotterdam approved the Rotterdam Study and written informed consent was obtained from all of the participants.

Ascertainment of BMI and obesity

At the research center, height and weight were measured standing in light clothes, without shoes, and BMI was calculated: weight (kg) / height $(m)^2$. We defined obesity as a BMI of 30 kg/m^2 or higher.

Assessment of sleep parameters

To obtain objective sleep parameters, we used the Actiwatch model AW4 (Cambridge Neurotechnology Ltd), an actigraph that can be worn like a watch and is equipped with an event marker button. Participants were instructed to wear the actigraph continuously over a period of 5-7 consecutive days and nights, on the nondominant wrist. During the actigraphy study period, participants kept a sleep diary. Participants were asked to press the event marker button on the actigraph each night when they began trying to fall asleep and again when they got out of bed each morning. To calculate sleep parameters from the raw actigraphy data, we used the Actiwatch algorithm that has been validated against polysomnography by Kushida et al.[22] With this algorithm, a score is calculated for each 30-s epoch, taking into

account the weighted value of previous and following epochs. We used a threshold of 20 to distinguish sleep from waking, since this high sensitivity setting yielded the best agreement with polysomnography with regard to total sleep time (TST) in Kushida et al.'s validation study.[22]

We applied the following rules to the data:

- Bed Time and Get Up Time were derived from the event marker buttons, and if these data were not present for a certain night, we derived them from the sleep diary, in order to determine Sleep Start and Sleep End.
- Sleep Start was defined using the first immobile period of at least 10 min after Bed Time with no more than one 30-s epoch of movement. The midpoint of that period was classified as Sleep Start.
- To define Sleep End, we identified the last period of at least 10 min of immobility before Get Up Time that had no more than one epoch of movement. The last epoch of this period was classified as Sleep End.
- TST is the time between Sleep Start and Sleep End, minus the time classified as awake by the algorithm.

The definitions of Sleep Start and Sleep End were derived from the Actiwatch manual and are equal to those used by the Actiwatch software.[23] The fragmentation index is a measure of the amount of interruption of sleep by physical movement. It is calculated as follows: 100 * the number of groups of consecutive immobile 30-s epochs divided by the total number of immobile epochs.[23]

Self-reported TST was assessed with a question from the Pittsburgh Sleep Quality Index (PSQI),[24] which was administered during the home interview.

Assessment of covariates

Educational attainment (low / middle / high), smoking (never / former / current) and alcohol consumption (average number of drinks per week) were assessed during the home interview. Napping during daytime was assessed with the sleep diary. Depressive symptoms were ascertained with the Center for Epidemiologic Studies Depression (CES-D) scale.[25] The CES-D is a self-report scale with 20 items, with a maximum score of 60. Scores of 16 or greater on the CES-D are traditionally interpreted as suggestive of clinically significant depression.[26]

To operationalize the occurrence of probable sleep apnea, two questions from the Pittsburgh Sleep Quality Index were used. In line with Fogelholm et al.[27] sleep apnea was considered probable in persons who reported (1) loud snoring at least 2 nights a week, with at least occasional respiratory pauses, or (2) respiratory pauses during sleep with a frequency of at least 1-2 nights weekly.

Statistical analysis

We performed multiple linear regression analyses to investigate the associations of the average actigraphically measured TST and fragmentation index per night with BMI. Fragmentation index was expressed as standard deviation units, and TST was centered at the mean, to facilitate interpretation. We tested both a linear and a quadratic model of TST and fragmentation index, and we analyzed TST and fragmentation index separately as well as together in one model. We adjusted all of the analyses for age, gender, educational attainment, smoking, alcohol consumption, alcohol consumption squared, napping during daytime, and depressive symptoms. Means were imputed for missing values for alcohol consumption (N = 31) and depressive symptoms (N = 20). A 'missing' category was added to the three categories of educational attainment (N = 23). Next, we performed analyses of covariance (ANCOVAs) with actigraphically measured TST as a categorical variable and BMI as a continuous outcome variable, both with and without fragmentation index in the model. To this end, we divided the mean actigraphically measured TST into five categories (< 5 h, 5 - < 6 h, 6 - < 7 h, 7 - < 8 h, 8 h and over). The 7 - < 8 h actigraphic TST category was used as the reference category. To check whether there were gender differences in the association between TST and BMI, we added the interaction term 'gender * TST' to the regression analyses.

Next, we investigated the association of TST and fragmentation index with obesity (BMI ≥ 30) with logistic regression analyses. Adjustment for covariates was equal to that of the linear regression analyses. All of the analyses were repeated after exclusion of participants with probable sleep apnea. Finally, we repeated the analyses with self-reported TST. All of the analyses were performed with SPSS version 11.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Table 1 shows the characteristics of the study population. A total of 266 participants (27.1 %) had a BMI of 30 kg/m^2 or higher, and were thus classified as obese. The average BMI of our study population was 27.9 (± 4.0) kg/m^2. Mean age was 68.4 (± 6.9) years (range 57 - 97), 52.0 % was female.

Nonresponse analysis showed that nonresponders, who visited the research center but refused to participate in the actigraphy study (N = 439), were on average 2.5 years older than responders ($p < 0.001$) and were more likely to be female (32.2 % vs. 25.1 %, $p = 0.002$). Refusal to participate was neither associated with BMI, nor with average TST as self-reported in the PSQI.

For the majority of participants (77.8 %), the study period included two weekend nights (Friday and Saturday night). Only one weekend night was included for 19.2 % of the participants, and for the remaining 3 %, data were collected on week nights only. The average actigraphic TST, the average self-reported TST and the average fragmentation index were not

Table 1. Characteristics of the study population, N = 983

Characteristic	Non-obese (BMI < 30 kg/m^2), N = 717	Obese (BMI ≥ 30 kg/m^2), N = 266	*p*-value[1]
Age, y, mean (SD)	68.6 (7.2)	67.9 (6.2)	0.11
Gender (female), N (%)	361 (50.3)	150 (56.4)	0.09
Educational attainment:			
low, N (%)	66 (24.8)	124 (17.3)	
Intermediate, N (%)	166 (62.4)	452 (63.0)	0.001
high, N (%)	26 (9.8)	126 (17.6)	
missing, N (%)	8 (3.0)	15 (2.1)	
Smoking:			
never, N (%)	214 (29.8)	76 (28.6)	
former, N (%)	389 (54.3)	155 (58.3)	0.44
current, N (%)	114 (15.9)	35 (13.2)	
Alcohol use, no. of drinks per week, mean (SD)	9.7 (10.7)	7.8 (10.6)	0.01
Napping during daytime (ever), N (%)	396 (55.2)	176 (66.2)	0.002
Probable sleep apnea, N (%)	61 (8.5)	33 (12.4)	0.07
Depressive symptoms (CES-D score), mean (SD)	4.7 (6.2)	5.5 (7.0)	0.12
Diabetes mellitus, N (%)	36 (5.2)	30 (12.4)	< 0.001
Actigraphic sleep measures			
Actigraphic TST:			
< 5 h, N (%)	27 (3.8)	19 (7.1)	
5 - < 6 h, N (%)	140 (19.5)	66 (24.8)	
6 - < 7 h, N (%)	337 (47.0)	113 (42.5)	0.002
7 - < 8 h, N (%)	191 (26.6)	52 (19.5)	
≥ 8 h, N (%)	22 (3.1)	16 (6.0)	
Actigraphic TST, h:min, mean (SD)	6:33 (0:47)	6:25 (0:58)	0.03
Fragmentation index, mean (SD)	6.4 (2.5)	7.1 (3.1)	0.001
PSQI sleep measures (N = 956)			
Self-reported habitual TST:			
< 5 h, N (%)	35 (5.0)	10 (3.9)	
5 - < 6 h, N (%)	68 (9.7)	35 (13.6)	
6 - < 7 h, N (%)	156 (22.3)	52 (20.2)	0.38
7 - < 8 h, N (%)	234 (33.5)	91 (35.4)	
≥ 8 h, N (%)	206 (29.5)	69 (26.8)	
Self-reported habitual TST, h:min, mean (SD)	6:55 (1:13)	6:53 (1:16)	0.72
Global PSQI score, mean (SD)	3.6 (3.6)	3.7 (3.4)	0.95

[1] Student's t-test for continuous variables, chi-squared test for categorical variables
CES-D: Center for Epidemiologic Studies Depression scale, TST: Total Sleep Time, PSQI: Pittsburgh Sleep Quality Index

significantly different between participants with 0, 1 or 2 weekend nights (All *p*-values > 0.20, ANOVA). This can probably be explained by the fact that only 6.0 % of participants still had a paid job for ≥ 20 h per week.

TST was centered at the mean and modeled as a continuous variable in the multiple linear regression analyses, with BMI as a continuous outcome measure. Sleep duration had a significant quadratic (U-shaped) relationship with BMI. The regression coefficient of TST squared

was 0.30, 95 % CI 0.08 to 0.52, and the regression coefficient of TST was -0.41, 95 % CI -0.71 to -0.11. BMI was lowest at a sleep duration of 7:13 h. Fragmentation index had a positive linear association with BMI: BMI increased with 0.59 kg/m^2 per SD of fragmentation (95 % CI 0.34 to 0.84). A quadratic term of fragmentation index, added to this model, was not significant. After exclusion of individuals with probable sleep apnea (N = 94), the quadratic association between TST and BMI was still significant (β = 0.27 (0.03 to 0.50)), as was the association between fragmentation and BMI (β = 0.53 (0.26 to 0.80)).

Table 2 shows the results of the ANCOVA analyses, with TST as a categorical variable and BMI as a continuous outcome variable. Persons who slept < 5 h had a 1.6 kg/m^2 (95 % CI 0.4 to 2.9) higher estimated BMI than those who slept 7 to < 8 h; persons who slept 5 to < 6 h had a 1.1 (0.3 to 1.8) kg/m^2 higher BMI than the reference category. BMI of long sleepers (≥ 8 h) did not significantly differ from the reference.

A high degree of sleep fragmentation was related to a shorter TST: Pearson's correlation coefficient between TST and fragmentation index was –0.48 (p < 0.001). When we adjusted the association between sleep duration and BMI for fragmentation index, the association was attenuated, although the quadratic model remained significant (β of quadratic term = 0.23, 95 % CI 0.01 to 0.45). The regression coefficient of fragmentation index changed from 0.59 (0.34 to 0.84) to 0.46 (0.17 to 0.75) when TST and TST squared were included in the model.

Figure 1 shows the relationship between categories of actigraphic TST and obesity. Compared to participants who slept 7 - < 8 h per night, a short actigraphically measured TST was associated with a considerably higher likelihood of obesity. The odds ratio for a TST of < 5 h per night was 2.76 (1.38 to 5.49). For a TST of 5 - < 6 h per night the odds ratio was 1.97 (1.26 to 3.08). A long sleep duration of > 8 h per night was also associated with a higher prevalence of obesity (OR 2.93 (1.39 to 6.16)). Moreover, a higher fragmentation index was associated with more obesity: OR = 1.36 (1.17 to 1.57) per standard deviation of fragmentation. When

Table 2. Association of actigraphic TST and BMI, N = 983

		BMI (kg/m^2)					
		Model A[1]			Model B[2]		
Actigraphic TST	N	Estimated mean (95% CI)	Difference with reference (7- <8 h) (95% CI)	*p*-value	Estimated mean (95% CI)	Difference with reference (7- <8 h) (95% CI)	*p*-value
< 5 h	46	29.0 (27.9, 30.2)	1.6 (0.4, 2.9)	0.01	28.3 (27.1, 29.5)	0.7 (-0.7, 2.0)	0.33
5 - < 6 h	206	28.5 (27.9, 29.0)	1.1 (0.3, 1.8)	0.004	28.3 (27.7, 28.8)	0.6 (-0.2, 1.4)	0.12
6 - < 7 h	450	27.8 (27.4, 28.2)	0.4 (-0.2, 1.0)	0.22	27.8 (27.5, 28.2)	0.2 (-0.4, 0.8)	0.50
7 - < 8 h (ref)	243	27.4 (26.9, 27.9)	reference	-	27.6 (27.1,28.1)	reference	-
≥ 8 h	38	28.5 (27.3, 29.8)	1.1 (-0.2, 2.5)	0.10	28.8 (27.5, 30.1)	1.2 (-0.2, 2.5)	0.08

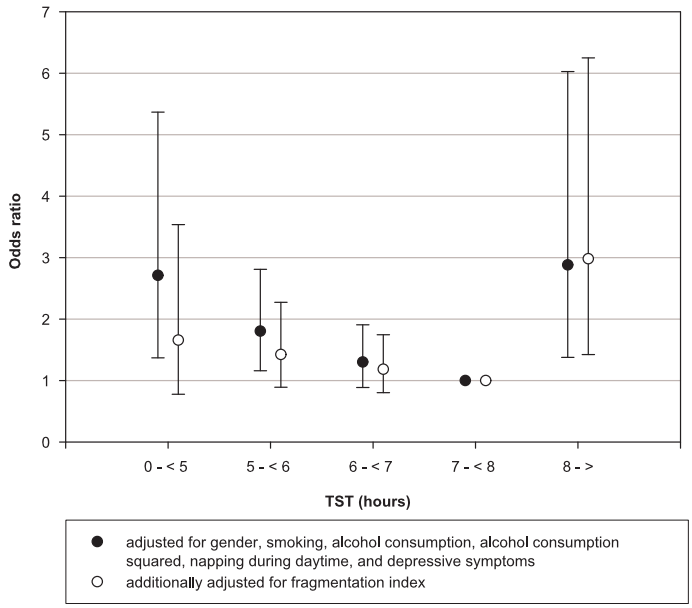
Test: ANCOVA. Analyses with TST as a continuous variable are presented in the text.

[1] Model A: adjusted for age, gender, educational attainment, smoking, alcohol consumption, alcohol consumption squared, napping during daytime, and depressive symptoms

[2] Model B: additionally adjusted for fragmentation index

TST: Total Sleep Time, BMI: Body Mass Index

Figure 1. Association of sleep duration and obesity (BMI ≥ 30), N = 983



we additionally adjusted the associations between short sleep and obesity for fragmentation index, they were substantially reduced and no longer significant (Figure 1). The association between long sleep and obesity was not attenuated (OR = 3.05 (1.45 to 6.42)).

There was neither a linear (β = 0.01; 95 % CI -0.20 to 0.22) nor a quadratic association between self-reported TST and BMI, nor were there any differences in BMI between categories of TST (ANCOVA; results not shown). Logistic regression analysis showed that there was no elevated risk of obesity in any of the categories of self-reported TST (Table 3).

All of the analyses were adjusted for age, gender, educational attainment, smoking, alcohol consumption, alcohol consumption squared, napping during daytime, and depressive symptoms. There was no significant interaction between gender and TST in either analysis (not shown).

Table 3. Association of self-reported habitual sleep duration and obesity (BMI ≥ 30), N = 956[1]

Self-reported sleep duration	N (%)	Odds ratio (95% CI)	*p*-value
< 5 h	45 (4.7)	0.67 (0.31 – 1.43)	0.29
5 - < 6 h	103 (10.7)	1.11 (0.67 – 1.85)	0.68
6 - < 7 h	208 (21.5)	0.85 (0.57 – 1.28)	0.44
7 - < 8 h	325 (33.6)	1.00 (reference)	
≥ 8 h	275 (28.0)	0.81 (0.56 – 1.18)	0.28

[1] Test: logistic regression, adjusted for age, gender, educational attainment, smoking, alcohol consumption, alcohol consumption squared, napping during daytime, and depressive symptoms

DISCUSSION

In this cross-sectional study of 983 community-dwelling elderly, we found a marked U-shaped association of actigraphic measures of sleep duration with BMI and obesity. Sleep fragmentation also increased the likelihood of a higher BMI and obesity. The relationships between short sleep and obesity disappeared after adjustment for sleep fragmentation, whereas the higher risk for long sleepers remained unchanged. However, a quadratic relationship between sleep duration and BMI still existed after adjustment for sleep fragmentation. Self-reported sleep duration was not associated with BMI or obesity.

Before we discuss these findings, some methodological comments have to be made. First, a selection effect may have occurred due to nonparticipation. However, it is unlikely that this has resulted in substantial bias, as (non)participation in the actigraphy study was neither associated with self-reported sleep duration, nor with BMI. Second, actigraphy is not the gold standard for distinguishing sleep from waking. TST derived from actigraphy data may differ with different actigraphy devices or algorithms. The algorithm that we used has been validated in a study of sleep disordered patients;[22] the appropriateness of this algorithm in a normal population has not been tested. However, the use of actigraphy enables studies involving multiple days and nights of testing, thereby increasing reliability,[11] and permits the evaluation of persons in their natural sleeping environment, whereas polysomnography is not feasible in large studies, and its ecological validity is sometimes questionable.[14] Third, polysomnography would have been necessary to accurately assess the presence of sleep apnea. Actigraphy does not allow adequate assessment of sleep apnea; although it seems conceivable that actigraphically measured sleep fragmentation is to some extent related to sleep apnea, it is certainly not a perfect measure.[28] In our study, sleep apnea was diagnosed as 'probable' by using self-reported snoring and nocturnal respiratory pauses. This solution for large studies has been described previously by Fogelholm et al.[27] Finally, the cross-sectional setting prevented us from inferring causality or chronological order of events.

Strengths of this study include its population-based design, and the objective measurement of weight and height. In addition, to our knowledge, ours is the largest obesity study that used multiple nights of actigraphy to assess sleep duration and sleep fragmentation so far. Finally, our study includes elderly participants, whereas most previous studies investigated younger populations.

The association between short sleep and higher BMI or obesity has repeatedly been found, although not consistently in the elderly. Moreover, it has not been confirmed with objective measures in a normal population. A number of studies reported a negative linear relationship between sleep duration and BMI, or an association between short sleep and the risk of obesity.[2-7] Some authors have linked the finding that the average self-reported sleep duration has decreased over the last decades to the 'obesity epidemic'.[6, 7, 29, 30] Several possible mechanisms to explain the association of short sleep and obesity are put forward in the literature,

and summarized in a review by Knutson et al.[1] Briefly, sleep deprivation leads to an altered glucose metabolism, possibly to lower energy expenditure, and to lower circulating levels of leptin and higher levels of ghrelin. Leptin is a hormone that decreases appetite, while ghrelin stimulates it; therefore, the hormonal changes that result from sleep deprivation cause an upregulation of appetite.

In the National Health and Nutrition Examination Survey I study, a higher BMI and a higher risk of obesity were reported in persons who slept < 7 h, compared to those sleeping 7 h. However, the authors found this association only in participants under 59 years.[6] Hasler and colleagues found that the relationship between short sleep and obesity diminished after the age of 34.[7] In a small study of 90 women of 50 years and above, Chaput et al.[31] found similar odds ratios of overweight/obesity with a self-reported sleep duration of < 7 h and ≥ 7 h. In the Sleep Heart Health study, a large community-based cohort study with participants aged 53-93 years, Gottlieb et al.[20] found no association between categories of self-reported sleep duration and BMI. Nevertheless, they found an increased risk of diabetes mellitus and impaired glucose tolerance in persons sleeping ≤ 6 and ≥ 9 h per night. Stamatakis et al.[32] investigated questionnaire data from the Alameda County Study and found no relationship between quartiles of BMI and short sleep duration in a crude analysis. A few more negative findings have been published based on the cross-sectional association of sleep duration and BMI or obesity. For example, a study in men of 40-70 years that investigated BMI as a confounder found no significant difference in BMI between categories of sleep duration.[33] In contrast to these negative results, our study demonstrated an association between short sleep and BMI as well as obesity in an elderly population.

In the Nurses' Health Study, an association was found between self-reported habitual sleep duration and subsequent weight gain over a 16 year follow-up period.[30] The relationship between sleep duration and weight gain was not confirmed by Lauderdale et al.[18] in the CARDIA Study with a follow-up time of 5 years. This study is the only other large cohort study that we are aware of that used actigraphy to measure sleep duration. Stranges et al.[34] could not confirm a longitudinal association between sleep duration and weight gain either, although they did find cross-sectional associations between sleep duration and BMI.

Persons with more fragmented sleep had a higher BMI and more obesity, and the association of short sleep with obesity was substantially attenuated after adjustment for sleep fragmentation. This indicates that sleep fragmentation may be part of the mechanism by which short sleep is related to a higher prevalence of obesity. Sleep fragmentation is inversely related to sleep duration, since the Actiwatch algorithm considers prolonged and intense movement as wakefulness. Therefore, a highly fragmented sleep goes together with a shorter actigraphically measured TST. Frequent arousals during sleep may diminish the regulatory effect on glucose metabolism of normal sleep, possibly by precluding a sufficient amount of slow wave sleep. This implies that the risk of a higher BMI or obesity for short sleepers is lower for those whose sleep is quiet and uninterrupted. Various causes may underlie a

high frequency of physical movement during sleep, e.g. insomnia, periodic limb movement disorder, nocturia, pain, environmental noise or a snoring bed partner.

Sleep apnea may also cause sleep fragmentation, and variation in sleep duration. Moreover, there is evidence for a strong association between sleep apnea and obesity.[35] We used a proxy measure to assess probable sleep apnea. Excluding those participants with probable sleep apnea only moderately changed our results, suggesting that the relations of sleep duration and sleep fragmentation with BMI are at least partly independent of sleep apnea. This is in line with the results of Fogelholm et al.,[27] however, these results should be interpreted with caution, as our measure of probable sleep apnea might not be sufficiently sensitive. Kohatsu et al.[2] adjusted for snoring as a proxy for sleep-related breathing disorder, which did not alter their results although snoring was independently related to BMI. Moreover, there is not sufficient evidence to suggest that patients with sleep apnea sleep any more or less than average, though they may spend more time in bed.[36]

The association between long sleep and obesity has received less attention in the literature, although some authors reported a U-shaped curve, indicating that short as well as long sleep duration are associated with a higher BMI.[8-10] Our study showed a clear and significant U-shaped association between sleep duration and BMI as well as between short *and* long sleep and obesity. The mechanisms linking long sleep to obesity are likely to be distinct from those mediating the adverse effects of short sleep, since the metabolic changes that occur as a consequence of sleep deprivation are not seen in long sleepers.[1] Little is known about the metabolic consequences and correlates of long sleep, although it has repeatedly been related to adverse outcomes such as mortality.[37] Due to the cross-sectional design of this study, we do not know whether long – or short – sleep duration causes higher BMI or vice versa. The direction of causality may be reversed, with a high BMI or related health problems leading to changes in sleep duration. The relationships may also be bidirectional or both phenomena may share a common cause.

Possible gender differences in the relationship between sleep duration and obesity have been a source of debate in the literature. Some authors reported a U-shaped association in women but not in men,[38] whereas others found a negative linear relationship in male, but no association in female adolescents.[39] In our study, the relationship between sleep duration and BMI or obesity did not differ in elderly men and women.

Self-reported sleep duration, assessed by questionnaire, was not associated with BMI or obesity in the elderly population participating in our study. This provides support for our hypothesis that the negative findings that were reported by others[6, 7, 20] may to some extent be explained by their use of self-report measures. Misperception of sleep duration may be of particular importance in an elderly population, because the prevalence of poor sleep quality, which frequently leads to underestimation of sleep duration, is higher in the elderly. Inadequate self-report of sleep due to cognitive decline also may be important in this age category. It has to be noted that the distribution of TST derived from self-report and actig-

raphy are different; self-reported TST is generally longer than actigraphically measured TST. Although 8 h of sleep is often expressed as the recommended amount, 8 h of actigraphically measured sleep was included in our 'long sleep' category, to which only 3.1 % of our study population belonged.

In view of our results, the earlier finding that the association between sleep duration and obesity is not present in the elderly needs to be re-evaluated. With multiple nights of actigraphic measurements, we found that both short and long sleeping elderly had a higher BMI and a higher likelihood of obesity, and that sleep fragmentation is important in the relation of short sleep with obesity. These associations were undetectable with self-report assessment of sleep duration. However, our cross-sectional design prevented us from gaining insight into possible temporal or causal relations, as was mentioned above. For this reason, we cannot rule out that obesity leads to a shorter or longer sleep duration, or to more fragmented sleep. To gain more insight in the possible causal pathways, longitudinal research is needed. The participants of this study will be followed-up in future examinations of Rotterdam Study, and the authors intend to investigate the association between sleep parameters and weight gain or weight loss in a longitudinal study. To further evaluate the role of sleep fragmentation in obesity and to preclude bias that can be introduced by self-report measures of sleep duration, using multiple measures of sleep parameters is recommended.

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Chapter 4.

Sleep duration and hypertension are not associated in the elderly

SUMMARY

Several large studies have shown that both short and long average sleep durations increase the risk of hypertension in adults. We investigated whether sleep duration is also associated with hypertension in the elderly. This cross-sectional study was conducted in 5058 participants of the population-based Rotterdam Study, aged 58-98 years. Blood pressure was measured at the research center. Hypertension was defined as a systolic blood pressure of ≥ 160 mm Hg and/or a diastolic blood pressure of ≥ 100 mm Hg or current use of antihypertensive medication.

In all of the participants, sleep duration was assessed by self-report. In a subsample of 975 subjects, it was additionally measured with actigraphy, a validated method that infers wakefulness and sleep from the presence or absence of limb movement. After adjustment for age and gender and additionally for body mass index, smoking, depressive symptoms, sleep medication use, diabetes mellitus, myocardial infarction, and stroke, none of the odds ratios (varying from 0.54; 95 % CI: 0.27 to 1.08; to 1.19; 95 % CI 0.89 to 1.58) reflected a significant association between sleep duration and hypertension, whether measured by self-report or actigraphy. This study strongly suggests that sleep duration was not associated with hypertension in the elderly.

INTRODUCTION

Epidemiologic studies have consistently shown that self-reported short or long sleep duration is associated with increased mortality.[1, 2] Whether this association can be explained by elevated blood pressure or other cardiac factors remains uncertain. Gottlieb et al.[3] found that self-reported habitual sleep duration above or below the median of 7 to 8 hours per night is associated with an increased prevalence of hypertension, particularly at the extreme of < 6 hours per night. Gangwisch et al.[4] reported that sleep durations of ≤ 5 hours per night were associated with a significantly increased risk of hypertension in subjects 32 to 59 years. The association between sleep duration and hypertension in the elderly is uncertain.

Our study aimed to investigate the associations of sleep duration with hypertension in an elderly community-dwelling population. We hypothesized that a markedly shorter or longer sleep duration than the median duration would be associated with a higher prevalence of hypertension. Our study was based on self-reported sleep duration, and in a subsample, sleep duration was also assessed with actigraphy.

METHODS

Study population

This study is embedded in the Rotterdam Study, a population-based cohort study aimed at assessing the occurrence of and risk factors for chronic diseases in the elderly.[5] In 1990, all of the inhabitants of a district of Rotterdam aged 55 years and over were invited, and 7983 agreed to participate (response: 78 %). In 2000, the cohort was extended with 3011 participants from the same district (response: 67 %), also aged 55 years and over. Between January 2002 and December 2005, 3115 participants from the original cohort and 2249 participants of the extended cohort underwent a home interview and visited the research center. For 5058 of these 5364 participants, valid data on both sleep duration and hypertension were available. From December 2004 onward, 1515 of these persons were asked to participate in the actigraphy study, 1076 (71 %) of whom agreed. Both valid actigraphy data and hypertension data were available for 975 of these subjects. Together they contributed 5999 valid nights (mean: 6.15, SD: 1.1). The Medical Ethics Committee of the Erasmus University Rotterdam approved the Rotterdam Study and written informed consent was obtained from all of the participants.

Ascertainment of hypertension

At the research center, trained examiners took two blood pressure measurements at the right brachial artery using a random-zero sphygmomanometer with appropriate adult cuff size and the participant in sitting position. The average of these two measurements was taken.

Hypertension was defined as a systolic blood pressure of ≥ 160 mm Hg, a diastolic blood pressure of ≥ 100 mm Hg, or current use of antihypertensive medication.[6] Medication use was ascertained by means of a standardized interview.

Sleep duration

Sleep duration was assessed by the following question in the home interview: "During the past month, how many hours of actual sleep did you get at night?" The results were then divided in 5 categories of sleep duration. Because polysomnographic measurements for more than one night are not feasible in large studies, we used actigraphy to obtain objective sleep parameters. Actigraphy is a method that infers wakefulness and sleep from the presence or absence of limb movement. It estimates sleep parameters more accurately than sleep diaries, and agrees reasonably with polysomnography.[7] With actigraphy, it is possible to measure several nights in the home environment with little burden for the participants and with acceptable costs.

We used the Actiwatch (Cambridge Neurotechnology Ltd), an actigraph that can be worn like a watch. Participants wore the actigraph over a period of 5 – 7 consecutive nights. To calculate sleep parameters from the raw actigraphy data, we used the Actiwatch algorithm, that has been validated against polysomnography by Kushida et al.[8] With this algorithm, a score is calculated for each 30-second epoch, taking into account the weighted value of previous and following epochs. We used a threshold of 20 to distinguish sleep from waking (high-sensitivity setting), because this yielded the best agreement with polysomnography with regard to total sleep time in the validation study by Kushida et al.[8]

Covariates

Weight and height were measured at the research center, and body mass index was calculated (weight in kilograms / height in meters squared). Smoking (never, former or current) and the use of sleep medication were determined in the home interview. Depressive symptoms were assessed with the Center for Epidemiologic Studies Depression (CES-D) scale.[9] Napping during daytime was assessed with a dichotomous question ("did you take a nap today?") in the sleep diary that accompanied the actigraphy study. Diabetes was defined as a fasting serum glucose level of ≥ 7 mmol/L (measured at the research center) or the use of antidiabetic medication. Information on myocardial infarction and stroke was obtained from medical charts.

Statistical analysis

To assess the association of self-reported and actigraphically measured sleep duration with hypertension, we performed logistic regression analyses. We adjusted all of the analyses for age and gender (model 1). Additionally, we adjusted for body mass index, smoking, depressive symptoms, napping during daytime (only actigraphy subgroup), sleep medication use, diabetes mellitus, myocardial infarction and stroke, with imputed means for missing values

(study population: N = 223; actigraphy subgroup: N = 20; model 2). We used the median sleep duration category as the reference category in all of the logistic regression analyses and repeated all of the analyses with lower cutoff points for the definition of hypertension (e.g. 140 and 90 mm Hg, as used by Gottlieb et al.[3]). Further analyses were performed in subjects who did not use antihypertensive medication, with systolic and diastolic blood pressure as continuous outcome variables in multiple linear regression models. In addition, we repeated all of the analyses for men and women separately and again after exclusion of participants who still had a paid job for ≥ 20 h per week (4.6 % of our study population and 6.2 % of our actigraphy subgroup).

RESULTS

Of the 5058 participants in our study (57.5 % female; mean age: 72.1 years; SD = 7.5 years; range: 58 to 98 years), 2485 (49.1 %) had hypertension. Of the subsample of 975 subjects (52.1 % female; mean age: 68.4 years; SD: 6.9 years; range: 59 to 97 years) who participated in the actigraphy study, 417 (42.8 %) had hypertension.

In our actigraphy study subgroup, Pearson's correlation coefficient between total sleep time as measured by questionnaire and mean actigraphically measured total sleep time was 0.25 ($p < 0.001$). This indicates that perceived sleep duration is not necessarily the same as

Table 1. Characteristics of the study population

Characteristic	Study population (N=5058)	Actigraphy study subgroup (N= 975)
Age, y, mean (SD)	72.1 (7.5)	68.4 (6.9)
Gender (female), %	57.5	52.1
Body mass index, kg/m^2, mean (SD)	27.6 (4.1)	27.9 (4.0)
Obesity, body mass index ≥ 30, %	24.2	26.9
Smoking:		
never, %	29.9	29.8
former, %	54.9	54.7
current, %	15.2	15.5
Depressive symptoms, CES-D score, mean (SD)	6.0 (7.4)	5.0 (6.5)
Self-reported sleep duration, h:min, mean (SD)	6:51 (1:17)	6:55 (1:14)
Actigraphically measured TST, h:min, mean (SD)	-	6:31 (0:50)
Napping during daytime, %	-	58.1
Use of sleep medication in the past month, %	15.4	12.0
Diabetes mellitus, %	8.0	6.9
Myocardial infarction (ever), %	2.9	2.6
Stroke (ever), %	4.0	3.2
Hypertension, %	49.1	42.8

CES-D: Center for Epidemiologic Studies Depression scale, TST: Total Tleep Time

actigraphically measured sleep duration. It should be noted, however, that the questionnaire was administered a few weeks before the actigraphy study.

Nonresponders, who visited the research center but refused to participate in the actigraphy study, were, on average, 2.5 years older than responders ($p < 0.001$) and were more likely to be female ($p = 0.002$). Refusal to participate was neither associated with the risk of hypertension ($p = 0.08$), nor with average self-reported sleep duration ($p = 0.42$), but was often related to the unattractive appearance of the watch. The characteristics of the study population are presented in table 1.

Table 2 shows the results of the logistic regression analyses. Since self-reported sleep duration was, on average, longer than actigraphically measured sleep duration, the actigraphy subgroup and the total study population have different reference categories for sleep duration. We did not find an association between either self-reported or actigraphically measured sleep duration and hypertension. Lower cutoff points for the definition of hypertension yielded very similar non-significant results (data not shown).

Sleep duration, measured by either self-report or actigraphy, was not associated with either systolic or diastolic blood pressure in a multiple linear regression analysis, both without and

Table 2. Association of sleep duration and hypertension

		Hypertension			
		Model 1*		Model 2†	
Sleep duration	Hypertension / Total	Odds ratio (95% CI)	*p*-value	Odds ratio (95% CI)	*p*-value
Total study population, N = 5058					
Self-reported TST, h					
< 5	141 / 287	0.95 (0.73 to 1.22)	0.68	0.94 (0.72 to 1.24)	0.67
5 - < 6	287 / 568	1.04 (0.85 to 1.26)	0.71	1.03 (0.84 to 1.27)	0.76
6 - < 7	577 / 1152	1.07 (0.92 to 1.25)	0.38	1.09 (0.93 to 1.28)	0.30
7 - < 8	759 / 1590	1.00 (reference)	-	1.00 (reference)	-
8 - < 9	595 / 1222	1.05 (0.90 to 1.22)	0.57	1.06 (0.91 to 1.24)	0.44
≥ 9	126 / 239	1.18 (0.90 to 1.56)	0.24	1.19 (0.89 to 1.58)	0.24
Actigraphy subgroup, N = 975					
Actigraphic TST, h					
< 5	14 / 46	0.60 (0.31 to 1.17)	0.13	0.54 (0.27 to 1.08)	0.08
5 - < 6	89 / 210	1.08 (0.77 to 1.52)	0.66	1.06 (0.75 to 1.52)	0.74
6 - < 7	188 / 443	1.00 (reference)	-	1.00 (reference)	-
7 - < 8	108 / 239	1.08 (0.78 to 1.49)	0.65	1.15 (0.82 to 1.60)	0.42
≥ 8	18 / 37	1.09 (0.55 to 2.16)	0.81	0.99 (0.48 to 2.03)	0.98

Test: logistic regression

* Model 1: adjusted for age and gender

† Model 2: adjusted for age, gender, body mass index, smoking, depressive symptoms, sleep medication use, diabetes mellitus, myocardial infarction, and stroke. Analyses of the actigraphy subgroup were additionally adjusted for daytime napping in model 2.

TST: Total Sleep Time

with a quadratic term to assess a possible U-shaped curve (Table 3). Repeating the analyses for men and women separately, and after exclusion of working participants, did not change the estimates (results not shown).

Table 3. Association of sleep duration and systolic and diastolic blood pressure in participants without antihypertensive medication

Sleep duration	Systolic blood pressure, mmHg		Diastolic blood pressure, mmHg	
	β (95% CI)	*p*-value	β (95% CI)	*p*-value
Total study population, N = 3309				
Linear model				
Self-reported TST, h	0.27 (-0.26 to 0.80)	0.31	0.13 (-0.15 to 0.41)	0.36
Quadratic model				
Self-reported TST, h	*-0.21 (-3.76 to 3.35)*	*0.91*	*0.17 (-1.72 to 2.06)*	*0.86*
Self-reported TST^2, h^2	0.04 (-0.23 to 0.30)	0.79	-0.003 (-0.15 to 0.14)	0.97
Actigraphy subgroup, N = 674				
Linear model				
Actigraphic TST, h	0.43 (-1.25 to 2.11)	0.61	0.04 (-0.86 to 0.93)	0.94
Quadratic model				
Actigraphic TST, h	*-1.46 (-18.4 to 15.5)*	*0.87*	*-1.24 (-10.3 to 7.83)*	*0.79*
Actigraphic TST^2, h^2	0.15 (-1.17 to 1.46)	0.83	0.10 (-0.60 to 0.80)	0.78

Test: multiple linear regression
All analyses adjusted for age, gender, body mass index, smoking, depressive symptoms, sleep medication use, diabetes mellitus, myocardial infarction, and stroke. Analyses of the actigraphy subgroup were additionally adjusted for daytime napping.
TST: Total Sleep Time

DISCUSSION

In a cross-sectional study of 5058 community-dwelling elderly subjects, we found no association between either self-reported or actigraphically measured sleep duration and hypertension or blood pressure. This adds important information to the findings of at least two other recently published, large population-based studies.[3, 4]

Gangwisch et al.[4] reported that sleep durations of ≤ 5 hours per night were associated with a significantly increased risk of hypertension in subjects 32 to 59 years, but that sleep duration and hypertension were unrelated, in an adjusted model, in people aged ≥ 60 years. Our findings are in agreement with this last result. Gangwisch et al.[4] suggested that the lack of an association between short sleep duration and hypertension incidence in older subjects could result from a lack of statistical power. In our study with 2485 subjects with hypertension aged ≥ 58 years, this is certainly not an appropriate explanation.

Gottlieb et al.[3] found that self-reported habitual sleep duration above as well as below the median of 7 to 8 hours per night is associated with an increased prevalence of hypertension

in subjects aged 40 to 100 years (mean age: 63.1 years; SD: 10.7 years). Our study seems to contradict these findings, although the higher age of our participants should be noted.

The biological mechanisms behind the earlier reported association of short sleep duration and hypertension in adults are still unclear. It has been hypothesized that short sleep duration causes metabolic changes that are associated with increased body mass index and elevated blood pressure. Possibly, this mechanism occurs in particular as a result of voluntary sleep restriction because of exogenous factors, such as a fixed time to get up and go to work. It might not occur when short sleep duration is the result of insomnia or a decreased need of sleep. That would explain the lack of association between short sleep duration and hypertension in older adults, who are often retired. Another possibility is that older people compensate for their nightly short sleep duration by daytime napping. However, in the actigraphy subgroup, we adjusted for napping and this did not markedly change the results.

There is evidence for a strong association between sleep apnea and hypertension,[10] and sleep apnea may also cause variation in reported or observed sleep durations. However, the association between sleep apnea and hypertension seems to be age dependent; in the Sleep Heart Health Study, it was not found among those aged ≥ 60 years.[11] This may to some extent explain the lack of association in the relationship between sleep duration and hypertension in the elderly, if sleep apnea is an important mechanism underlying this association in younger people.

Neither the study by Gangwisch et al.[4] nor the study by Gottlieb et al.[3] used objective measures of sleep duration. If the perception of sleep duration is distorted by factors that are unrelated to hypertension, this may cause nondifferential misclassification and, thus, bias the results toward the null value. If, however, misperception is related to risk factors for hypertension, the resulting differential misclassification can bias the results in either direction. Our actigraphic measurements of sleep duration confirmed the findings of the self-report data. This adds to the credibility of the results, because actigraphic measurements are not influenced by an individual's perception of sleep duration. Likewise, other strengths of our study are the measured (as opposed to self-reported) blood pressure, body weight, and height.

Several limitations of our study need to be discussed. First, the participation rate in our study was not 100 %. However, the occurrence of selection bias is unlikely, because (non) participation was neither associated with the self-reported average sleep duration nor with the risk of hypertension. Second, wrist actigraphy does not perfectly measure sleep duration when compared with the gold standard of polysomnography. However, an important advantage of actigraphy over polysomnography is that it is unlikely to affect bedtime, sleep latency, and sleep duration. Third, we could not rule out the possibility of residual confounding, which may have obscured the associations under study.

Because of the cross-sectional design of this study, we cannot determine causal relationships or rule out bidirectional relationships. The problems with cross-sectional data, however, tend to be with spurious associations. So, the finding of a lack of any association between

sleep duration and hypertension or blood pressure makes it unlikely that there actually is a causal association in the elderly.

Perspectives

The results from this study suggest that sleep duration and hypertension are not related in an elderly population. This implies that, above the age of 60, hypertension probably does not contribute to the higher mortality found in short and long sleepers. Future research into the associations of sleep duration and mortality should, therefore, preferably focus on mechanisms other than hypertension.

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Chapter 5.

Long sleep duration is associated with serum cholesterol in the elderly

SUMMARY

Objective Epidemiological studies have repeatedly found increased mortality associated with both habitual short and long sleep duration. The mechanisms behind these associations are unclear. We investigated whether objectively measured sleep duration, time in bed, and sleep fragmentation were associated with total cholesterol and high density lipoprotein (HDL) cholesterol in community-dwelling elderly persons.

Methods This cross-sectional study was conducted among 768 participants of the Rotterdam Study, aged 57 to 97 years. Sleep parameters were assessed with actigraphy, a validated method that infers wakefulness and sleep from arm movement. Cholesterol levels in serum were determined in fasting blood samples. All regression analyses were adjusted for age, gender, body mass index, smoking, depressive symptoms, and heart failure.

Results Sleep duration was positively associated with total cholesterol level: $\beta = 0.11$ (95% confidence interval = 0.03 to 0.18) mmol/l per hour of sleep. Persons who slept longer, and spent more time in bed, also had a higher total/HDL cholesterol ratio. A less fragmented sleep was also associated with higher total cholesterol. Some of these associations showed significant interactions with age. The association between time in bed and total/HDL ratio was mainly driven by persons aged < 65, whereas the relationship between sleep fragmentation and total cholesterol level was most prominent in persons aged ≥ 70.

Conclusions A longer sleep duration was related to higher total cholesterol level and a higher total/HDL cholesterol ratio. Two separate mechanisms, a longer time in bed and sleep fragmentation, seem to explain these associations in different age categories.

INTRODUCTION

Epidemiological studies have repeatedly found higher rates of mortality with both long, i.e. typically more than 8 hours per night, and short, i.e. less than 7 hours per night, habitual sleep durations.[1-7] As cardiovascular disease is the leading cause of death for adult men and women in developed countries,[8] many studies have investigated the relationship between sleep duration and cardiovascular disease. In the Nurses' Health Study, short and long self-reported sleep durations were independently associated with a modestly increased risk of coronary events.[9] The mechanisms behind these associations, however, remained unclear. To elucidate the possible pathways from short and long sleep duration to cardiovascular disease and cardiovascular mortality, the associations between sleep duration and several cardiovascular risk factors have been studied. A number of studies reported an inverse linear relationship between sleep duration and body mass index (BMI) or an association between short sleep duration and obesity.[10-13] Some authors found a U-shaped association, suggesting that short as well as long sleep duration is associated with increased risk of a high BMI.[4, 14, 15] Other epidemiologic research, including our own work, has related amount of sleep time to hypertension,[16-18] to glucose metabolism or to the risk of diabetes.[19-21] To our knowledge, only a few studies have investigated the association between sleep parameters and cholesterol level, with conflicting results. Bjorvatn et al. found no association between sleep duration and total cholesterol level in 40 to 45-year-old subjects after adjustment for gender, smoking and body mass index.[11] Williams et al. found decreased high density lipoprotein (HDL)-cholesterol levels with short and long sleep duration among normotensive, but not among hypertensive women aged 43 to 69 years with type 2 diabetes.[22] Both studies used self-report measures of sleep duration. Ekstedt and colleagues used polysomnographic data to examine the association between sleep parameters and cholesterol levels in 24 young adults and found that total sleep time was positively related to LDL/HDL ratio. Moreover, they reported that a more fragmented sleep was related to higher total cholesterol and a less favorable lipid profile.[23]

We investigated whether sleep duration, time in bed, and sleep fragmentation were associated with cholesterol levels, in an elderly community-dwelling population. As the relationship between cholesterol and health changes with increasing age, we also investigated possible interaction effects of sleep parameters with age. All of the sleep parameters were measured with multiple nights of actigraphy. Actigraphy is a method that infers wakefulness and sleep from the presence or absence of arm movement. Several authors have concluded that actigraphy is a reliable method for assessing sleep-wake patterns in adults.[24-28]

METHODS

Study population

This study is embedded in the Rotterdam Study, a population-based cohort study aimed at assessing the occurrence of and risk factors for chronic diseases in the elderly.[29] In 1990, all of the inhabitants of a district of Rotterdam aged 55 years and over were invited and 7983 agreed to participate. In 2000, the cohort was extended with 3011 participants from the same district, also aged 55 years and over. Every 3 to 4 years, these persons undergo an extensive examination, consisting of a home interview and two visits to the research center. In December 2004, a grant was obtained for an additional actigraphy study, and from this moment onward, 1515 participants were asked to take part in the actigraphy study, 1076 (71 %) of whom agreed. We could not include every person visiting the research center due to the limited number of actigraphs that were initially available and for other logistic reasons, but inclusion was independent of any characteristics of the participants. Valid actigraphy data for at least two nights and data for cholesterol levels were available for 986 of these subjects. Participants who used cholesterol lowering medication (N = 218) were excluded, which left a study population of 768 persons for analysis. In total, 4726 nights of actigraphic measurements (mean 6.2 ± 1.1) were recorded in these persons. The Medical Ethics Committee of the Erasmus University Rotterdam approved the Rotterdam Study and written informed consent was obtained from all of the participants.

Measurement of cholesterol levels

Total cholesterol and HDL cholesterol concentrations in serum were determined within two weeks after sampling by an automated enzymatic procedure in fasting blood samples drawn at the research center.

Sleep parameters

To obtain objective sleep parameters, we used the Actiwatch model AW4 (Cambridge Neurotechnology Ltd), an actigraph that can be worn like a watch and is equipped with an event marker button. Participants were instructed to wear the actigraph continuously over a period of five to seven consecutive days and nights, on the non-dominant wrist. During the actigraphy study period, participants kept a sleep diary. Participants were asked to press the event marker button on the actigraph each night when they began trying to fall asleep and again when they got out of bed each morning. To calculate sleep parameters from the raw actigraphy data, we used the Actiwatch algorithm that has been validated against polysomnography by Kushida et al..[30] With this algorithm, a score is calculated for each 30-s epoch, taking into account the weighted value of previous and following epochs. We used a threshold of 20 to distinguish sleep from waking, as this high sensitivity setting yielded

the best agreement with polysomnography with regard to total sleep time in Kushida et al.'s validation study.[30]

We applied the following rules to the data:

- Bed time and get up time were marked by the participants by pressing the event marker buttons, and if these data were not present for a certain night, we derived them from the sleep diary, in order to determine sleep start and sleep end.
- Sleep start was defined using the first immobile period of at least 10 min after bed time with no more than one 30-s epoch of movement. The midpoint of that period was classified as sleep start.
- To define sleep end, we identified the last period of at least 10 min of immobility before get up time that had no more than one epoch of movement. The last epoch of this period was classified as sleep end.
- Time in bed (TIB) is the time between bed time and get up time.
- Total sleep time (TST) is the time between sleep start and sleep end minus the time classified as awake by the algorithm.

The definitions of Sleep Start and Sleep End were derived from the Actiwatch manual and are equal to those used by the Actiwatch software.[31] The fragmentation index is a measure of the amount of interruption of sleep by physical movement. It is calculated as follows: 100 * the number of groups of consecutive immobile 30-s epochs divided by the total number of immobile epochs.[31]

Self-reported TST and TIB were assessed with questions from the Pittsburgh Sleep Quality Index (PSQI),[32] which was administered during the home interview.

Covariates

Weight and height were measured at the research center, and were used to calculate BMI (weight in kilograms/height in meters squared). Smoking was determined in the home interview. Depressive symptoms were assessed with the Center for Epidemiologic Studies Depression Scale.[33] The CES-D is a self-report scale with 20 items, with a maximum score of 60. Scores of 16 or greater on the CES-D are traditionally interpreted as suggestive of clinically significant depression.[34] Heart failure was defined as moderate or poor left ventricular function, as assessed with echocardiography.[35] To operationalize the occurrence of probable sleep apnea, two questions from the PSQI were used. In line with Fogelholm et al.,[36] sleep apnea was considered probable in persons who reported 1) loud snoring at least 2 nights a week, with at least occasional respiratory pauses, or 2) respiratory pauses during sleep with a frequency of at least 1-2 nights weekly.

Statistical analysis

We performed regression analyses to investigate the associations of actigraphically measured TST, TIB and fragmentation index with total cholesterol level, HDL cholesterol level, and the

ratio of total / HDL cholesterol. Fragmentation index was expressed as standard deviation units to facilitate interpretation. We tested both linear and quadratic models of TST, TIB and fragmentation index. Means were imputed for missing values of body mass index (N = 12) and depressive symptoms (N = 14). All of the analyses were adjusted for age, gender, body mass index, smoking, depressive symptoms and heart failure, as these variables were considered potential confounders of the relationships between sleep and cholesterol level. Depressive symptoms are an important determinant of sleep quality, and could be related to cholesterol level as loss of appetite is a symptom of depression. Moreover, depressive symptoms are an important marker of general health, or frailty, in an elderly population.[37] Heart failure was also added to the models to control for comorbidity. We tested the interaction of all three sleep parameters with age, in relation to all of the outcome measures. Because several of the interaction terms were significant, we stratified the study population by age groups and performed linear regression analyses with all of the outcome measures for each of the age groups. Cut-offs for age groups (65 and 70 years) were chosen such that a) the boundaries of the groups were round numbers, and b) each age group contained an approximately similar number of persons. We repeated all of the analyses after exclusion of persons with probable sleep apnea. Additional analyses were performed to further explore the significant associations: we investigated models with additional adjustment for the other sleep parameters. To illustrate the relationship between TST and total cholesterol, we performed an analysis of covariance with categories of TST, adjusted for age, gender, body mass index, smoking, depressive symptoms and heart failure. Finally, we repeated the analyses with self-reported TST and TIB. All of the analyses were performed with SPSS version 11.0 (SPSS Inc., Chicago, IL).

RESULTS

Table 1 presents the characteristics of the study population. Mean age was 68.5 years (range 57-97) and 52.9 % were female. A non-response analysis showed that nonresponders, who visited the research center but refused to participate in the actigraphy study (N = 439), were on average 2.5 years older than responders ($p < 0.001$) and were more likely to be female (32.2 % vs. 25.1 %, $p = 0.002$). Refusal to participate was neither associated with average sleep duration as self-reported in the home interview, nor with cholesterol level.

Table 2 shows the sleep parameters of the study population, stratified for gender and age category. On average, our study population slept 6:32 (SD = 0:50) h per night, of the 8:19 (SD = 0:47) h they spent in bed. TST and TIB were related to each other: Pearson's correlation coefficient between TST and TIB was 0.68 ($p < 0.001$). This correlation did not differ between age groups.

The associations between actigraphic sleep parameters and cholesterol measures are presented in Table 3. It shows that persons with a longer TST had higher total cholesterol

Table 1. Characteristics of the study population, N = 768

Characteristic	Mean	SD	%
Age, y	68.5	7.0	
Gender (female)			52.9
Total cholesterol level, mmol/l	5.9	0.9	
HDL cholesterol level, mmol/l	1.5	0.4	
Total/HDL cholesterol ratio	4.2	1.2	
Body mass index, kg / m^2	27.8	4.0	
Smoking			14.5
Depressive symptoms, CES-D score	4.8	6.2	
Heart failure (moderate/poor left ventricular function)			2.7
Probable sleep apnea			9.0
Actigraphic total sleep time, h:min	6:32	0:50	
Self-reported total sleep time, h:min	6:56	1:14	

SD: standard deviation, CES-D: Center for Epidemiologic Studies Depression scale.

Table 2. Actigraphic sleep parameters of the study population, stratified for gender and age category, N = 768

Age category		N	Actigraphic TST, h:min, mean (SD)	Actigraphic TIB, h:min, mean (SD)	Fragmentation index, mean (SD)
Total, all ages		768	6:32 (0:50)	8:19 (0:47)	6.5 (2.6)
Men	59-64 y	140	6:14 (0:48)	8:01 (0:45)	7.2 (2.8)
	65-69 y	105	6:25 (0:51)	8:11 (0:46)	6.7 (2.6)
	70-97 y	117	6:27 (0:51)	8:23 (0:46)	7.3 (2.6)
Women	59-64 y	165	6:38 (0:43)	8:23 (0:41)	5.8 (2.3)
	65-69 y	111	6:37 (0:53)	8:24 (0:49)	6.2 (2.7)
	70-97 y	130	6:46 (0:48)	8:29 (0:48)	5.7 (2.4)

levels (β = 0.11 mmol/l per hour of TST, 95 % confidence interval (CI): 0.03 to 0.18). The R^2 of the entire model, i.e. of the linear association between actigraphic TST and total cholesterol with adjustment for age, gender, body mass index, smoking, depressive symptoms, and heart failure, was 0.12. The R^2 of a model with only actigraphic TST as an independent variable was 0.02. A longer TST was also related to a higher, i.e. less favorable, total/HDL ratio (β = 0.12, 95 % CI: 0.02 to 0.22). R^2 of this model was 0.09, of the unadjusted model 0.00.

A longer TIB was related to a lower HDL cholesterol level and also to a worse total/HDL ratio, but not to total cholesterol level. Fragmentation index was negatively associated with total cholesterol. Quadratic terms of TST, TIB, and fragmentation index were not associated with either of the cholesterol measures.

Next, we explored whether age modified the associations between sleep parameters and cholesterol level. The interaction of TIB with age (as a continuous variable) was significant for HDL level (β = 0.01 (0.002 to 0.01), $p = 0.006$) as well as for total/HDL ratio (β = -0.02 (-0.03 to

Table 3. Association of actigraphic sleep parameters and serum cholesterol, stratified in three separate age groups, N = 768

		Total cholesterol (mmol/l)		HDL cholesterol (mmol/l)		Ratio total / HDL cholesterol	
Age strata	Actigraphic sleep parameters	β (95% CI)	*p*-value	β (95% CI)	*p*-value	β (95% CI)	*p*-value
Total	Total sleep time, h	0.11 (0.03, 0.18)	.008	-0.02 (-0.05, 0.01)	.25	0.12 (0.02, 0.22)	.02
	Time in bed, h	0.05 (-0.03, 0.14)	.22	-0.05 (-0.09,-0.02)[2]	.003	0.16 (0.06, 0.27)[3]	.002
	Fragmentation index, per SD	-0.07 (-0.14, -0.01)[1]	.03	-0.02 (-0.04, 0.01)	.23	-0.02 (-0.10, 0.06)	.63
59-64 years	Total sleep time, h	0.18 (0.05, 0.31)	.006	-0.06 (-0.11, -0.003)	.04	0.24 (0.08, 0.40)	.003
(N = 305)	Time in bed, h	0.21 (0.07, 0.34)	.003	-0.09 (-0.15, -0.04)	.001	0.37 (0.21, 0.54)	<.001
	Fragmentation index, per SD	0.01 (-0.10, 0.11)	.85	-0.01 (-0.05, 0.03)	.66	0.04 (-0.08, 0.17)	.50
65-69 years	Total sleep time, h	-0.06 (-0.19, 0.08)	.40	-0.01 (-0.07, 0.05)	.82	-0.05 (-0.22, 0.13)	.60
(N = 216)	Time in bed, h	-0.13 (-0.27, 0.02)	.08	-0.06 (-0.13, -0.001)	.05	0.04 (-0.15, 0.23)	.68
	Fragmentation index, per SD	-0.04 (-0.16, 0.08)	.54	-0.01 (-0.06, 0.05)	.81	-0.02 (-0.18, 0.14)	.79
70-97 years	Total sleep time, h	0.20 (0.05, 0.34)	.009	0.01 (-0.05, 0.07)	.68	0.16 (-0.03, 0.34)	.10
(N = 247)	Time in bed, h	0.05 (-0.10, 0.21)	.51	0.001 (-0.06, 0.06)	.98	0.06 (-0.13, 0.26)	.52
	Fragmentation index, per SD	-0.22 (-0.35, -0.10)	<.001	-0.04 (-0.08, 0.01)	.16	-0.11 (-0.27, 0.05)	.18

Test was multiple linear regression. Analyses were adjusted for age, gender, body mass index, smoking, depressive symptoms, and heart failure.

[1] interaction of fragmentation index with age is significant for total cholesterol, $p < 0.05$

[2] interaction of time In bed with age is significant for HDL cholesterol, $p < 0.01$

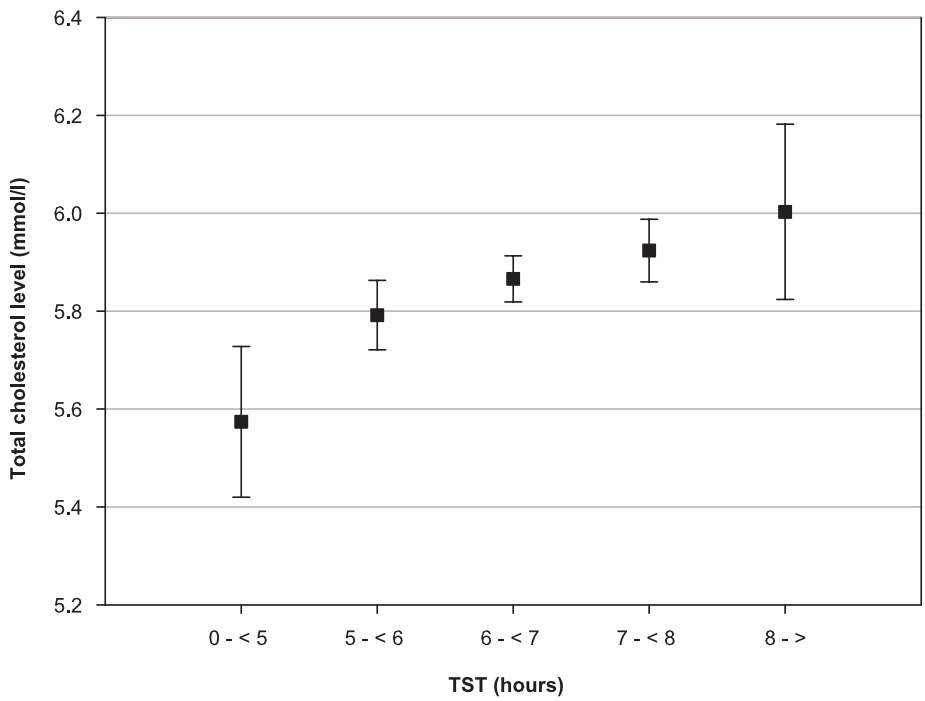
[3] interaction of time In bed with age is significant for Ratio total / HDL cholesterol, $p < 0.05$

-0.004), p = .01). Also, the interaction of fragmentation index with age was significant in the analysis of total cholesterol: β of interaction term = -0.01 (-0.02 to 0.000), p = 0.04).

We repeated all of the analyses after exclusion of those persons with probable sleep apnea (N = 69). This did not result in any substantial changes (data not shown).

Because of the modifying effect of age, we performed stratified analyses for three age categories; these analyses illustrate the observed interaction effects and are added in Table 3. Although not all of the interactions with age were significant, we present all of the analyses for the three age groups, in order to offer a complete overview. The association between fragmentation index and total cholesterol was due to the strong effect in the highest age category of 70 years and older. Per SD of fragmentation, total cholesterol decreased with 0.23 mmol/l (95 % CI -0.35 to -0.10) in this age group. In contrast, TIB was only positively associated with total/HDL ratio in the youngest age group, < 65 years, and negatively with HDL level in the two youngest age groups, < 70 years. Figure 1 illustrates the association between TST and total cholesterol level. Per 1 h category of TST, the mean cholesterol levels with standard errors are depicted.

Figure 1. Association between categories of TST and total cholesterol level (N = 768)



Test was ANCOVA. Adjusted for age, gender, body mass index, smoking, depressive symptoms, and heart failure. Bars represent standard errors of mean values.

In an additional analysis, we examined whether the significant associations between TST and total cholesterol for the whole study population, and the association between fragmentation index and total cholesterol for the oldest subgroup, were still significant when adjusted for the other sleep parameters. We found that the relationship between TST and total cholesterol remained significant after adjustment for TIB: β = 0.13, 95% CI 0.03 to 0.23, $p = 0.01$. However, when additionally adjusted for fragmentation index, the association was no longer significant. This is probably because of the fact that TST and fragmentation index measure related constructs. In the subgroup of participants aged 70 or over, higher sleep fragmentation was still associated with lower total cholesterol level when the analysis was additionally adjusted for both TST and TIB (β = -0.21, 95% CI -0.39 to -0.03, $p = 0.03$).

Table 4 presents the results of the analyses with self-reported sleep parameters, performed in 714 participants with valid responses on both TST and TIB. A linear association existed between both self-reported TST and HDL-cholesterol (β = -0.04, 95% CI -0.06 to -0.02, $p = 0.001$), and between self-reported TST and total/HDL ratio (β = 0.09, 95% CI 0.02 to 0.16, $p = 0.01$). The association between self-reported TIB and HDL-cholesterol was also significant. This indicates that a longer self-reported TST was related to a lower HDL-cholesterol level and a higher total/HDL ratio, which is in line with the results of the actigraphic data. However, in contrast to the results with actigraphic TST, there was no association between self-reported TST or TIB and total cholesterol level. Except for the association between TST and HDL cholesterol level, all of the associations were stronger with actigraphic data than with self-report data.

Table 4. Association of self-reported sleep parameters and serum cholesterol, N = 714

	Total cholesterol (mmol/l)		HDL cholesterol (mmol/l)		Ratio total / HDL cholesterol	
Sleep parameters	β (95% CI)	*p*-value	β (95% CI)	*p*-value	β (95% CI)	*p*-value
Self-reported TST, h	-0.02 (-0.07, 0.04)	.48	-0.04 (-0.06, -0.02)	.001	0.09 (0.02, 0.16)	.01
Self-reported TIB, h	-0.00 (-0.07, 0.06)	.90	-0.03 (-0.06, -0.01)	.02	0.07 (-0.01, 0.15)	.07

DISCUSSION

In this cross-sectional study of 768 community-dwelling elderly subjects, who did not use cholesterol lowering medication, a longer sleep duration was associated with a higher total cholesterol level and a less favorable lipid profile. It has to be noted that the explained variances of these regression models were at best modest. A longer sleep duration is strongly related to a longer time in bed; the use of actigraphy allows the distinction between time in bed and sleep duration. Our analyses showed that the relationship between sleep duration and cholesterol was driven by the strong association between a longer time in bed and a higher total cholesterol level in the youngest age group of people under 65. However, in persons aged 70 or older, the association between sleep duration and cholesterol seemed

to be explained by sleep fragmentation, which was related to a lower total cholesterol level. Indeed, there were significant interactions between age and sleep parameters. To our knowledge, ours is the first study of sleep and cholesterol that used multiple nights of actigraphy to assess sleep parameters in a large sample. Moreover, we included elderly participants, whereas most previous studies investigated younger populations.

Before we discuss these findings, some methodological comments have to be made. First, a selection effect may have occurred due to nonparticipation. However, it is unlikely that this has resulted in substantial bias, because participation in the actigraphy study was neither associated with self-reported sleep duration, nor with cholesterol level. Second, actigraphy is not the gold standard for distinguishing sleep from waking. TST derived from actigraphy data may differ with different actigraphy devices or algorithms. The algorithm that we used has been validated in a study of sleep disordered patients;[30] the appropriateness of this algorithm in a normal population has not been tested. However, the use of actigraphy enables studies involving multiple days and nights of testing, thereby increasing reliability,[24] and permits the evaluation of persons in their natural sleeping environment, whereas polysomnography is not feasible in large studies, and its ecological validity is sometimes questionable.[28] Third, polysomnography would have been necessary to accurately assess the presence of sleep apnea. Actigraphy does not allow adequate assessment of sleep apnea.[38] In our study, sleep apnea was diagnosed as 'probable' by using self-reported snoring and nocturnal respiratory pauses, as described previously by Fogelholm et al.[36] Fourth, the relationships of sleep parameters with cholesterol could have been confounded to some extent by lifestyle factors such as food frequency and physical activity. Unfortunately, these data were not available for our study population. Finally, the cross-sectional setting prevented us from inferring causality or chronological order of events.

The relationship between sleep duration and cholesterol that we found seems to be attributable to different aspects of sleep, depending on the age group. In the analyses with HDL level and total/HDL ratio, the interaction of TIB with age was significant; in the analysis with total cholesterol, fragmentation index showed a significant interaction with age.

In the youngest age group of persons aged 59 to 64, both TST and TIB were associated with higher total cholesterol, lower HDL cholesterol, and therefore with a higher total/HDL ratio. This was not the case in persons aged ≥ 65. Apparently, in younger subjects, a longer sleep duration is related to an unfavorable lipid profile. We found this association with both actigraphic data and self-report measures. Several mechanisms could explain this association. It is known from longitudinal studies that sleep duration can affect glucose metabolism, but whether this causal pathway also applies to cholesterol levels remains to be investigated. Another possibility is that both a long sleep duration and an unfavorable lipid profile are caused by lifestyle factors, such as a high fat intake. Also, persons who spend more time in bed may on average be less active during a 24-hour period, and activity is known to influence

cholesterol levels. Moreover, high cholesterol levels may cause illness that influences sleep. Unfortunately, we were not able to further elucidate potential causal pathways.

In the group of participants over age 70, persons with a high sleep fragmentation had lower total cholesterol levels, whereas sleep fragmentation was not related to any of the other cholesterol measures in any of the other age groups. In our study, sleep fragmentation is defined as the amount of uninterrupted immobile episodes relative to the total amount of time spent without movement. In other words, it is a measure of the frequency of interruption of sleep by physical movement. Because the Actiwatch algorithm considers prolonged and intense movement as wakefulness, sleep fragmentation is inversely related to actigraphically measured TST.

It is difficult to conceive of a mechanism by which highly fragmented sleep causes low total cholesterol levels in elderly people. A high frequency of physical movement during sleep may be brought about by, e.g., insomnia, periodic limb movement disorder, nocturia, pain, illness, environmental noise, or a snoring bed partner. Some of these causes, especially illness, may be a common basis for both high sleep fragmentation and low total cholesterol level, as low cholesterol level may be a marker of poor health in the elderly.[39]

Previous research of sleep and cardiovascular risk or disease has often focused on the role of sleep apnea. The increased risk of cardiovascular disease in persons with obstructive sleep apnea is thought to be mainly explained by exposure to intermittent hypoxia, which can lead to oxidative stress, inflammation, atherosclerosis, endothelial dysfunction, and hypertension.[40-42] It has also been shown that obstructive sleep apnea is associated with the metabolic syndrome,[43] although others argue that obesity, and not obstructive sleep apnea, is the main determinant of lipid abnormalities and other metabolic outcomes.[44] Since all of our analyses were adjusted for BMI, we know that the associations that we found were not explained by obesity. Exclusion of persons with probable sleep apnea did not markedly influence our results, which makes it unlikely that our results can be entirely ascribed to sleep apnea.

The associations between TST and cholesterol levels that we found are only partially in line with the other studies of sleep duration and lipid levels. Williams et al. found decreased HDL-cholesterol levels with both short and long sleep duration in women aged 43 to 69 years with type 2 diabetes in the Nurses' Health Study, but this finding was restricted to those women without hypertension.[22] These associations were adjusted for BMI, as well as additional lifestyle and medical factors. In contrast to our study, they did not find an association between sleep duration and total cholesterol level. In a large study of 8860 persons, Bjorvatn et al. studied the association between sleep duration and metabolic measures.[11] In an unadjusted analysis, they found higher total cholesterol levels in 40- to 45-year-old subjects with short sleep duration, but this was attributed to variables like gender, smoking and BMI. There is an important methodological difference between these studies and ours: both used self-report

measures of sleep duration only. We could not detect an association between TST and total cholesterol level with these measures either. Another difference to our study is the younger age of the participants. However, in a third study by Ekstedt et al., a night's sleep of 24 young adults was examined with polysomnography. They found that TST was positively related to the LDL/HDL ratio,[23] which is in accordance with our results, despite the considerably younger age of the participants. Their results with regard to sleep fragmentation differed from ours: it was a significant predictor for higher total cholesterol and LDL cholesterol. It has to be noted that, in their study, sleep fragmentation was defined as the number of sudden transient cortical arousals per hour, which is hardly comparable to our measure of sleep fragmentation, although both are presumably indicators of some kind of restlessness of sleep.

It is difficult to explain our results in the light of the association between sleep duration and mortality, particularly since the association between cholesterol levels and mortality is not straightforward in the elderly. High serum cholesterol remains a risk factor for myocardial infarction in the elderly,[45] but in elderly people, low concentrations of serum cholesterol also predict increased mortality. Probably, this is due to a common underlying disease process.[46] The association of long sleep duration with cholesterol that we found seems to reflect two different mechanisms, depending on the age of the participants. In persons under 65, a longer sleep duration, due to spending much time in bed, is related to high total cholesterol and an unfavorable lipid profile. Interestingly, this above-mentioned association was both demonstrated with actigraphic and self-report data. In people over 70, a highly fragmented sleep is associated with low cholesterol levels, which could be due to underlying illness. Longitudinal research is needed to elucidate the (causal) pathways among sleep, cholesterol, and mortality. In addition to epidemiological research, experimental research may shed light on the biological mechanisms underlying the relation between these psychological and somatic factors. The substantial discrepancy between TIB and TST in this study, i.e., the average time spent in bed awake, suggests that sleep efficiency could be improved without compromising sleep duration. Small-scale studies have shown a reduction of sleep problems after behavioral interventions. Although TIB was reduced, TST did not decrease.[47, 48] It is thus tempting to speculate that such an altered sleeping pattern may also favorably influence cholesterol levels, but this needs to be demonstrated in experimental studies. For any type of further research in this domain, we recommend to use objective measures of sleep duration and sleep quality, pay close attention to interactions with age, and meticulously adjust for potential confounders.

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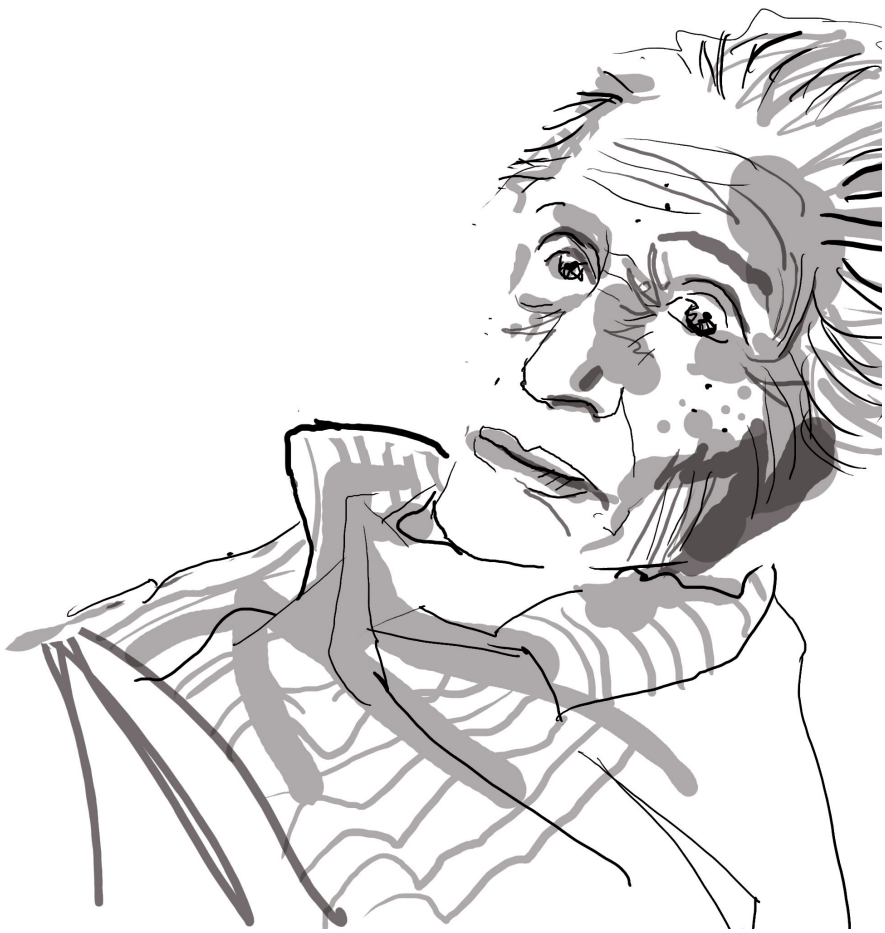
Part III.

Sleep and psychiatric disorders



Chapter 6.

Sleep in depression and anxiety disorders

SUMMARY

Objective Sleep disturbance is common in psychiatric disorders such as depression. However, the relationship of depression with Total Sleep Time (TST), a core parameter in sleep research, is unclear. This study aims to investigate TST and other sleep parameters in elderly persons with and without depressive disorders and anxiety disorders.

Method The study was embedded in the Rotterdam Study, a community-based study of elderly persons living in a district of Rotterdam, The Netherlands. Between January 2002 and December 2005, sleep parameters were assessed with the Pittsburgh Sleep Quality Index in 5019 persons aged 58 - 100. DSM-IV diagnoses of depressive and anxiety disorders were also ascertained. Associations between psychiatric disorders and sleep parameters were investigated with multivariate statistical methods.

Results On average, depressed persons spent more time in bed than the reference group. However, neither the average TST of depressed persons nor TST of persons with an anxiety disorder differed from that of persons without these disorders. Rather, the relationships of TST with depressive disorders and anxiety disorders were adequately described by a quadratic model ($p < 0.001$). These associations were stronger in people who did not use psychoactive medication. Participants with a depressive disorder and a comorbid anxiety disorder reported a 1 h shorter TST ($p < 0.001$).

Conclusion The interrelatedness of sleep parameters and psychiatric disorders is complex. Both long and short sleepers are more likely to have a depressive disorder or an anxiety disorder than persons with a sleep duration of 7 - < 8 h.

INTRODUCTION

Total Sleep Time (TST) is a core parameter in clinical sleep medicine and epidemiologic sleep research. It is related to well-being, health and mortality.[1, 2] Individual differences in TST may result from psychiatric disorders, such as depression, because depression is strongly related to sleep disturbance[3-8]: in 40 % to 90 % of subjects with diagnosed depression, complaints of poor sleep quality are observed.[5, 7, 8] The association between depression and sleep disturbance has been extensively studied. Polysomnographic sleep research has shown alterations of sleep architecture in depression, in particular an impaired sleep efficiency, a reduction of slow-wave sleep, and changes in rapid eye movement (REM) sleep.[5, 9] Several hypotheses regarding physiological mechanisms underlying sleep disturbance in depression have been discussed in an elaborate review by Tsuno et al.[5] The association of depression with poor sleep quality has also been studied in epidemiological research. These studies show that the relationship is bidirectional: on the one hand, depression strongly increases the risk of poor sleep quality, and on the other hand, poor sleep quality is a predictor for future depressive episodes.[4-6, 8, 10, 11] This relationship holds even after accounting for previous depression.[9] Although the relationship between depression and perceived or measured sleep disturbance is of great clinical interest, from an epidemiological perspective, other sleep parameters are important as well. Most previous studies that examined associations between mental health and sleep disturbance did not analyze other sleep parameters such as TST, the time spent in bed (TIB) or the time needed to fall asleep (sleep onset latency, SOL). The few studies that did investigate the association between TST and depression reported conflicting results. Chang et al.[11] found that those getting 7 hours of sleep or less were more likely to develop a depressive disorder than those getting more than 7 hours of sleep, but this association was only marginally significant in an adjusted model. Taylor et al.[12] could not detect any association between TST or SOL and depression or anxiety. Some epidemiological studies found a higher likelihood of depression, or a higher number of depressive symptoms, in both short and long sleepers.[1, 13] One previous study reported on the association between long sleep and depression,[2] but since long sleep was the focus of this study, they did not report whether a U-shaped curve was present. These differences in observations may be a consequence of differences in assessment methods of both sleep and psychiatric disorders. In most population-based studies questionnaires are used for the ascertainment of psychiatric disorders, the use of psychiatric interviews is exceptional.

Poor sleep can also be a consequence or symptom of an anxiety disorder.[14-17] It is, for example, an important symptom of generalized anxiety disorder,[15] which is the most common anxiety disorder among older adults.[18] It has also been shown that insomnia is common in patients with panic disorder[17, 19], and related to 'trait'anxiety.[12] Whereas sleep in depressive disorders has been extensively studied, the study of sleep in anxiety disorders is less well developed. In particular, the relationship between anxiety disorders and sleep parameters

has scarcely been studied in population samples. Anxiety disorders frequently coexist with depressive disorders,[20] and this comorbidity may affect sleep even more than having only one disorder.

Many previous studies of sleep disturbance and psychiatric disorders were performed in clinical populations or otherwise selected groups, which limits the generalizability of the results.

The present study examines various sleep parameters in 5019 community-dwelling elderly persons. As both insomnia and hypersomnia can be symptomatic of depressive disorders according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV),[21] we hypothesize that both long and short sleep durations are associated with depressive disorders. As anxiety disorders are likely to involve increased arousal, we expect an association between short sleep and anxiety, but not between long sleep and anxiety disorders. In addition, we are interested in the relationships of other sleep parameters (TIB and SOL) with depression and anxiety.

METHODS

Study population

This study is embedded in the Rotterdam Study, a population-based cohort study aimed at assessing the occurrence of and risk factors for chronic diseases in the elderly.[22] In 1990, all inhabitants of a district of Rotterdam aged 55 years and over were invited to participate. In 2000, the study population was extended with a second cohort of people aged 55 years and over. Between January 2002 and December 2005, 3547 participants from the original cohort and 2500 participants of the extended cohort underwent a home interview. Of these 6047 participants, 173 persons were excluded because of considerable cognitive impairment (MMSE[23] score < 22), as we expected the assessment of both psychiatric disorders and sleep to be unreliable in these persons. For 5019 of the remaining 5874 participants, complete and valid data on sleep, depression and anxiety disorders were available. The Medical Ethics Committee of the Erasmus University Rotterdam approved the Rotterdam Study and written informed consent was obtained from all participants.

Assessment of sleep parameters

We assessed subjective sleep quality with the Dutch version of the Pittsburgh Sleep Quality Index (PSQI)[24] as a part of the home interview. The PSQI is a self-rating questionnaire which measures sleep quality and disturbance retrospectively over a 1-month period, resulting in a global score between 0 and 21, with higher scores indicating poorer sleep quality. Self-reported TST and SOL were derived from two individual PSQI questions. TIB was calculated from self-reported bed time and get up time.

Assessment of depression and anxiety

Depressive disorders were diagnosed using a two-step procedure. First, participants were screened for depressive symptoms with a validated Dutch version of the Center for Epidemiologic Studies Depression (CES-D) scale[25, 26] during the home interview. As a second step, subjects with a CES-D score above the cut-off of ≥ 16 underwent a semi-structured psychiatric interview with the Schedules for Clinical Assessment in Neuropsychiatry (formerly known as Present State Examination),[27] performed by an experienced clinician. Depressive disorders (major depression, minor depression and dysthymia) were classified according to the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) criteria.[21] As part of the initial home interview, a slightly adapted Munich version of the Composite International Diagnostic Interview (M-CIDI)[28, 29] was administered, to assess the following anxiety disorders according to DSM-IV criteria[21]: generalized anxiety disorder, specific phobia, social phobia, agoraphobia without panic disorder, and panic disorder with or without history of agoraphobia. As the prevalences of most of the separate disorders were low in our study population, we used two dichotomous variables indicating whether or not a person had at least one of the DSM-IV depressive disorders, or one of the anxiety disorders. However, generalized anxiety disorder and agoraphobia could also be analyzed separately, as these were the two largest groups.

Assessment of other variables

The use of psychoactive medication (antidepressants, anxiolytics, sedatives, hypnotics) was assessed in the home interview. Cognitive function was assessed with the Mini Mental State Examination.[23] Scores on this test range from 0 to 30, with higher scores indicating a better cognitive performance. To evaluate functional disability, we used the Stanford Health Assessment Questionnaire,[30] a subjective measure of physical health with emphasis on the ability to perform daily activities in five different domains. Larger scores on this questionnaire represent more disability. All of the questionnaires were administered as part of the home interview.

Statistical analysis

We divided our study population into four groups: persons without any depressive or anxiety disorder (reference group), persons with only a depressive disorder, persons with only an anxiety disorder, and persons with both a depressive disorder and an anxiety disorder. We used analysis of covariance to estimate age- and gender-adjusted mean values of self-reported TST, SOL, TIB and global PSQI score for each of the groups, and differences with the values of the reference group.

To investigate whether quadratic relationships existed between TST and depressive disorders or anxiety disorders, we performed logistic regression analyses with a continuous measure of TST as the independent variable and depressive disorder and anxiety disorder, respectively, as dichotomous dependent variables. It has to be noted that with neither of

our analyses, we imply a causal or temporal direction of the associations under study. We tested both linear models and models where a quadratic term was added, since both short and long sleep may be related to psychiatric disorders. These analyses were repeated for the two largest groups of persons with specific anxiety disorder diagnoses. When we found that the relationship between TST and depressive and anxiety disorders was best described by a quadratic model, we repeated the analyses with categories of TST: < 5, 5 - 6, 6 - 7, 7 - 8, 8 - 9 and 9 > h, to illustrate the results. These last analyses were repeated in the participants who did not use psychoactive medication (N = 3862). Additionally, we used ANCOVAs to examine whether depressive persons with short TST (< 7 h, N = 99) differed from depressive persons with long TST (≥ 8 h, N = 48), with respect to comorbidity with functional disability and the number of depressive symptoms. To conclude, we investigated whether the occurrence of generalized anxiety disorder and agoraphobia, the two largest groups of specific anxiety disorder diagnoses, was related to being either a long or a short sleeper. All of the analyses were adjusted for age and gender. All analyses were performed with SPSS version 11.0 (SPSS Inc., Chicago, IL).

RESULTS

Table 1 presents the characteristics of the study population. Of the 5019 participants in our study, 56.7 % were female, and the mean age was 72.4 years (SD = 6.7, range 58 - 100). Table 2 shows the average sleep parameters, and the prevalence of depressive disorders and anxiety disorders of the study population. DSM-IV criteria for a depressive disorder were met by 179 participants (3.6 % of the total study population), 407 (8.1 %) had one or more anxiety disorders. Participants reported on average 6.88 h (SD = 1.27) of sleep per night.

Table 1. Characteristics of the study population, N = 5019

Characteristic	**Total study population**	**No** depressive disorder or anxiety **disorder**	**Depressive disorder**, no anxiety disorder	**Anxiety disorder**, no depressive disorder	**Both depressive and anxiety disorder**
	N = 5019	N = 4499	N = 113	N = 341	N = 66
Age, years, mean (SD)	72.4 (7.6)	72.3 (7.6)	75.3 (8.8)	71.7 (7.2)	73.9 (7.7)
Gender (female), N (%)	2848 (56.7)	2453 (54.5)	78 (69.0)	264 (77.4)	53 (80.3)
Cognitive function (MMSE score), mean (SD)*	27.7 (1.8)	27.7 (1.8)	27.1 (2.1)	27.5 (1.8)	26.9 (2.0)
Depressive symptoms, CES-D score, mean (SD)	6.0 (7.4)	4.9 (5.7)	24.6 (7.2)	9.6 (9.1)	30.0 (8.4)
Functional disability, HAQ score, mean (SD)	1.5 (0.6)	1.5 (0.5)	2.1 (0.8)	1.7 (0.6)	1.9 (0.7)
Use of psychoactive medication, N (%)	805 (17.2)	613 (14.7)	57 (53.3)	104 (32.1)	31 (50.8)

*Note: persons with MMSE score < 22 have been excluded

All of the percentages refer to the cases with information on this variable (valid percentage).

MMSE: Mini Mental State Examination. CES-D: Center for Epidemiologic Studies Depression scale. HAQ: Health Assessment Questionnaire.

Table 2. Depressive disorders, anxiety disorders and sleep parameters in the study population, N = 5019

Characteristic		mean (SD)	N (%)
Sleep parameters:	TST, h, mean (SD)	6.88 (1.27)	
	SOL, min, mean (SD)	21.6 (28.8)	
	TIB, h, mean (SD)	7.74 (1.10)	
	Global PSQI score, mean (SD)	3.9 (3.6)	
DSM-IV Depressive disorders (total)*, N (%)			179 (3.6)
Major depressive disorder, N (%)			98 (2.0)
Minor depressive disorder, N (%)			62 (1.2)
Dysthymia, N (%)			19 (0.4)
DSM-IV Anxiety disorders (total)*			407 (8.1)
Generalized Anxiety Disorder, N (%)			111 (2.2)
Social phobia, N (%)			56 (1.1)
Specific phobia, N (%)			79 (1.6)
Agoraphobia without history of panic disorder, N (%)			195 (3.9)
Panic disorder with or without agoraphobia, N (%)			28 (0.5)

* Categories of depressive disorders are mutually exclusive, categories of anxiety disorders are not.
TST: Total Sleep Time. SOL: Sleep Onset Latency. TIB: Time in Bed. PSQI: Pittsburgh Sleep Quality Index.

Table 3 shows the age- and gender-adjusted estimated means of TST, SOL, TIB and global PSQI score for groups of participants with depressive disorders, anxiety disorders, or both. TST in persons with a depressive disorder only, or an anxiety disorder only, did not differ from TST of persons in the reference category. However, participants with both disorders reported a 1.07 h (95% CI: 0.76 to 1.37) shorter TST than persons without these disorders. SOL was 8.9 min (95 % CI: 3.7 to 14.1) longer in depressed participants than SOL in the reference category, 5.6 min (95 % CI: 2.5 to 8.7) longer in persons with an anxiety disorder, and 15.2 min (95 % CI: 8.4 to 22.0) longer in participants with both disorders. TIB was significantly longer in participants with only a depressive disorder than in any of the other groups (Table 3).

Table 4 shows that the relationship of TST with depressive disorders was adequately described by a quadratic - U-shaped - model (odds ratio (OR) of quadratic term: 1.10; 95 % CI: 1.05 to 1.15, $p < 0.001$) as well as with anxiety disorders (OR of quadratic term: 1.06; 95 % CI: 1.02 to 1.20, $p = 0.002$). Linear models were also significant for depressive disorders as well as anxiety disorders, both with ORs < 1, indicating that the associations of short sleep with both disorders were stronger than the associations of long sleep. The analyses were repeated for the two largest groups of persons with specific anxiety disorder diagnoses, generalized anxiety disorder (N = 111) and agoraphobia without history of panic disorder (N = 195). This showed that TST also had a clear quadratic relationship with generalized anxiety disorder (OR of quadratic term: 1.10; 95 % CI: 1.04 to 1.17, $p = 0.001$). The relationship of TST with agoraphobia, however, was best described by a linear model (OR 0.89, 0.80 to 1.00, $p = 0.04$); a quadratic model was not significant. This indicates that short sleepers were more likely to have this disorder than long sleepers.

Table 3. Sleep parameters in depressive and anxiety disorders, N = 5019

Sleep parameter	Reference category*	Depressive disorder, no anxiety disorder			Anxiety disorder, no depressive disorder			Both depressive and anxiety disorder		
	N = 4499	N = 113			N = 341			N = 66		
	Estimated mean	Estimated mean	Difference with reference (95% CI)	*p*-value of difference	Estimated mean	Difference with reference (95% CI)	*p*-value of difference	Estimated mean	Difference with reference (95% CI)	*p*-value of difference
TST (h)	6.91	6.90	-0.01 (-0.25, 0.22)	0.91	6.80	-0.10 (-0.24, 0.04)	0.14	5.84	-1.07 (-1.37, -0.76)	< 0.001
SOL (min)	20.8	29.7	8.9 (3.7, 14.1)	0.001	26.4	5.6 (2.5, 8.7)	< 0.001	36.0	15.2 (8.4, 22.0)	< 0.001
TIB (h)	7.73	8.06	0.33 (0.13, 0.54)	0.002	7.82	0.09 (-0.04, 0.21)	0.16	7.53	-0.20 (-0.47, 0.07)	0.14
PSQI score	3.7	6.2	2.5 (1.9, 3.1)	< 0.001	4.8	1.1 (0.8, 1.5)	< 0.001	8.6	4.9 (4.1, 5.8)	< 0.001

Test: ANCOVA. All of the analyses are adjusted for age and gender

*No depressive disorder, no anxiety disorder

TST: Total Sleep Time. SOL: Sleep Onset Latency. TIB: Time in Bed. PSQI: Pittsburgh Sleep Quality Index.

Table 4. Association of TST and DSM-IV depressive and anxiety disorders, N = 5019

	DSM-IV depressive disorders		DSM-IV anxiety disorders	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Linear model				
TST (h)	0.80 (0.71 – 0.89)	< 0.001	0.86 (0.79 – 0.93)	< 0.001
Quadratic model				
TST (h)	*0.24 (0.13 – 0.42)*	*< 0.001*	*0.40 (0.25 – 0.65)*	*< 0.001*
TST^2 (h^2)	1.10 (1.05 – 1.15)	< 0.001	1.06 (1.02 – 1.20)	0.002

Test: logistic regression. All analyses are adjusted for age and gender

TST: Total Sleep Time

Table 5. Association of categories of TST and DSM-IV depressive and anxiety disorders

Total study population, N = 5019		DSM-IV depression			DSM-IV anxiety disorder		
TST, h	N total	N (%) with depression	Odds ratio (95% CI)	*p*-value	N (%) with anxiety disorder	Odds ratio (95% CI)	*p*-value
< 5	267	26 (9.7)	4.60 (2.68 – 7.90)	< 0.001	44 (16.5)	2.26 (1.55 – 3.31)	< 0.001
5 - < 6	546	35 (6.4)	2.98 (1.82 – 4.87)	< 0.001	58 (10.6)	1.36 (0.97 – 1.91)	0.07
6 - < 7	1134	38 (3.4)	1.61 (1.00 – 2.59)	0.05	90 (7.9)	1.05 (0.79 – 1.40)	0.74
7 - < 8	1617	32 (2.0)	reference	-	114 (7.1)	reference	-
8 - < 9	1211	33 (2.7)	1.41 (0.86 – 2.32)	0.17	80 (6.6)	0.92 (0.68 – 1.24)	0.59
≥ 9	244	15 (6.1)	3.15 (1.68 – 5.93)	< 0.001	21 (8.6)	1.23 (0.75 – 2.00)	0.41
Persons who do not use any psychoactive medication, N = 3862							
< 5	180	14 (7.8)	7.01 (3.21 – 15.3)	< 0.001	28 (15.6)	2.99 (1.85 – 4.82)	< 0.001
5 - < 6	382	17 (4.5)	3.96 (1.90 – 8.27)	< 0.001	34 (8.9)	1.56 (1.01 – 2.40)	0.05
6 - < 7	851	14 (1.6)	1.53 (0.71 – 3.28)	0.27	59 (6.9)	1.26 (0.88 – 1.82)	0.21
7 - < 8	1290	13 (1.0)	reference	-	68 (5.3)	reference	-
8 - < 9	978	16 (1.6)	1.69 (0.81 – 3.53)	0.17	52 (5.3)	1.01 (0.70 – 1.47)	0.96
≥ 9	181	6 (3.3)	3.18 (1.29 – 8.53)	0.02	9 (5.0)	0.95 (0.46 – 1.95)	0.89

Test: logistic regression. All of the analyses are adjusted for age and gender. TST: Total Sleep Time

Table 5 presents the associations of categories of TST with depressive disorders and with anxiety disorders, to illustrate the quadratic relationships. The table shows that persons with a TST of < 6 h and persons with a TST of > 9 h were more likely to have a depressive disorder. However, only persons in the lowest TST category, < 5 h, had a significantly higher risk of having an anxiety disorder. Table 5 also presents the results of the same analysis in a subgroup of participants who did not use any psychoactive medication. The ORs of depression in the lowest TST categories, as well as the OR of anxiety disorders in the < 5 h category, were substantially higher than the ORs in the total study population. This prompted us to perform an additional stratified analysis (results not presented in the table). In the group of persons who used psychoactive medication, the ORs for the lowest TST categories fell outside the CIs of the ORs in the group without psychoactive medication: e.g. the OR for depression in the lowest TST category of < 5 h was 2.49 (1.12 to 5.57), whereas in persons without medication it was 7.01 (3.21 to 15.3).

We also compared comorbidity with functional disability, as a measure of general medical condition, and CES-D scores (number of depressive symptoms), between depressive persons with short TST (< 7 h, N = 99) and depressive persons with long TST (≥ 8 h, N = 48). Adjusted for age and gender, there were no significant differences between these groups in functional disability (data not shown). However, depressed persons with short sleep had higher CES-D scores than depressed persons with long sleep (28.1 vs. 24.6, $p = 0.02$, ANCOVA).

DISCUSSION

In this cross-sectional study of 5019 community-dwelling elderly subjects, we found that the average TST in elderly persons with either a depressive disorder or an anxiety disorder did not differ from the average TST of those without these disorders. Rather, both short and long sleepers were more likely to have a depression or an anxiety disorder. These associations were stronger in participants who did not use psychoactive medication. When the time spent in bed, instead of TST, was analyzed in relation to depressive disorders, we found that persons with a depressive disorder did spend more time in bed than non-depressed persons. Finally, participants with a depressive disorder and a comorbid anxiety disorder reported a substantially shorter TST than other elderly persons.

Our study has several strengths. First, it is a large population-based study. In a community sample, one may encounter milder and untreated forms of psychiatric disorders that are not present in clinical samples. Moreover, it has been shown that persons with psychiatric disorders who do not seek help are different from patient populations, also with respect to sleep disturbance in depression.[31] Second, DSM-IV diagnoses of depressive disorders were carefully ascertained by experienced clinicians. Epidemiological research on this subject is often based on less precise measures of depressive disorders, which can result in misclassification. This methodological difference may explain the low prevalence of depression in our study, in comparison with other epidemiological studies in elderly persons.[32]

However, our study also has some limitations. First, the Composite International Diagnostic Interview, which we used to assess anxiety disorders, is a lay-administered diagnostic interview which is not equivalent to an experienced clinician's assessment. Second, our assessment of anxiety disorders did not include Acute Stress Disorder, Posttraumatic Stress Disorder and Obsessive Compulsive Disorder. This implies that some persons in the 'no anxiety disorder' categories may in fact have had one of these anxiety disorders. Third, we combined different categories of depressive disorders and also of anxiety disorders in order to obtain sufficient statistical power for our analyses. However, two of the anxiety disorder categories could be analyzed separately. There was some evidence that different categories of anxiety disorders have different relationships with sleep. Fourth, the cross-sectional design of our study precluded the inference of temporal relationships. Finally, we used self-report measures of sleep. Although we used a validated questionnaire, self-report measures can be biased, in particular in depressed persons.[33]

In this study, we assessed TST, TIB and SOL by questionnaire; these parameters have rarely been studied in relation to psychiatric disorders in large population samples. In some studies TST and TIB are used interchangeably,[34] which makes it unclear what exactly is meant by 'long or short sleep'. Only when both TST and TIB are taken into account, short sleep due to insom-

nia or sleep disturbance can be distinguished from short sleep with high sleep efficiency. The latter may be due to voluntary sleep restriction or less need of sleep.

Our analyses of TST confirmed our hypothesis of an association of both short and long TST with depression. This is in accordance with the observation that both insomnia and hypersomnia can be symptoms of depressive disorders.[21] Taylor et al.[12] noted that self-reported insomnia was strongly associated with both depressive and anxiety symptoms in a community-based study of 772 persons. However, they did not find any association between TST or SOL and depression or anxiety. This may have resulted from their assessment of depression and anxiety with self-report questionnaires, which is a less precise method than psychiatric interviews. Also, they did not present models with quadratic terms. Chang et al.[11] studied insomnia as a risk factor for depression in young men. They found that insomnia, and to a lesser extent sleeping ≤ 7 hours per night, increased the risk of subsequent depression. Studies such as these, which focus on sleep disturbance as a precursor of depressive disorders, rarely discuss long sleep or long time in bed. A cross-sectional association between long sleep and depression has been previously reported.[2] The U-shaped curve has also been described previously in three Japanese studies: both long and short sleep were related to depressive symptoms, as measured by CES-D, in Japanese adults,[1, 13] and to subjective well-being in Japanese elderly.[35] We found the U-shaped curve with psychiatric disorders that were diagnosed according to DSM-IV. We also found that depressed persons with short TST had higher CES-D scores than depressed persons with long TST, which may suggest that short sleepers have more severe depressions.

The results of our analyses with TIB did not follow the same pattern as the results of TST. We found that depressed individuals, on average, reported longer TIB than non-depressed persons, unless they also had a comorbid anxiety disorder. Spending much time in bed may be a result of symptoms of depression, such as fatigue, loss of energy, loss of interest or pleasure in activities, or indecisiveness.[21] The complex interrelatedness of depression, TST and TIB is probably best described by two separate mechanisms. On the one hand, poor or too little sleep may be both a precursor and a consequence of depression.[4-6, 8, 10, 11] On the other hand, long sleep is closely related to long time in bed and is more likely to be a symptom or consequence of depression. Whether a depression is characterized by insomnia or by long sleep and spending much time in bed may be a difference between individuals, or sleep patterns may change in the course of a depressive disorder.

To the best of our knowledge, no previous studies have investigated the association between sleep parameters and anxiety disorders in a population-based setting. We observed that the association between TST and anxiety disorders could also be described by a quadratic model. Our hypothesis concerning a relationship between short sleep and anxiety was confirmed, but apparently, long sleep duration is to some extent associated with anxiety disorders too,

although the quadratic relationship is less marked than with depression. SOL and subjective sleep quality were also significantly impaired in persons with anxiety disorders. This is in accordance with our hypotheses, as anxiety disorders manifest with heightened arousal, which is also implicated when sleep initiation or maintenance are disturbed.[19] Interestingly, TST had a clear quadratic relationship with generalized anxiety disorder, whereas the relationship of TST with agoraphobia was best described by a linear model. This suggests that different mechanisms are involved in sleep disturbance in these specific disorders. Ford and Kamerow[4] also reported a higher risk of depression as well as anxiety disorders in persons with insomnia, as well as in persons with hypersomnia. They noted that the relationship between anxiety disorders and sleep disturbances followed a pattern similar to that between depression and sleep disturbances, although the ORs were lower. However, apart from self-reported sleep complaints, they did not investigate other sleep parameters.

Comorbidity of depressive disorders and anxiety disorders is common.[4, 20, 36] In this study, TST was substantially shorter in persons with both a depressive disorder and an anxiety disorder, although the average TIB of these persons did not differ significantly from the average TIB in the reference group. Comorbidity of depression and anxiety disorders was also related to substantially worse self-reported sleep quality in terms of SOL and global PSQI score. These results suggest that persons with both disorders suffer from major sleep disturbance. Roth et al. investigated the relationship between comorbidity of psychiatric disorders and the occurrence of sleep problems. They reported that respondents meeting criteria for three or more 12-month DSM-IV disorders had much higher odds of sleep problems than respondents with one or two DSM-IV disorders.[37]

Thase[38] demonstrated that antidepressants exert both beneficial and, at times, detrimental effects on subjective and objective measures of sleep. Because of the large number of participants in our study, we were able to study the association of TST with depression and anxiety disorders in participants who did not use either antidepressants, anxiolytics, sedatives or hypnotics. In this subgroup, the associations of short TST with depression and anxiety disorders were stronger than in the total study population; in the group of persons who used psychoactive medication the associations were markedly weaker. This suggests that medication use increases (perceived) sleep duration in depressed persons. Another possible explanation for this finding is that the use of psychoactive medication lowers the risk of depression and anxiety disorders in short sleepers. Contrary to what might be expected, our results do not indicate that severity of sleep-related symptoms increases the likelihood of medication use. This confounding by indication would have led to weaker associations between short TST and psychiatric disorders in an unmedicated subgroup.

In summary, sleep parameters and psychiatric disorders are intertwined in complex ways. We found that both long and short TST are associated with depressive disorders in an elderly population, and the association between TST and anxiety disorders can also be described by

a quadratic model. The use of psychoactive medication appears to attenuate these relationships. In persons with depressive disorders, a long TIB is common. TST is substantially shorter in persons with a depressive disorder and a comorbid anxiety disorder. Future research with objective measures of sleep parameters would contribute to a better understanding of these phenomena.

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Chapter 7.

General Discussion

GENERAL DISCUSSION

The objective of this thesis was twofold. Firstly, its aim was to investigate assessment methods of habitual sleep in population-based studies. In particular, the focus was on actigraphy, a method that infers sleep and wakefulness from the presence or absence of arm movement. Its second aim was to gain insight into the relationship of sleep duration with cardiovascular risk factors and psychiatric disorders. The research described in this thesis was embedded within the Rotterdam Study, a large prospective cohort study of community-dwelling inhabitants of a district of Rotterdam, aged 55 and over. The main findings of the research described in this thesis will be reviewed and discussed in the light of current knowledge.

Aging and sleep

Sleep patterns evolve across the aging process. In comparison with young and middle-aged adults, older persons show more fragmented sleep and lower sleep efficiency (total sleep time (TST) divided by the time spent in bed). The decrease in sleep efficiency continues with aging, whereas other sleep parameters, such as TST, remain relatively stable after the age of 60.[1] Aging has also been associated with increased daytime napping.[2] Furthermore, sleep complaints are common in the elderly, and the occurrence of insomnia increases with age.[3, 4] However, poor sleep quality is often secondary to medical and psychiatric illness and circadian changes, rather than to aging, or to age-related sleep changes, per se.[5]

In elderly people, the circadian rhythm is normally not entrained by work routine or other obligations. Inter-individual variability in sleep patterns can therefore be attributed to personal characteristics, rather than to exogenous factors. Moreover, if sleep parameters have an effect on certain health outcomes, this will probably only be detectable after the accumulation of effects over a number of years. For these reasons, it was advantageous to perform the research described in this thesis in an elderly population, rather than in younger persons.

Study design

The Rotterdam Study has been designed to investigate the occurrence of, and risk factors for chronic diseases in elderly persons.[6] In 1990, all of the inhabitants of a district of Rotterdam aged 55 years and over were invited and 7983 agreed to participate. In 2000, the cohort was extended with 3011 persons from the same district, also aged 55 years and over. Every 3 to 4 years, these participants undergo an extensive examination, consisting of a home interview and two visits to the research center. Since December 2002, the home interview contains the Pittsburgh Sleep Quality Index (PSQI).[7] In December 2004, we obtained a grant for an additional actigraphy study. From this moment onward, 1515 participants were asked to take part in this actigraphy study, 1076 (71 %) of whom agreed. These persons were instructed to wear an actigraph over a period of five to seven consecutive days and nights. During the actigraphy study period, participants kept a sleep diary. We could not include every person

visiting the research center, due to the limited number of actigraphs that were initially available and for other logistic reasons. However, inclusion was independent of the characteristics of the participants. The studies described in chapters 1 through 5 are mainly based on the data of the subgroup who participated in the actigraphy study.

As data on sleep had not been collected in previous waves of the Rotterdam Study, only cross-sectional data were available for the research described in this thesis. However, the participants of these studies will be followed-up in future examinations of the Rotterdam Study, which enables longitudinal investigations of the cross-sectional relationships between sleep and health.

MEASURING SLEEP

Several methods are available for the assessment of sleep parameters and sleep patterns. The most commonly used measurement instruments are described below.

Polysomnography

Polysomnography (PSG) is a comprehensive recording of the physiological changes that occur during sleep. It monitors many body functions including brain activity (EEG), eye movements (EOG), muscle activity (EMG), heart rhythm (ECG), and breathing function or respiratory effort. Conventionally, polysomnographic recordings are classified according to the rules published in 1968 by Rechtschaffen and Kales.[8] This method is considered the gold standard for distinguishing sleep from waking. It is also an essential tool for other purposes such as the clinical evaluation of narcolepsy and sleep apnea, as well as selected cases of insomnia.[9] PSG is typically performed in a sleep laboratory, although ambulatory PSG, which can be performed at home, is increasingly common. In spite of the fact that PSG is the most accurate measure of sleep available, its use is hardly feasible in population-based studies. Firstly, it is expensive and time-consuming, which limits the possibility of taking measurements over multiple nights in large groups of people. Secondly, PSG measurements are probably not representative of a person's sleep pattern in normal circumstances, because the PSG devices may affect his or her usual bedtime, sleep latency and sleep hours, even when it is home based.[10] This is an important limitation for researchers who are interested in habitual sleep patterns.

Self-report measures

In large studies, the use of self-report measures is the most practical method to assess sleep duration, sleep quality and other sleep parameters. Two common types of self-report measures can be distinguished: questionnaires and sleep diaries. Questionnaires, which can be administered in either a 'paper and pencil' form or in a (telephone) interview, are retrospec-

tive over a recent period, e.g. the last month. Several validated questionnaires exist, e.g. the Pittsburgh Sleep Quality Index (PSQI)[7] and the Epworth Sleepiness Scale (ESS).[11] The use of validated questionnaires has the obvious advantage of making the results comparable to the results of others. However, some researchers also formulate their own questions (e.g. Kronholm et al.[12] and Stranges et al.[13]). In the studies described in this thesis, we used the PSQI, primarily because it is widely used and well validated. The PSQI contains subjective estimates of habitual Total Sleep Time (TST), Time In Bed (TIB) and Sleep Onset Latency (SOL), and it also provided data to calculate a proxy measure of sleep apnea. In chapters 1, 2 and 6, we also used the global PSQI score as a measure of general subjective sleep quality, which is the original purpose of the questionnaire.

When, in research or in diagnostic procedures, specific data on the timing of sleep over several nights are needed, these data are usually collected with a sleep diary or sleep log. A sleep diary contains questions that have to be answered as soon as possible after awakening; some sleep diaries, such as the one we used in our actigraphy study, also contain questions that should be answered at night before going to sleep. Common questions in a sleep diary are: "At what time did you go to bed last night?" "How long did it take you to fall asleep?" "At what time did you wake up?" "At what time did you get up?" "How many hours of sleep did you get?" These are the necessary questions to calculate the core sleep parameters TST, TIB, SOL and sleep efficiency (SE). Furthermore, a sleep diary usually contains some rating of sleep quality; either a visual analogue scale, a categorical question, or more specific questions about tiredness or sleepiness during daytime, number of nightly awakenings or reasons for sleep disturbance.

Results obtained with self-report measures depend on the perception of sleep and on variables that influence reporting, and may thus be biased. For example, in the Sleep Heart Health Study, self-reported sleep duration estimates were, on average, about an hour longer than PSG measurements.[14] Insomniacs, as a group, show a greater propensity than normal sleepers to underestimate TST,[15, 16] although this may depend on the type of insomnia.[17] Erroneous information on determinants or outcomes of a study, leading to misclassification of subjects for either the determinant or the outcome, is called information bias. This is an important notion throughout this thesis and will be discussed more extensively later.

Actigraphy

According to the American Academy of Sleep Medicine's Standards of Practice Committee, actigraphy is a reliable method for assessing sleep-wake patterns in adults.[18] An actigraph is a device that can be worn around the wrist like a watch. It measures movement, or more precisely, accelerations of the wrist. The accelerometer within the actigraph produces a signal as the wearer moves. This signal is measured 32 times per second and processed to provide the digital integration of the amount and duration of movement. The data are stored in the memory of the actigraph and then downloaded to a computer. Several algorithms are available

to calculate sleep parameters from the raw actigraphy data. In the studies described in this thesis, we used the Actiwatch algorithm that has been validated against polysomnography by Kushida et al.[19] in a study of patients with sleep disorders. After applying the algorithm, we were able to calculate sleep parameters such as TST, TIB and SOL. We also calculated the fragmentation index, a measure of the amount of interruption of immobile periods with episodes of movement. Since there are no published articles comparing the different algorithms,[20] the use of this particular algorithm may have introduced some underestimation or overestimation of the 'true' sleep parameters. However, we repeated some of our analyses with different sensitivity settings of the algorithm, and this did not markedly change the results.

In normal sleepers, agreement coefficients between PSG and actigraphy of 0.90 and above have been reported.[21] The accuracy of actigraphy to detect sleep and wakefulness, when compared with polysomnography, can be lower in insomniacs,[22] as they tend to lie in bed motionless, but awake, for long time periods. However, actigraphy data were more accurate than sleep diary data when compared with PSG in insomniacs.[23] Unfortunately, within the limitations of the Rotterdam Study setting, we were not able to compare actigraphy and self-report measures to PSG.

The use of actigraphy has many advantages. Although it is not the gold standard, it is still an objective measure of sleep parameters that is not subject to reporting bias or bias due to perception. Furthermore, parameters such as the fragmentation index cannot be calculated with self-report data. Because it is less expensive, less invasive and less time-consuming than PSG, using actigraphy enables studies involving multiple days and nights of testing, thereby increasing reliability,[24] and permits the evaluation of large numbers of participants. Moreover, it enables the study of sleep patterns of persons in their natural sleeping environment.

Clinical use of actigraphy

As actigraphy is a non-invasive method which yields objective information about sleep patterns, it has been suggested that it might be a convenient diagnostic tool for sleep disorders, e.g. in general practice. However, the value of actigraphy as a diagnostic instrument depends on the sleep disorder. It is particularly feasible for the diagnosis of circadian rhythm disorders, such as advanced sleep phase syndrome, delayed sleep phase syndrome, and shift work disorder.[18] It is not a valid instrument for assessing sleep apnea,[25] a common underlying cause of sleep complaints. For other sleep disorders, such as insomnia and restless legs syndrome, it is only partially adequate. It is possible to use actigraphy to confirm that the sleep pattern is disturbed, but the information it yields is not sufficiently specific to ascertain causes of the disturbance. Therefore, if the information obtained by interview and possibly a sleep diary does not enable the general practitioner to ascertain a diagnosis, the patient should be referred to a specialized sleep center.[26]

An initial purpose of this thesis was to study Paradoxical insomnia, formerly called Sleep state misperception, with actigraphy. Paradoxical insomnia is a condition in which a person

sleeps normally, but perceives (part of) his sleep as wakefulness, and therefore complains about not sleeping at all, or only sleeping very few hours. It is a separate diagnostic category in the International Classification of Sleep Disorders,[27] although it is debatable whether it is not just an extreme form of the common underestimation of sleep duration in insomniacs. The estimated prevalence of this condition is 5 % of all insomniacs.[28, 29] We hypothesized that comparing actigraphic measures with sleep diary measures would shed more light on the phenomenon of Paradoxical Insomnia. However, it has been shown in laboratory studies that the sleep EEGs of persons with this disorder are clearly different from those of normal sleepers. These differences only become apparent when the amplitudes of different types of brain waves that occur during slow wave sleep are studied.[28] It has also been demonstrated that persons with Paradoxical Insomnia have an increased metabolic rate, when compared with normal sleepers, although there were no differences in TST and SOL.[30] This means that sleep complaints which do not seem to agree with the 'real' sleep duration, still have a physiological background. Furthermore, in patients with Paradoxical Insomnia, their subjective estimation of TST is often more in accordance with actigraphic measures than with PSG measures.[31] Supposedly, these persons move more frequently during sleep. This makes it very difficult to detect this disorder with actigraphy. Taking these considerations into account, we had to conclude that our methods were not appropriate for studying this disorder. However, we were still interested in discrepancies in sleep parameters obtained with different measurement methods.

Agreement of self-report measures with actigraphy

In our actigraphy study (chapters 1-5), the average TST as reported in the diary was longer than the average TST measured actigraphically. This is in accordance with previous literature; in the CARDIA study, mean self-reported sleep duration was on average almost an hour longer than sleep duration measured actigraphically.[10]

Disagreement between diary and actigraphy measures is discussed in chapter 1. There are several possible ways to handle the concept '(dis)agreement between two measurement methods'. A number of authors used a correlation coefficient to describe the agreement between self-reported and objectively measured sleep duration.[32-34] However, a correlation coefficient is not sufficiently informative with regard to agreement, since a correlation is only a measure of the extent to which two variables are linearly related, regardless of their measurement scales.[35] As a consequence, strong disagreement between measured values can be present in spite of a high correlation between self-reported and measured sleep duration. We devised two separate measures of disagreement between subjective and actigraphic sleep duration. First, the 'level of disagreement', expressed as the average of the absolute differences between night-by-night diary estimates of TST and actigraphically measured TST. Second, the 'direction of disagreement', expressed as the average of the normal differences. The 'direction of disagreement' signals whether an individual has a tendency to over- or un-

derestimate TST in his diary when compared with the actigraphically measured TST: positive differences indicate that diary estimates are higher than actigraphic parameters, whereas negative differences reflect lower subjective than actigraphic values. The aim of the study was to describe disagreement between measures of TST and investigate possible determinants of both types of disagreement.

We found that 34 % of participants did not estimate their sleep duration in a diary within a range of one hour from their actigraphically measured TST, which means that using different measurement methods indeed yields different results. Moreover, the differences between measurement methods depended on certain characteristics of the participants. Poor sleep quality was consistently associated with a high level of disagreement between assessment methods. Gender, age, bed time, get up time, depressive symptoms, cognitive function and functional disability were also associated with level or direction of disagreement between subjective and actigraphic measures of TST.

Scientific implications

These results have important implications for studies aimed at investigating associations between sleep duration and health outcomes. Discrepancies between measurement methods imply that at least one of the methods introduces information bias in this type of study. Two types of information bias exist. If misclassification of the determinant is unrelated to the outcome, or misclassification of the outcome is unrelated to the determinant, this is referred to as nondifferential misclassification. If the misclassification of the determinant is different depending on the outcome, or vice versa, the misclassification is differential. Nondifferential misclassification generally leads to underestimation of associations, whereas the effect of differential misclassification is less predictable. As the discrepancies in sleep parameters between measurement methods are related to characteristics that may also be associated with the health outcome under study, this misclassification is frequently differential, which can either mask a true effect or cause spurious relations.

Gender differences

Chapter 2 illustrates the discrepancies between measurement methods from another perspective. One of the variables that influenced the difference between self-reported sleep duration and actigraphically measured sleep duration was gender. In their diaries, women reported shorter TST than men, but when TST was measured with actigraphy, women showed longer TST than men. When other sleep parameters were considered, women also reported poorer sleep than men, whereas their actigraphically measured sleep was actually better. The gender differences in subjective sleep parameters were attenuated after adjustment for marital status, the use of sleep medication and depressive symptoms and other covariates, but all of the differences remained significant. Gender differences in actigraphic sleep parameters were only marginally explained by adjustment for covariates, although differences in alcohol

consumption accounted for part of the gender differences in actigraphic TST and SE. As we were not able to explain all of the gender differences in sleep parameters, other mechanisms must explain why women sleep longer and better than men when sleep is measured with actigraphy, and why they nevertheless report less and poorer sleep than men.

SLEEP AND CARDIOVASCULAR RISK FACTORS

The U-shaped curve between sleep duration and mortality

Epidemiological studies have repeatedly found higher rates of mortality with both long, i.e. typically more than 8 hours per night, and short, i.e. less than 7 hours per night, habitual sleep durations.[36-42] In an effort to explain the mechanisms underlying this relationship, many researchers have investigated the relationship between sleep duration and cardiovascular disease. In the Nurses' Health Study, short and long self-reported sleep durations were independently associated with a modestly increased risk of coronary events.[43] The mechanisms behind these associations, however, remained unclear. To elucidate the possible pathways from short and long sleep duration to cardiovascular disease and mortality, the associations between sleep duration and several cardiovascular risk factors have been studied. A number of studies reported a relationship between sleep duration and body mass index (BMI) or an association between sleep duration and obesity.[44-46] Epidemiologic research has also related amount of sleep time to hypertension,[47, 48] to glucose metabolism and to the risk of diabetes.[46, 49]

In this thesis, we studied the associations of sleep parameters with three major cardiovascular risk factors: obesity, hypertension and cholesterol levels. We used both actigraphic and self-report measures to assess sleep duration and other sleep parameters. The association of sleep with obesity has been of particular interest, and several mechanistic questions have been raised. Therefore, this subject will be elaborately discussed below, whereas the studies of hypertension and cholesterol will be briefly reviewed. Finally, the possible role of sleep apnea in these studies will be discussed, and some general concluding comments will be made with regard to the three studies of sleep and cardiovascular risk factors.

Sleep and obesity

A growing body of epidemiological evidence indicates that sleep duration is associated with elevated BMI and an increased prevalence of obesity. Several studies, summarized by Knutson et al. in a recent review,[46] point toward a role of particularly short sleep, or sleep deprivation, in the development of obesity, impaired glucose metabolism and diabetes. Others have reported a U-shaped association between sleep duration and BMI, suggesting that short as well as long sleep duration increases the risk of a high BMI.[39, 50, 51] In our study of the relationship between sleep parameters and BMI and obesity, we found a marked quadratic

(U-shaped) association: both short and long sleep duration, as measured with actigraphy, were related to a higher BMI and a higher prevalence of obesity. Sleep fragmentation also increased the likelihood of a higher BMI and obesity. The relationships between short sleep and obesity nearly disappeared after adjustment for sleep fragmentation, whereas the higher risk for long sleepers remained unchanged. This may imply that sleep fragmentation is part of the mechanism by which short sleep is related to a higher prevalence of obesity. Interestingly, self-reported TST was not associated with BMI or obesity.

Several controversies exist with regard to the association between sleep duration and obesity. Does short, or long, sleep duration really cause obesity? The direction of the causal relationship may also be reversed, for example if obesity causes sleep apnea, or other physical problems that in turn influence sleep duration. Another matter of debate is whether the statistical association between sleep duration and obesity reflects clinically relevant findings. Furthermore, some researchers have suggested that we, as a society, are chronically sleep-deprived, and that, assuming there is a causal relationship between short sleep and obesity, this may be related to the obesity epidemic.[45, 52-54] Therefore, they argue, enhancing sleep duration may help to prevent obesity. Other authors have criticized this point of view.

Investigations of causality have been performed in experiments and in longitudinal observational studies. Laboratory experiments have shown that sleep deprivation leads to alterations in glucose metabolism including decreased glucose tolerance and insulin sensitivity. The neuroendocrine regulation of appetite was also affected, as circulating levels of leptin decreased and levels of ghrelin increased.[49] Leptin is a hormone that lowers appetite, while ghrelin stimulates it; therefore, the hormonal changes that result from sleep deprivation cause an upregulation of appetite.[46] These findings suggest that a chronic sleep debt might indeed be causally related to increased BMI. However, longitudinal epidemiological studies show conflicting results. Whereas in the Nurses' Health Study an association was found between self-reported habitual sleep duration and subsequent weight gain over a 16 year follow-up period,[54] the relationship between sleep duration and weight gain was not confirmed by Lauderdale et al.[55] in the CARDIA Study with a follow-up time of 5 years. Stranges et al.[13] and Björkelund et al.[56] could not confirm a longitudinal association between sleep duration and weight gain either, although they did find cross-sectional associations between sleep duration and BMI.

The clinical relevance of the association between sleep duration and obesity is commonly not debated in papers describing such an association (e.g. [46, 50, 53]) However, Horne[57] is critical of the clinical relevance of the reported associations. After a thorough review of the literature, he concluded that, at best, sleep only plays a minor physiological role in causing obesity. Weight gain in short sleepers, he argues, is unlikely to exceed one kilogram per year, over a period of many years.[57] In our study, the average BMI of those with a TST of < 5 hours was 29.0 kg /m^2, this was 1.6 (95% CI: 0.4 to 2.9) kg /m^2 higher than BMI of the reference category

with a 7 - < 8 hours TST. For a person with a height of 1.70 m, this is a difference in weight of 4.6 kg (95% CI: 1.2 to 8.4). The confidence interval is wide, due to the relatively low number of very short sleepers, but nevertheless, a difference in BMI of 1.6 seems to be clinically relevant. However, this is a cross-sectional association; the difference in weight gain over a long follow-up period may be smaller.

A number of authors have uttered their concerns about today's society being chronically sleep-deprived as a result of increased work stress, and the 24/7 availability of entertainment.[52, 54, 58] Some authors have linked the finding that the average self-reported sleep duration has decreased over the last decades to the 'obesity epidemic',[45, 52-54] and it has even been suggested that government campaigns to improve sleep might contribute to the prevention of obesity.[46, 53, 58, 59] Both suggestions have been strongly criticized by other researchers. Both Groeger et al.[60] and Horne[61] state that actual data that show that society is sleep-deprived do not exist. According to Horne, population studies in the United Kingdom over the last 40 years have consistently shown that the average daily sleep for adults is 7 to 7.5 hours.[61] Horne also considers it ridiculous to sleep more in order to prevent obesity or lose weight, and recommends to rather invest time in exercise.[57] The results of the studies described in this thesis do not support the notion that public health campaigns to enhance sleep would help to prevent obesity, and thus increase life expectancy. However, neither has it been proven that it would not. Patel et al.,[54] who reported a longitudinal association between sleep duration and weight gain, argued that the modest increase that they found (1 kg increase over 16 years) may appear small, but that even modest weight gain can have important health effects. Moreover, they found that usual sleep times of less than 7 hours were associated with a substantial increase in the risk of major (> 15 kg) weight gain and incident obesity.[54] However, a major increase in the number of people obtaining sufficient sleep may lead to substantial improvements of public health in another way. Since the most prominent effects of sleep deprivation are apparent in the frontal cortex, the intermediate mechanism would probably not be related to obesity, but rather to the prevention of accidents.[57]

Sleep and hypertension

At least two previous large population-based studies have shown that both short and long average TSTs increase the risk of hypertension in adults.[47, 48] In our study, described in chapter 4, we investigated the possible association between self-reported TST and both blood pressure and hypertension, in a study population of 5058 persons. In a subgroup of 975 persons who participated in the actigraphy study, we used actigraphically determined TST to study the same associations. Neither with self-reported TST nor with actigraphic TST, a significant association was apparent between TST and blood pressure or hypertension. A possible explanation for the discrepancy between previous studies and ours is that the average age of our study population was higher. At a higher age, other mechanisms than sleep duration may

be important in determining blood pressure. Also, our study population consisted of elderly persons of whom the majority were retired or otherwise not employed. Therefore, another possibility is that the freedom to choose their timing of sleep may have attenuated the association between sleep duration and hypertension. According to our study, hypertension is not a likely underlying mechanism of the association between habitual sleep duration and mortality.

Sleep and cholesterol

The importance of age in the study of sleep and (risk factors of) cardiovascular disease is best illustrated in chapter 5. This study was performed in persons who did not use cholesterol lowering medication. We investigated whether objectively measured TST, TIB and sleep fragmentation were associated with total cholesterol and high density lipoprotein (HDL) cholesterol levels. These associations were described separately for three different age categories. We found that, in the overall group, longer TST was related to a higher total cholesterol level and a higher total/HDL cholesterol ratio (a less favorable lipid profile). The association of long TST with cholesterol level that we found seemed to reflect two different mechanisms, depending on the age of the participants. Our analyses showed that, in the youngest age group of people under 65 years, the relationship between TST and cholesterol was driven by the strong association between a longer TIB and a higher total cholesterol level. In these persons, a longer sleep duration was also related to an unfavorable lipid profile. It is noteworthy that this association was both demonstrated with actigraphic and self-report data. However, in persons aged 70 or older, the association between TST and cholesterol seemed to be explained by sleep fragmentation, which is inversely related to TST. Thus, in the oldest subgroup, a more fragmented sleep, and therefore a shorter TST, was associated with a lower total cholesterol level. This association could well be due to underlying illness. It is difficult to explain our results in the light of the association between sleep duration and mortality, particularly since the association between cholesterol levels and mortality is not straightforward in the elderly. High serum cholesterol remains a risk factor for myocardial infarction in the elderly,[62] but in elderly people, low concentrations of serum cholesterol also predict increased mortality. Longitudinal research is needed to elucidate the (causal) pathways between sleep, cholesterol and mortality.

Sleep apnea

Previous research of sleep and cardiovascular risk or disease has often focused on the role of sleep apnea, a sleep disorder characterized by pauses in breathing during sleep. Sleep apnea is a risk factor for cardiovascular disease, and it is also strongly related to obesity.[63] The increased risk of cardiovascular disease in persons with obstructive sleep apnea is thought to be mainly explained by exposure to intermittent hypoxia, which can lead to oxidative stress, inflammation, atherosclerosis, endothelial dysfunction and hypertension.[64-66] It has also been

shown that obstructive sleep apnea is associated with the metabolic syndrome,[67] although others argue that obesity, and not sleep apnea, is the main determinant of lipid abnormalities and other metabolic outcomes.[68]

To accurately assess the presence of sleep apnea, PSG would have been necessary, as actigraphy does not allow adequate assessment of sleep apnea.[25] In our studies, sleep apnea was considered probable in persons who reported 1) loud snoring at least 2 nights a week, with at least occasional respiratory pauses, or 2) respiratory pauses during sleep with a frequency of at least 1-2 nights weekly. This proxy measure has been previously described by Fogelholm et al.[69] In our studies, self-reported snoring or breathing pauses had many missing values, due to the fact that a substantial proportion of participants slept alone in a bedroom and were thus not aware of their snoring or respiratory pauses. Therefore we only used this variable to exclude persons with probable sleep apnea. This exclusion did not substantially change any of our results.

Consistency across measurement methods

Since both self-report measures and actigraphic measures may be biased to some extent, the results of epidemiological studies using these measures would be most convincing if the results were equal with both assessment methods. In our investigations, the lack of association between TST and hypertension was consistent across measurement methods. However, the associations that we found between actigraphically measured TST and BMI or obesity could not be replicated with self-report measures. The results of our research on cholesterol were partly consistent across methods. Both a longer actigraphically measured TST and a longer self-reported TST were related to a lower HDL-cholesterol level and a higher total/HDL ratio. However, the association between actigraphic TST and total cholesterol level could not be replicated with self-reported TST. In none of our studies, we found any associations with self-report measures that were not confirmed by actigraphy data. We can conceive of three possible explanations for the discrepancies. Firstly, movement during the night may be more important than perceived sleep duration for the (causal) relationships between sleep duration and cardiovascular risk factors. Secondly, actigraphy may be more precise than self-report, and some of the associations may not be strong enough to be detected with imprecise methods, especially in this elderly population. Both with regard to obesity[45, 53] and to hypertension,[47] it has been reported that the strength of the association with sleep duration diminishes with age. No matter which explanation is most likely, relying on only one measure of sleep duration may cause spurious associations or obscure true associations. Therefore, we recommend, whenever possible, to use multiple measures of sleep duration, to perform analyses with each, and to examine the consistency of the results over assessment methods.

SLEEP AND PSYCHIATRIC DISORDERS

The high prevalence of psychiatric disorders in the (elderly) population has to be considered in epidemiologic studies of sleep parameters. Depression, and other psychiatric disorders such as anxiety disorders, may cause substantial sleep disturbance and individual differences in other sleep parameters.[70-73] Some authors have suggested that depression may be involved in the mechanisms explaining the U-shaped curve between sleep duration and mortality, particularly at the 'long sleep tail' of the curve.[41] However, others reported that depression did not have a substantial moderating influence on the association of sleep with mortality.[38, 43]

Our study of sleep in depression and anxiety disorders, described in chapter 6, was a large population-based study, comprising 5019 participants of the Rotterdam Study. The prevalence of psychiatric disorders in the subgroup that participated in the actigraphy study was too low to examine actigraphic sleep parameters in depression and anxiety disorders; therefore this study was based on questionnaire (PSQI) data. We found that the average TST in elderly persons with either a depressive disorder or an anxiety disorder did not differ from the average TST of those without these disorders. Rather, both short and long sleepers were more likely to be depressed or to have an anxiety disorder than persons with a TST of 7 - 8 hours. These associations were stronger in persons who did not use psychoactive medication. Persons with a depressive disorder generally spent more time in bed than non-depressed persons. Finally, participants with both a depressive disorder and a comorbid anxiety disorder reported a substantially shorter TST than other elderly persons.

In chapter 1, we showed that depressive symptoms were positively related to disagreement between self-report and actigraphic measures of sleep duration. Such findings imply that individuals may report sleep duration with all kinds of unmeasured biases, that may result from psychiatric disorders.[74] Self-reported sleep duration is surely a complex proxy for many factors, and those factors may not be equivalent on the long and short tails of the distribution.[74] In studies of sleep duration and health, and of sleep duration and mortality, psychiatric disorders should be carefully taken into account. They may be important confounders, precursors or intermediates of the relations under study.

SUGGESTIONS FOR FURTHER RESEARCH

In the cross-sectional studies described in this thesis, temporal relations and causality could not be ascertained. To further investigate these relationships, longitudinal research is needed. The data we collected for the purpose of the studies in this thesis will be analyzed again in the future, when follow-up data will have been recorded. Moreover, there are still many other unresolved questions about the repeatedly found U-shaped relationship between (self-

reported) sleep duration and mortality. It seems very plausible that different mechanisms are responsible for the increased mortality at each end of the tail. In the following paragraphs, some possible explanations that have not been studied in this thesis will be put forward, and some of these will be extended into suggestions for further research.

Sleep need

It has been shown that habitual sleep duration is approximately normally distributed in the population.[12, 54] Supposedly, the distribution of the amount of sleep a person needs per night also shows a normal curve. Both sleep habits and sleep need vary across the life span. The current research on habitual sleep duration implicitly assumes that persons at the 'short' tail of the distribution sleep too little, and people at the 'long' end sleep too much. However, an average of five hours of sleep per night may not at all be too short for some persons, whereas for others this may be serious sleep deprivation. Moreover, it has been shown that inter-individual variability in vulnerability to sleep deprivation is large.[75]

It is likely that the discrepancy between habitual sleep duration and sleep need, at both ends of the distribution, is responsible for outcomes such as increased risk of obesity, depressive disorders and mortality, rather than short or long sleep per se. Unfortunately, there is no method to objectively assess sleep need. Researchers have tried to measure sleep need by letting people sleep in a laboratory for several nights for as long as they liked.[76] The amount of sleep they obtained under these conditions was supposed to reflect the need. However, it has been shown that people can sleep more than they actually need,[61] so this may not be an accurate measure.

Another way of measuring sleep need is asking people what they perceive as their necessary amount of sleep. It is reasonable to assume that people know with what amount of sleep they feel good. Lindberg et al.[77] questioned 529 adult subjects about their sleep symptoms and psychological status by means of questionnaires. Females reported a significantly longer mean TST than males. Despite this, the difference between reported sleep and reported need of sleep was greater in females than in males. Lindberg et al. did not analyze this discrepancy as a determinant of unfavorable outcomes, but this would be an interesting suggestion for further research.

Variability of sleep patterns

Another interesting new research subject would be the effect of variability of sleep patterns, i.e. the timing of sleep, on health and mortality. On the one hand, it is commonly assumed that a stable rhythm is advantageous for health and life expectancy. On the other hand, a rhythm without variability could reflect an inactive lifestyle and a lacking social network, which is also related to adverse health outcomes, such as an increased risk of future cardiac events and all-cause mortality.[78] Actigraphy is particularly suited to study sleep-wake rhythms over a longer time span. Measures of variability can be devised for each of the collected

sleep parameters, and these can be related to health outcomes and mortality. An interesting hypothesis would be that the group of persons with slightly variable rhythms showing a little variation in bedtime, get up time and other sleep parameters, will have the lowest mortality risk. That implies that a higher mortality risk is to be expected in persons with extremely stable rhythms and with extremely variable rhythms. In other words, stability of sleep patterns would also show a U-shaped curve with mortality.

Physical activity

An interesting possible confounder of the relationship between sleep and health is physical activity. Unfortunately, these data were not available for our study population, neither were our daytime actigraphy data suitable for analysis in terms of standardized levels of activity. It has been reported, in a randomized trial, that a moderately intense exercise program improved self-reported sleep quality in older adults with moderate sleep complaints. Also, in the experimental condition, average sleep duration increased by 42 minutes, whereas this was not the case in the control condition.[79] However, at least three large epidemiological studies could not detect an association between physical activity and sleep duration.[13, 53, 54] Nevertheless, it would be interesting to study physical activity in relation to actigraphic sleep measures. They may only be related in a specific subgroup, or physical activity may be associated with other sleep parameters than TST, such as TIB or sleep fragmentation. These possible relationships may in turn be important for the study of cardiovascular risk factors and psychiatric disorders.

CONCLUSIONS

To date, no measure has been invented to assess habitual sleep patterns with perfect accuracy. Results obtained with different assessment methods can be biased in different ways. With these considerations in mind, the best way to deal with this problem is to use as many measures of sleep as possible. A validated questionnaire can be used to assess subjective sleep quality, a sleep diary or, whenever possible, actigraphy to assess sleep patterns over multiple nights, and preferably one night of PSG to ascertain sleep apnea and sleep disorders such as narcolepsy or restless legs syndrome. If the results of association studies are consistent over the different measurement methods, this increases the credibility of the results.

Except for the night of PSG, our studies met these criteria, and therefore we had excellent data for our research on the associations between sleep and cardiovascular risk factors. Briefly, we found that both short and long sleep were associated with a higher BMI and the prevalence of obesity, and that there was no association between sleep duration and hypertension. Furthermore, a longer sleep duration was related to a higher total cholesterol level and a higher total/HDL cholesterol ratio (a less favorable lipid profile), with different

underlying mechanisms in different age groups. Finally, we reported that both long and short sleep were related to depressive disorders and anxiety disorders in a complex way, but this study was based on self-report measures only.

Future longitudinal studies with a long follow-up period are needed to shed more light on the temporal associations between sleep parameters and health. All of these investigations will contribute to the final answer to the question with which this thesis started: why do we sleep?

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SUMMARY

The objective of this thesis was twofold. Firstly, its aim was to investigate methods of assessing habitual sleep in population-based studies. The focus was mainly on actigraphy, a method that infers sleep and wakefulness from the presence or absence of arm movement (Part I). Its second aim was to gain insight into the relationships of sleep duration with both cardiovascular risk factors (Part II) and psychiatric disorders (Part III). The research was conducted within the setting of the Rotterdam Study, a large prospective cohort study of community-dwelling inhabitants of a district of Rotterdam, aged 55 and over. A total of 1076 persons participated in an additional actigraphy study: they wore an actigraph and kept a sleep diary for, on average, six consecutive nights. The research described in chapters 1 through 5 is mainly based on this subsample of the Rotterdam Study population.

In **chapter 1** of this thesis, a study is described in which we compared two different methods of assessing Total Sleep Time (TST): actigraphy and sleep diaries. We calculated the level of disagreement with regard to TST between the results of the two measurement methods. In 34 % of the participants, the estimated TST in the sleep diaries deviated more than 1 hour from actigraphically measured TST. Poor sleep quality, as measured by actigraphic and subjective measures, was consistently associated with a high level of disagreement between assessment methods, albeit in opposite directions. Poor actigraphically measured sleep quality was often accompanied by longer subjective estimates of TST, whereas subjectively poor sleepers tended to report shorter TSTs in their diaries than were measured with actigraphy. Gender, age, bed time, get up time, depressive symptoms, cognitive function and functional disability were also associated with either level or direction of disagreement between subjective and actigraphic measures of TST. This phenomenon may bias the results of epidemiological studies into the (medical) consequences or correlates of sleep duration, as the determinants of disagreement are likely to be associated with many of these possible outcome measures.

Chapter 2 illustrates discrepancies between measurement methods from another perspective. In this study, gender differences in subjective and actigraphic sleep parameters were investigated. Women reported shorter TST, and less favorable sleep onset latency, sleep efficiency (TST divided by the time spent in bed) and global sleep quality than men. When assessed with actigraphy, however, women were found to have longer and less fragmented sleep than men; only actigraphic sleep onset latency did not differ between men and women. Gender differences in self-reported sleep parameters were partly explained by depressive symptoms and sleep medication use, which are both more common in women and related to poor self-reported sleep quality. The shorter actigraphically measured TST in men was partly explained by their higher alcohol consumption. However, none of the gender differences in self-reported or actigraphic sleep measures could be fully explained by adjustment for multiple covariates.

In **chapter 3**, the association of sleep measures with body mass index (BMI) and obesity is investigated. We found a marked U-shaped association of actigraphically measured TST with BMI and obesity: both short sleep and long sleep were related to a higher BMI and a higher prevalence of obesity. Sleep fragmentation also increased the likelihood of a higher BMI and obesity. The relationship between short sleep and obesity was attenuated after adjustment for sleep fragmentation, whereas the higher risk for long sleepers remained unchanged. However, a quadratic relationship between TST and BMI still existed after adjustment for sleep fragmentation. Exclusion of participants with probable sleep apnea only marginally changed these associations. Self-reported TST was not associated with BMI or obesity. Our cross-sectional design prevented us from gaining insight into possible temporal or causal relations. For this reason, we cannot rule out that obesity leads to a shorter or longer sleep duration, or to more fragmented sleep.

Chapter 4 concentrates on the possible relationship between TST and hypertension, as several large studies have shown that both short and long habitual TSTs increase the risk of hypertension in adults. This cross-sectional study was conducted with self-report measures of TST in 5058 participants of the Rotterdam Study, and with actigraphic measures in the actigraphy study subgroup. After adjustment for age and gender and additionally for BMI, smoking, depressive symptoms, sleep medication use, diabetes mellitus, myocardial infarction and stroke, no significant association was apparent between TST, whether measured by self-report or actigraphy, and blood pressure or hypertension.

In the study reported in **chapter 5**, we investigated whether objectively measured TST, time in bed and sleep fragmentation were associated with total cholesterol and high density lipoprotein (HDL) cholesterol level. This study was performed in 768 persons who did not use cholesterol lowering medication. We found that longer TST was related to a higher total cholesterol level and a higher total/HDL cholesterol ratio (a less favorable lipid profile). A longer TST was strongly related to a longer time in bed. The association of long TST with cholesterol that we found seems to reflect two different mechanisms, depending on the age of the participants. Our analyses showed that the relationship between TST and cholesterol was driven by the strong association between a longer time in bed and a higher total cholesterol level in the youngest age group of people under 65. However, in persons aged 70 or older, the association between TST and cholesterol seemed to be explained by sleep fragmentation, which was related to a lower total cholesterol level. This association could well be due to underlying illness.

The study described in **chapter 6** included 5019 participants of the Rotterdam Study. In these persons, self-reported TST and other sleep parameters were examined in relation to depressive disorders and anxiety disorders. We found that the average TST in elderly persons with one of these disorders did not differ from the average TST of those without these disorders. Rather, both short and long sleepers were more likely to be depressed or to have an anxiety disorder than persons with a TST of 7 - 8 hours. These associations were stronger

in people who did not use psychoactive medication. Persons with a depressive disorder spent more time in bed than non-depressed persons. Finally, participants with a depressive disorder and a comorbid anxiety disorder reported a substantially shorter TST than persons without these disorders or with one of these disorders. The above indicates that in studies of sleep duration and health, psychiatric disorders should be carefully taken into account. They may be important confounders, precursors or intermediates of the relations under study.

In **chapter 7**, the results of these investigations are reviewed and discussed in the context of current knowledge, and suggestions for further research are proposed.

SAMENVATTING

Het doel van dit proefschrift was tweeledig. Ten eerste: het onderzoeken van de methodologische problemen die optreden bij het meten van de gebruikelijke slaapduur in een bevolkingsstudie. De nadruk lag hierbij vooral op actimetrie, een methode waarmee slaap wordt vastgesteld op basis van de aan- of afwezigheid van bewegingen van de arm (deel I). Het tweede doel was om meer inzicht te verkrijgen in de relatie tussen slaapduur en zowel risicofactoren voor hart- en vaatziekten (deel II) als psychiatrische stoornissen (deel III). Het onderzoek is uitgevoerd binnen het Erasmus Rotterdam Gezondheids Onderzoek (ERGO), een groot prospectief cohortonderzoek naar inwoners van de wijk Ommoord in Rotterdam, in de leeftijdsgroep van 55 jaar en ouder. In totaal namen 1076 personen binnen het ERGO-onderzoek deel aan een extra actimetrie-onderzoek: zij droegen gemiddeld 6 achtereenvolgende dagen en nachten een actimeter en hielden een slaapdagboek bij. Het onderzoek dat beschreven wordt in de hoofdstukken 1 tot en met 5 is voornamelijk gebaseerd op de groep deelnemers aan dit extra onderzoek.

In **hoofdstuk 1** van dit proefschrift beschrijf ik eerst een onderzoek waarin we twee methoden voor het meten van de totale slaapduur (*total sleep time; TST*) hebben vergeleken: actimetrie en slaapdagboeken. We berekenden het verschil in TST tussen de resultaten van beide meetmethoden. Van de deelnemers schatte 34% in het dagboek een TST die meer dan een uur afweek van de met actimetrie gemeten TST. Een slechte slaapkwaliteit, gemeten met actimetrie dan wel met het dagboek, was gerelateerd aan een hoge mate van discrepantie tussen de twee meetmethoden, zij het in tegenovergestelde richtingen. Een slechte slaapkwaliteit volgens de actimetrie ging vaak samen met een langere subjectieve inschatting van TST, terwijl mensen die subjectief slecht sliepen vaker een kortere TST in hun dagboek vermeldden dan met actimetrie gemeten was. Geslacht, leeftijd, bedtijd, tijd van opstaan, depressieve klachten, cognitief functioneren en lichamelijke beperkingen waren ook gerelateerd aan ofwel de mate van discrepantie of de richting van het verschil tussen zelfgerapporteerde en actimetrisch gemeten TST. Dit fenomeen kan de resultaten van epidemiologische studies naar de relatie tussen TST en gezondheid vertekenen, omdat de variabelen die verband houden met de discrepantie tussen de twee meetmethoden waarschijnlijk ook verband houden met veel mogelijke uitkomstmaten van dergelijke studies.

Hoofdstuk 2 illustreert discrepanties tussen meetmethoden vanuit een ander perspectief. In dit onderzoek werden man-vrouwverschillen in zelfgerapporteerde en actimetrische slaapparameters bekeken. Vrouwen rapporteerden een kortere TST, ze hadden meer tijd nodig om in slaap te vallen, een lagere slaapefficiëntie (TST gedeeld door de tijd in bed) en gaven een slechtere beoordeling van hun algemene slaapkwaliteit dan mannen. Daarentegen vonden we met actimetrie dat vrouwen juist langer en minder gefragmenteerd sliepen dan mannen; alleen de tijd die nodig was om in slaap te vallen was hetzelfde voor mannen en vrouwen. Man-vrouwverschillen in zelfgerapporteerde slaapparameters konden deels

verklaard worden door depressieve klachten en het gebruik van slaapmedicatie, die beiden vaker voorkomen bij vrouwen en een verband hebben met slechte subjectieve slaapkwaliteit. De kortere actimetrische slaapduur van mannen werd deels verklaard door hun hogere alcoholconsumptie. Toch kon geen van de man-vrouwverschillen volledig verklaard worden door te corrigeren voor gerelateerde variabelen.

In **hoofdstuk 3** onderzochten we het verband tussen slaapmaten en *body mass index (BMI)* en obesitas. We vonden een duidelijk U-vormig verband tussen actimetrische TST met zowel BMI als met obesitas: zowel kort slapen als lang slapen was gerelateerd aan een hogere BMI en een hogere kans op obesitas. Gefragmenteerd slapen verhoogde ook het risico op een hogere BMI en obesitas. De relatie tussen kort slapen en obesitas werd verzwakt door te corrigeren voor slaapfragmentatie, terwijl het verband tussen lang slapen en obesitas onveranderd bleef. Een kwadratisch verband tussen slaapduur en BMI bleef bestaan na correctie voor slaapfragmentatie. Het uitsluiten van deelnemers die waarschijnlijk aan slaap apneu leden veranderde deze relaties maar een heel klein beetje. Zelfgerapporteerde TST had geen verband met BMI of obesitas. Onze cross-sectionele onderzoeksopzet maakte het niet mogelijk om relaties in de tijd of causale verbanden aan te tonen. Daarom kunnen we niet uitsluiten dat de resultaten betekenen dat overgewicht of obesitas leidt tot een kortere of langere slaapduur, of tot meer gefragmenteerd slapen.

Hoofdstuk 4 richt zich op de mogelijke relatie tussen TST en hypertensie, omdat verschillende grote studies hebben aangetoond dat zowel een korte als een lange gebruikelijke slaapduur bij volwassenen het risico op een hoge bloeddruk verhoogt. Dit cross-sectionele onderzoek is uitgevoerd met een slaapvragenlijst bij 5058 deelnemers aan het ERGO-onderzoek, en met actimetrische maten bij de subgroep die aan het actimetrie-onderzoek heeft deelgenomen. Na correctie voor leeftijd en geslacht en daarnaast voor BMI, roken, depressieve klachten, het gebruik van slaapmedicatie, diabetes, en het doorgemaakt hebben van een hartinfarct of een beroerte, was er geen statistisch significant verband tussen TST, of dit nu met een vragenlijst of met actimetrie gemeten was, en bloeddruk of hypertensie.

In het onderzoek dat wordt beschreven in **hoofdstuk 5** hebben we bekeken of er een verband was tussen enerzijds objectief gemeten TST, de tijd die in bed is doorgebracht (TIB), en slaapfragmentatie, en anderzijds het totale cholesterolgehalte in het bloed en het *high density lipoprotein (HDL)*-cholesterol gehalte. Dit onderzoek werd uitgevoerd bij 768 deelnemers die geen cholesterolverlagende medicatie gebruikten. We vonden dat een langere TST verband hield met een hoger totaal cholesterolgehalte en met een hogere (ongunstiger) totaal/HDL cholesterol-verhouding. Een langere TST was sterk geassocieerd met een langere TIB. Het verband tussen een langere TST en cholesterol dat we vonden lijkt terug te voeren op twee verschillende mechanismen, afhankelijk van de leeftijd van de deelnemers. Onze analyses lieten zien dat het verband tussen TST en cholesterol veroorzaakt werd door een sterke relatie tussen een langere TIB en een hoger totaal cholesterolgehalte in de jongste leeftijdsgroep van mensen onder de 65 jaar. In mensen van 70 jaar en ouder leek de relatie

tussen TST en cholesterol verklaard te worden door slaapfragmentatie, dat geassocieerd was met een lager totaal cholesterolgehalte. Deze relatie zou veroorzaakt kunnen worden door een onderliggend ziekteproces.

Het onderzoek dat aan de orde komt in **hoofdstuk 6** omvatte 5019 deelnemers aan het ERGO onderzoek. Bij deze mensen zijn met een vragenlijst gemeten slaapparameters bekeken in relatie tot depressieve stoornissen en angststoornissen. We vonden dat de gemiddelde TST bij ouderen met één van deze stoornissen niet verschilde van de gemiddelde TST van mensen zonder deze stoornissen. We vonden wel dat zowel kort- als langslapers een verhoogde kans hadden om een depressie of een angststoornis te hebben. Deze verbanden waren sterker bij mensen die geen antidepressiva of kalmerende medicatie gebruikten. Mensen met een depressie brachten meer tijd in bed door dan mensen zonder depressie. Ten slotte rapporteerden mensen met zowel een depressie als een angststoornis een veel kortere TST dan mensen zonder deze stoornissen of met één stoornis. Uit het bovenstaande volgt dat het in onderzoek naar de relatie tussen TST en gezondheid belangrijk is om psychiatrische stoornissen in de analyses te betrekken, omdat ze een belangrijke invloed kunnen uitoefenen op deze verbanden.

Ten slotte zet ik in **hoofdstuk 7** de belangrijkste conclusies uit de onderzoeken op een rij en plaats ik ze in een context. Ook doe ik enige voorzetten voor mogelijk vervolgonderzoek.

DANKWOORD

En dan is het af, en is het tijd om de mensen te bedanken die hebben bijgedragen aan het proces dat tot dit proefschrift leidde. In de eerste plaats zijn dat natuurlijk de duizenden ERGO-deelnemers die zich telkens weer geduldig aan al onze onderzoeken hebben onderworpen. In het bijzonder gaat mijn dank uit naar alle deelnemers die een week lang, dag en nacht, een horloge hebben gedragen waarop je niet eens kunt zien hoe laat het is.

De grondlegger van het ERGO-onderzoek is tevens mijn promotor, prof. dr. Bert Hofman. Beste Bert, dank dat je me in de gelegenheid hebt gesteld om dit onderzoek te doen op jouw afdeling. Gedurende het hele traject was je er op de momenten dat ik je nodig had.

Veel dank ben ik verschuldigd aan mijn copromotor en dagelijks begeleider, dr. Henning Tiemeier. Beste Henning, we hebben het mooi voor elkaar gekregen samen. Ik heb me altijd heel erg gesteund gevoeld door jou en jouw vlotte, deskundige en interactieve begeleiding. Ik heb veel van je geleerd, en, misschien nog wel belangrijker, het was ook gewoon erg leuk om samen met jou aan de stukken te werken.

Mijn tweede copromotor, dr. Arie Knuistingh Neven, was al betrokken bij het actimetrie-project toen het nog maar een idee was, en is steeds betrokken gebleven. Beste Arie, hartelijk dank voor je inbreng gedurende de hele periode.

De overige leden van de kleine en grote promotiecommissie wil ik graag bedanken voor hun bereidheid mijn proefschrift te lezen en er met mij over te discussiëren. Prof. dr. Jacqueline Witteman en dr. Joke Tulen dank ik daarnaast hartelijk voor hun waardevolle bijdragen aan mijn artikelen. Prof. dr. Gerard Kerkhof heeft mij al in 1998 aangestoken met zijn enthousiasme voor slaaponderzoek. Beste Gerard, je vroeg me toen al eens of ik niet zou willen promoveren. Op dat moment wilde ik eerst iets anders doen, maar uiteindelijk kwam het er toch van. De cirkel is rond nu je een plaats hebt in mijn promotiecommissie. I would like to thank Dr. Eve van Cauter and Dr. Daniel Gottlieb for considering their participation in my defense committee worth a transatlantic journey.

Het actimetrie-onderzoek was een samenwerkingsproject met TNO in Delft. Ik bedank dr. Henk Miedema en Henk Vos hartelijk voor de prettige samenwerking.

Het draaiende houden van het ERGO-onderzoek is een gezamenlijke inspanning van een heleboel mensen, werkzaam voor en achter de schermen. Zij verdienen allemaal een woord van dank, en een aantal van hen wil ik graag specifiek noemen.

De spil waar het ERGO-centrum om draait is Anneke Korving. Anneke, heel erg bedankt voor al je hulp en steun bij 'dat gedoe met die horloges'. Je bent goud waard voor ERGO, onder andere omdat je meer verstand van mensen hebt dan de meeste psychologen.

De ERGO-interviewsters, Monie, Agnes, Edith, Trudi, Saskia en Henriëtte, hebben zich, naast hun interviewwerkzaamheden, op verschillende manieren enthousiast voor 'mijn' dataverza-

meling ingezet. Hartelijk dank daarvoor. De ERGO-uitschrijfartsen wil ik bedanken voor het uitdeel- en instructiewerk.

Frank van Rooij is ERGO's bijzonder accurate datamanager. Frank, er is een lange lijst dingen om je voor te bedanken. Ik noem bijvoorbeeld je hulp bij het in elkaar zetten van mijn ingewikkelde actimetriedatabestanden, je snelle en adequate antwoorden op mijn vragen van allerlei aard, alle SPSS-trucs die ik van je leerde, en onze zeer motiverende taartweddenschap.

Marcel, Alwin, Nano, René en René, Eric, Dick, Jolande en Anneke, de andere bewoners van de gezelligste kamer van de Epi, hartelijk dank voor alle hulp bij computer- en diverse andere problemen. Anneke de Koning, ook veel dank voor je inzet en accuratesse bij de dataverzameling; het was heel prettig dat ik de tweede helft met een gerust hart aan jou kon overlaten.

Dika Luijendijk, met jou heb ik een tijdlang een kamer, lief en leed, en een aantal lastige klussen gedeeld. Veel praten en lachen met jou maakte mijn werk heel veel leuker, zelfs al ging het vaak over depressie(data).

Marieke Dekker, jij zorgde niet alleen voor een hoop gezelligheid, maar was ook een heel belangrijke steun en toeverlaat. Ik kon altijd bij je terecht met wat er ook maar te bespreken viel, werkgerelateerd of niet-werkgerelateerd, leuk of minder leuk. Veel dank voor alles en voor het feit dat je naast me staat tijdens de verdediging.

Alle andere Epi-collega's, en parttime kamergenote Martina in het bijzonder, wil ik bedanken voor de gezelligheid, bijvoorbeeld tijdens de lunches, en hulp bij allerhande ad hoc vragen. Sjoerd, het was jammer dat ons slaap-en-cognitie-stuk in het water viel, ik had graag met je samengewerkt.

Sinds 1 april 2008 werk ik bij GGZ Dijk en Duin in Castricum. Ik wil dr. Jaap van Weeghel, dr. Barbara Schaefer en mijn andere nieuwe collega's daar heel hartelijk bedanken voor alle flexibiliteit, steun en belangstelling die ik van hen heb ontvangen bij de afronding van dit proefschrift.

Mijn vriendinnen en vrienden, en ook mijn salsa- en tangopartners van de afgelopen jaren, wil ik op deze plek graag bedanken voor hun steun, trouw en gezelligheid, en voor alle gevoelsmatige input ter afwisseling van het cerebrale proefschriftgebeuren.

Marieke Bouma, jij was de laatste jaren letterlijk en figuurlijk altijd dichtbij, dat je ook tijdens de promotie naast me staat lijkt me vanzelfsprekend en heel prettig. Frank, Marieke D en Femke, dank voor het meelezen tijdens de eindsprint.

Last but certainly not least, lieve pap en mam, ik weet dat jullie trots op me zijn, en dat dat niet afhangt van wel of niet promoveren. Heel veel dank voor alle bagage die jullie me hebben meegegeven.

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ABOUT THE AUTHOR

Julia van den Berg was born on November 18, 1976, in Hoofddorp, The Netherlands. Having completed secondary school at the Stedelijk Gymnasium in Haarlem in 1994, she started to study Psychology at Leiden University. During her study, she worked as an interviewer for a research project at the Department of Child Psychiatry of Sophia Children's Hospital in Rotterdam. In 1999, she graduated in Clinical and Health Psychology, cum laude. After her graduation, she worked at the VALK Foundation in Leiden (1999), Bureau Jeugdzorg Rijnland in Leiden (1999-2001), and the Netherlands Institute of Mental Health and Addiction in Utrecht (2001-2004).

In December 2004, she started the work presented in this thesis, at the Psychiatric Epidemiology unit of the Department of Epidemiology & Biostatistics of the Erasmus Medical Center in Rotterdam (head: Prof. dr. A. Hofman), under the auspices of Dr. Henning Tiemeier. She obtained a Master's degree in Epidemiology at the Netherlands Institute for Health Sciences (NIHES) in June 2007. Since April 2008, she has been employed as a researcher by GGZ Dijk en Duin, a mental health institute, in Castricum.