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Epidemiological perspectives on sleep: health-related outcomes and subjective–objective sleep assessments

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EPIDEMIOLOGICAL PERSPECTIVES ON SLEEP: HEALTH-RELATED OUTCOMES AND SUBJECTIVE–OBJECTIVE SLEEP ASSESSMENTS

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I spent all day yesterday watching the grass grow

What I learned is

The grass really grows slow

Mark Sandman – *Patience*

ABSTRACT

This thesis aimed to expand knowledge about self-reported habitual sleep in relation to health outcomes and objectively measured sleep.

Study I was a cross-sectional analysis of 40,197 Swedish adult volunteers participating in the National March, a fundraising event for the Swedish Cancer Society held in 1997. We compared the entire distribution of BMI between subjects with different sleep patterns. Relative to those who reported 6–8 h or good-quality sleep, the upper tail of the BMI distribution, representing the heaviest 10% of the population, was extended towards higher values by 0.39–1.79 kg/m^2 among subjects with ≤5 h, ≥9 h or poor-quality sleep. The medians were similar. The extension of the upper tail without a corresponding change in the central tendency suggests that unfavorable sleep patterns are associated with BMI in a subset of people.

Study II examined sleep duration and insomnia symptoms (difficulty falling asleep or maintaining sleep, early morning awakening, and nonrestorative sleep) in relation to risk of cardiovascular events (incident myocardial infarction, stroke or heart failure, or death from all cardiovascular diseases). During a follow-up of 13.2 y among the same volunteers as in study I (n = 41,192), subjects who reported sleeping ≤5 h showed an increased risk of cardiovascular events relative to those who slept 7 h (adjusted hazard ratio = 1.24; 95% confidence interval, CI: 1.06–1.44). Additional adjustment for BMI, self-rated health, and other pertinent factors attenuated this relationship. We observed no excess risk among those who slept 6 h, ≥8 h, or who had insomnia symptoms. Thus, no independent association was found between sleep habits and incident cardiovascular events.

Study III tested whether subjects with and without obstructive sleep apnea syndrome (OSAS) could be accurately distinguished from each other using self-report symptoms typical of the disease obtained from the Karolinska Sleep Questionnaire (KSQ). Among 103 subjects referred to a large sleep clinic in Stockholm, 60% had OSAS. Sensitivity and specificity of self-reported apnea/snoring symptoms were 0.56 (95% CI: 0.44–0.69) and 0.68 (0.52–0.82). Corresponding figures for self-reported sleepiness symptoms were 0.37 (0.25–0.50) and 0.71 (0.55–0.84). Diagnostic accuracy of apnea/snoring and sleepiness symptoms reported in the KSQ was poor; clinical use cannot be recommended.

Study IV analyzed the association of sleep quality and restoration from sleep reported in the KSQ with standard polysomnography parameters recorded on multiple occasions in 31 adults without sleep problems. Stage 2 sleep predicted worse sleep quality and slow-wave sleep predicted better sleep quality. Slow-wave sleep was also related to less subjective restoration from sleep, but this association disappeared with adjustment for age. We found some evidence in support of polysomnographic correlates of self-reported habitual sleep quality.

LIST OF SCIENTIFIC PAPERS

I. **Westerlund A**, Bottai M, Adami HO, Bellocco R, Nyrén O, Åkerstedt T, Trolle Lagerros Y. Habitual sleep patterns and the distribution of body mass index: cross-sectional findings among Swedish men and women. *Sleep Med.* 2014 Jul 29. doi: 10.1016/j.sleep.2014.06.012. (Epub ahead of print)

II. **Westerlund A**, Bellocco R, Sundström J, Adami HO, Åkerstedt T, Trolle Lagerros Y. Sleep characteristics and cardiovascular events in a large Swedish cohort. *Eur J Epidemiol.* 2013;28:463-73.

III. **Westerlund A**, Brandt L, Harlid R, Åkerstedt T, Trolle Lagerros Y. Using the Karolinska Sleep Questionnaire to identify obstructive sleep apnea syndrome in a sleep clinic population. *Clin Respir J.* 2014 Jan 20. doi: 10.1111/crj.12095.

IV. **Westerlund A**, Trolle Lagerros Y, Kecklund G, Axelsson J, Åkerstedt T. Relationships between questionnaire ratings of sleep quality and polysomnography in healthy adults. Accepted for publication in *Behav Sleep Med*.

CONTENTS

LIST OF ABBREVIATIONS

AHI	Apnea-hypopnea index
BMI	Body mass index
CI	Confidence interval
CVD	Cardiovascular disease
EEG	Electroencephalogram
EMG	Electromyogram
EOG	Electrooculogram
HR	Hazard ratio
ICD	International classification of diseases
KSQ	Karolinska Sleep Questionnaire
NPV	Negative predictive value
NREM	Non-rapid eye movement
OSA(S)	Obstructive sleep apnea (syndrome)
PIN	Personal identity number
PPV	Positive predictive value
PSG	Polysomnography
PSQI	Pittsburgh Sleep Quality Index
REM	Rapid eye movement

1 INTRODUCTION

Along with diet and physical activity, adequate sleep is increasingly emphasized as crucial to health. The past decade or so has seen a marked increase in studies examining the potential long-term consequences of too little or poor-quality sleep [1]. Indeed, links have been demonstrated between various aspects of sleep and a range of chronic diseases and poor health outcomes, such as obesity, diabetes, depression, hypertension, cardiovascular disease, and mortality.

Thus, epidemiology – defined as *"the study of the occurrence and distribution of health-related events, states, and processees in specified populations, including the study of the determinants influencing such processes, and the application of this knowledge to control relevant health problems"* [2] – has greatly advanced the understanding of the role of sleep in ill health and its importance for public health. The research community, however, struggles with deciphering whether disturbances in the amount or quality of sleep are causally related to or rather the consequence of ill health [3]. An issue directly related to these challenges pertains to the measurement of sleep, and whether measures of sleep typically used in epidemiological studies (*i.e.*, self-reports) are valid.

This thesis includes four studies. The first two are concerned with shedding light on and quantifying the relationship between multiple aspects of sleep and body weight/obesity and cardiovascular disease, respectively. The latter two studies are focused on the measurement of sleep from two distinct perspectives: the diagnostic accuracy of self-reported sleep for the obstructive sleep apnea syndrome, which is a common sleep disorder, and the validity of self-reported sleep quality in terms of physiological sleep.

2 BACKGROUND

2.1 DEFINITIONS AND CHARACTERISTICS OF SLEEP

Sleep is an essential and universal behavior, at least in mammals and birds. Still its function is not fully understood. Current theories on why we sleep include the following. (1) Sleep is needed to restore the energy resources of the body; (2) staying awake leads to unfavorable immunoactivation and therefore we have to sleep; and (3) sleep is needed for brain plasticity and restoration of synaptic homeostasis, facilitating learning and memory [4].

Sleep can be described by its behavioral and physiological components. Behaviorally, sleep is characterized as being a reversible state of decreased consciousness and reduced responsiveness to the environment. During sleep, humans typically lie down with their eyes closed. Physiologially, sleep is associated with changes in, e.g., brain wave activity, muscle activity, breathing, heart rate, blood pressure, body temperature, and endocrine systems. Recordings of sleep are based on brain activity measured by the electroencephalogram (EEG), muscle activity by the electromyogram (EMG), and eye movement by the elctrooculogram (EOG); together, EEG, EMG, and EOG constitute the polysomnogram. Two distinct sleep states have been derived from these physiological parameters: rapid eye movement (REM) sleep and non-rem (NREM) sleep. During NREM sleep, mental activity is typically low, as is cortical brain activity; the body is movable. During REM sleep, cortical activity is increased, dreams commonly vivid, the body paralyzed, and there are periods of rapid eye movement [5]. NREM sleep is further divided into stages 1, 2, 3, and 4, where the latter two make up slow-wave (or deep) sleep. Each of these four stages and REM sleep exhibit their own typical EEG pattern.

In the normal adult, sleep onset is via NREM sleep, which alternates with REM sleep in a cyclic fashion throughout the night. The average length of the NREM–REM cycle across the night is 90–110 minutes, and there are typically a total of 4–5 cycles. As the night progresses, the amount of slow-wave sleep decreases, and REM sleep increases. In the normal young adult, NREM sleep accounts for

75–80% of total sleep time. Stage 2 sleep is the dominating sleep stage and constitutes 45–55% of total sleep [5]. Changes in sleep occur with age; for instance, total sleep time decreases and the percentage of time spent in slow-wave sleep decreases [6]. The decrease in slow-wave sleep appears to be more pronounced in men than women [7]. Below, the progression of sleep across the night is illustrated in a hypnogram; this particular one is representative of a normal adult (Figure 1).

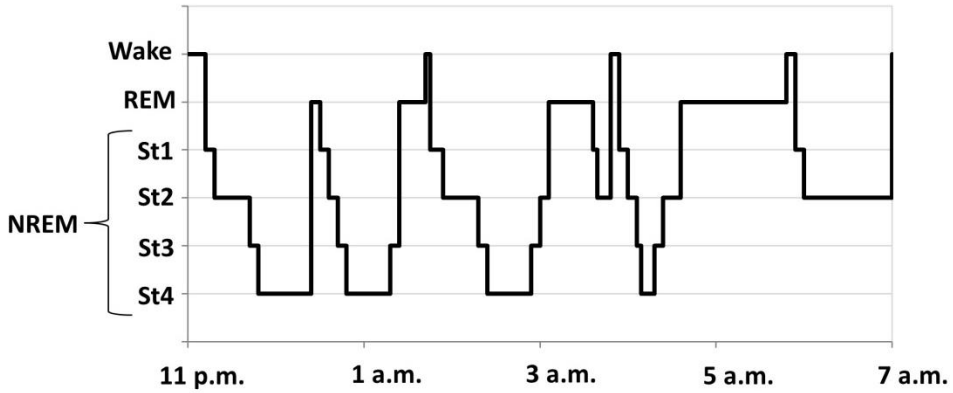

Figure 1. Illustration of distribution of sleep stages across the night in a normal adult. According to updated sleep terminology [8], the term "N" is used for NREM sleep stages. Stage 1 is N1, stage 2 is N2, and stages 3 and 4 are grouped together in N3. "R" is used for REM sleep. In study III in this thesis, the updated manual [8] was used for scoring of breathing events. In study IV, sleep scoring criteria according to Rechtschaffen and Kales [9] were used.

2.2 CONCEPTS OF SLEEP RESTRICTION AND SLEEP NEED

A sufficient amount and quality of sleep is needed for optimal daytime functioning and well-being. When the habitual or usual amount of sleep is reduced, chronic sleep restriction, also termed partial sleep deprivation, is thought to result [10]. As indicated by experimental data, it significantly reduces alertness and cognitive function [11, 12]. Another term for chronic sleep restriction is sleep debt. Based on this terminology, basal sleep need may be defined as "habitual sleep duration in the absence of pre-existing sleep debt," and sleep restriction or sleep debt in turn as "the fundamental duration of sleep below which waking deficits [e.g., daytime sleepiness, sleep propensity, cognitive deficits] begin to accumulate" [13]. Based on at least to experimental studies [12, 14],

it has been suggested that the basal sleep need in adults is between 7.5 and 8.5 h [10].

Prevalence estimates for sleep restriction are lacking, which may not be all too surprising given its conceptualization. However, two studies conducted in Sweden [15] and Finland [16] during the 1990s measured insufficient sleep (defined as the absolute or relative difference between self-reported habitual sleep duration and sleep need) in two population-based samples. Insufficient sleep was prevalent, ranging from 12% [15] to 20% [16].

In epidemiological studies, short habitual sleep duration (typically <5 or <6 h of sleep) may serve as a proxy for chronic sleep restriction to some extent.

2.3 PREVALENCE AND TRENDS OF INADEQUATE SLEEP

There is a common notion that sleep habits have changed over time. Reduced sleep duration and increased sleep problems are thought to be the results of the modern, 24/7 society as characterized by artificial lighting, increasing demands to work outside office hours, increased night-time use of internet, cell phones, and other devices; the list goes on. Indeed, humans are capable of overriding the bodily regulation systems of sleep. It has been claimed that we are living in a chronically sleep deprived society [17].

Undeniably, sleep problems are prevalent. According to a recent Swedish telephone survey [18], 24.6% in a sample of nationally representative adults reported having insomnia symptoms, defined as difficulty initiating or maintaining sleep, at least three times per week the past month. Insomnia disorder, defined as insomnia symptoms causing daytime consequences, was reported by 10.5%. In both instances, prevalence was higher in women [18]. These prevalence estimates appear to be in line with other population-based surveys [19, 20]. As regards development over time, in a large sample of Finns [21], short-term insomnia symptoms increased in the working-age population between 1972 and 2005. Short-term sleep problems also increased among women residing in Gothenburg , who were followed from 1968 to 2005 [22].

In a British representative population sample surveyed in 2003, average past-week sleep duration on weekdays and weekends was 6.9 h and 7.2 h, with no detectable difference between sexes [23]. On weekdays, 19% reported sleeping less than 6 h, and 13% reported sleeping 8 h or more. Corresponding figures for weekends were 17% and 22%. In the 2009 Sleep in America Poll [24], average self-reported sleep was 6.7 h on weekdays, and 7.0 h on weekends. Twenty percent slept less than 6 h on weekdays and 14% on weekends, while 28% slept 8 h or more on weekdays and 44% on weekends. In the study by Mallon et al. [18], average sleep duration was approximately 6.9 h on weekdays, and approximately 7.8 h on weekends. Thus, in all three studies, there was a shift towards longer sleep hours on weekends consistent with, but not necessarily equal to, an attempt to compensate for sleep lost during the week.

Recent studies investigating whether sleep duration has changed over time offer a somewhat heterogeneous picture. Based on time use survey data, Bin et al. [25] investigated changes in the prevalence of short (≤6 h) and long sleep (>9 h) durations between the 1970s and the 2000s in 10 industrialized countries. The prevalence of short sleep increased in some countries (e.g., Norway) and decreased in others (e.g., Sweden, and USA). A mixed pattern was also evident for long sleep, with increasing prevalence in, e.g., Sweden, and decreasing prevalence in Italy and Canada [25]. In the Finnish sample referred to above [21], average habitual self-reported sleep duration decreased by 18 minutes over 33 years. An increase was seen in the proportion of working-age men who slept 7 h, at the expense of a decrease in the proportion sleeping 8 h. The percentages who reported sleeping less than 7 h or less than 6 h did not change. Similar results were observed among the Gothenburg women [22]. Recently published data from the National Health Interview Survey in the US [26], however, indicated changes in the extremes of the distribution of sleep duration between 1977 and 2009. The prevalence of very short (<5 h) and short (5–6 h) habitual sleep durations increased from 1.7% to 2.4% and from 19.7% to 26.7%. The prevalence of long sleep (>8 h) decreased from 11.6% to 7.8% [26]. Although a possible explanation for the heterogeneity in results across studies is the different sleep measures used (time use vs. habitual sleep), a systematic review including data from 15

countries from the 1960s to the 2000s found no indication thereof [27]. The results from the review were mixed, showing that average sleep duration increased in some countries and decreased in others. It was unclear, however, whether the proportions of short and long sleepers had changed [27].

2.4 CORRELATES OF INADEQUATE SLEEP

As evidenced above, there is considerable inter-individual variability in reported sleep durations. To what extent this reflects variations in biological sleep need or chronic sleep restriction/sleep debt resulting from a forced or voluntary reduction of sleep duration is largely unknown. A small experiment among young adult women suggested that sleep debt was higher among women with short habitual sleep durations relative to those with longer habitual sleep durations [28]. Nonetheless, there is a multitude of factors associated with self-reports of sleep. Some of these factors may be seen more or less as "voluntary" correlates of reduced sleep time and others as "forced" correlates.

For instance, insomnia symptoms (difficulty falling asleep, wakening during the night or too early, etc.) are more common in both short and long sleepers compared with medium-length (7–8 h) sleepers [29], and in those with insufficient sleep [16]. Because insomnia is not only the most common sleep disorder but also among the commonest of mental disorders [30], the relation between insomnia symptoms or disorder with reports of depressive or anxious mood is unsurprising [18, 19, 31]. Also, nondepressed individuals with insomnia have a higher risk of developing depression relative to those without sleep complaints [32]. Insomnia symptoms are overall more common in women than men [18, 19, 31, 33], and some symptoms appear to be more prevalent at older ages [31].

Short and long sleep durations have been associated with mental health problems (other than insomnia) [34-36], and with unemployment, lower educational level, and other socioeconomic aspects [34-37]. Depression and low socioeconomic status have been suggested to explain the relationship between long sleep and poor health outcomes [36]. Additionally, work-related factors (e.g., work hours, ability to control work time, work stress, shift work) are related to short or reduced

sleep and sleep problems [16, 34, 38-41]. Short sleepers have been reported to spend more time socializing, relaxing, and engaging in leisure activities compared with longer sleepers [38].

Short/long sleep durations and insomnia symptoms are associated with worse self-rated health [42, 43]. Also, they are all associated with reports of prevalent diabetes, hypertension, and/or cardiovascular disease [34, 36, 42, 43], and with the metabolic syndrome [44, 45]. Low levels of physical activity have been related to short [35] and long [34, 35] sleep durations. Other health-related behaviors, including current or former smoking and alcohol consumption (both few and numerous drinks/wk), were associated with short and long sleep durations [34]. Lastly, the relationship of self-reported sleep duration with age is not self-evident, meaning that although sleep time as measured by polysomnography (PSG) appears to decline with age, this is not always the case for self-reports [23, 34-36, 38].

These associations reflect a complex web of interrelated mechanisms of sleep regulation in the population. They also demonstrate the challenges in trying to delineate the relationships between sleep habits and later disease; and in trying to understand what self-reported sleep really represents.

2.5 SLEEP AND OBESITY

While plausible, it may not be convincingly established whether sleep habits have deteriorated over time in society as a whole, and whether this has led to increases in chronic sleep deprivation. Recent years' interest in quantifying the long-term consequences of inadequate sleep can still be understood from several perspectives: prevalence estimates of short sleep duration and sleep problems are high; inadequate sleep is associated with reductions in perceived health, increased risks of accidents [46], other safety issues [47], and work absenteeism [48, 49]; high societal costs [50, 51]; and importantly, sleep habits are potentially modifiable and thus a target for intervention.

Weight gain and obesity are possible consequences of inadequate sleep [52-54]. Between 1980 and 2013, worldwide prevalence of obesity and overweight

combined increased by 28% in adults, equivalent to a rise from 29% to 37% in men, and from 30% to 38% in women [55]. Rates are higher in higher-income than lower-income countries, and Sweden is no exception [55]. Because rates of obesity have increased so rapidly, it is unlikely that genetic changes in the population account for this trend. Instead, environmental and/or behavioral factors – possibly including inadequate sleep habits – are likely to explain the increased rates of obesity worldwide [56].

2.5.1 Possible mechanisms

Two types of pathways can be outlined as possible explanations to the observed associations between inadequate sleep and weight gain or obesity. Naturally, these relate to energy balance. Best supported is perhaps the idea that sleep restriction leads to increased appetite and/or more time to eat, with increased energy intake as the net result. Evidence appears less supportive of reduced energy expenditure as a consequence of sleep restriction.

A randomized, crossover study in 12 young, healthy, normal-weight men tested whether two nights of experimental sleep restriction (4 h time in bed) changed appetite regulation compared with two nights of sleep extension (10 h time in bed) [57]. Results showed that levels of the satiety hormone leptin were reduced and levels of the appetite-stimulating hormone ghrelin increased during sleep restriction. Moreover, sleep restriction was associated with increased ratings of hunger and appetite, especially for calorie-dense foods with high carbohydrate content [57]. Another study among men found similar results after one night of sleep restriction [58].

Later experiments have measured energy intake directly. During at least 5 nights of partially restricted sleep, energy intake increased [59-62], especially from fat [61, 62], in studies including men and women. In two of these studies, sleep restriction promoted weight gain [60, 61]. One [62] study found no change in energy expenditure, and another [60] an increase in energy expenditure but not enough to compensate for the increased energy intake. Other laboratory protocols in men have found decreases in resting and postprandial energy expenditures [63] or in physical

activity during the daytime spent under free-living conditions [64]. None of the studies found any changes in energy intake [63, 64]. Overall, these results are suggestive of a positive energy balance caused by experimentally induced sleep restriction. It remains unknown to what degree chronic sleep restriction under real-life conditions might contribute to sustained energy imbalance.

2.6 SLEEP AND CARDIOVASCULAR DISEASE

Cardiovascular diseases (CVD), in particular coronary heart disease and stroke, are the leading cause of death globally, responsible for 17.5 million deaths or 3 in every 10 deaths in 2012 [65]. The proportion of deaths from CVD is higher in higher-income countries than in low-income countries [65]. In Sweden, deaths from CVD have been declining since the late 1980s [66]; so has the incidence of acute myocardial infarction [67].

In addition to obstructive sleep apnea syndrome (OSAS) [68], short and long sleep durations have emerged as potential risk factors for development or death from CVD [69]. Insomnia symptoms are also associated cardiovascular risk [70], and there are indications that individuals with both short sleep and sleep problems have the highest risk [71]

2.6.1 Possible mechanisms

There are several potential explanations for the observed relation between inadequate sleep and CVD. Because of the known relationship with obesity, appetite dysregulation and decreased energy expenditure from reduced sleep could contribute to CVD. Experiments have also shown that sleep deprivation or impaired sleep quality are associated with reduced insulin sensitivity and glucose control [72-74], which through the incidence of type 2 diabetes [75] could explain the link to CVD. Increased levels of cortisol, a marker of stress, may also contribute [73]. Furthermore, sleep restriction has been shown to increase the secretion of the proinflammatory markers interleukin-6, tumor necrosis factor-α [76], and C-reactive protein [77], representing yet another pathway to CVD. Acute total sleep deprivation has been shown to result in increased blood pressure [77, 78].

Apart from these experimental studies, self-reports of short habitual sleep duration have been independently related to risk factors for CVD, including incident hypertension [79] and high blood cholesterol [80]. A recent study among US adults showed that chronic insomnia with short objective sleep duration as measured by PSG also was associated with incident hypertension after adjustment for multiple confounders [81]. In a cross-sectional study among Taiwanese adults without history of cardiovascular disease, long, but not short, habitual sleep duration was independently associated with arterial stiffness, a marker of atherosclerosis, among men only [82].

2.7 OBSTRUCTIVE SLEEP APNEA SYNDROME

2.7.1 Disease characteristics

OSAS is a sleep-related breathing disorder characterized by abnormal breathing events during sleep. These events – complete cessation (apnea) or partial obstruction (hypopnea) of breathing – occur repeatedly during sleep as a consequence of upper airway collapse. The breathing pauses are often associated with oxygen desaturation (hypoxemia) and end in brief arousals from sleep, resulting in pronounced sleep fragmentation and reduced amounts of slow-wave sleep and REM sleep [83]. OSAS is typically associated with loud snoring and, given the impaired sleep quality, the classic symptom of the disease is excessive daytime sleepiness. Individuals with OSAS often report having reduced quality of life, cognitive performance, and social functioning [84, 85].

The apnea-hypopnea index (AHI) is the predominant measure used to determine presence and severity of OSAS. The AHI reflects the total number of apneas and hypopneas per hour of sleep. As long as daytime symptoms are included in the disease definition, five or more breathing events are typically used to define its presence [86]. According to the severity classification, *mild* disease is defined as an AHI of 5 or more but less than 15, *moderate* disease as an AHI of 15 to 30, and *severe* disease as an AHI over 30. However, different disease definitions are in use. When the condition is not clinically defined, *i.e.*, daytime symptoms are not accounted for, it is referred to as "OSA." The AHI threshold to define presence

or severity of OSA can be, but is not necessarily, the same as for OSAS; commonly, a threshold of 15 events/h of sleep is used.

2.7.2 Occurrence, risk factors, and possible consequences

Due to the many definitions of OSAS in use, prevalence estimates vary. In a number of population-based studies with varying age ranges and AHI thresholds for OSA, reported prevalence was between 9% and 62% [87-91]. When sleepiness complaints are included, prevalence figures expectedly become lower; estimates of 1–2 % in women and approximately 4% in men have been reported [89, 92]. The prevalence of both OSA and OSAS has increased over time [93]. Obesity [89, 90, 92], age [87, 88, 90, 94], and male sex [87-90, 92] are strong risk factors.

Untreated OSAS may have severe consequences to health, and has been independently associated with hypertension [95]; diabetes [96]; depression [97]; cardiovascular disease, most notably stroke [68, 98, 99]; and all-cause mortality [100] in prospective studies. It is a treatable condition, however. Treatment options include continuous positive airway pressure, dental and mandibular advancement devices, surgical procedures, and weight loss [101]. For simplicity, OSAS will be used to denote the condition from here on, unless the distinction between OSAS and OSA is warranted.

2.7.3 Diagnostic modalities

The "gold" standard for diagnosing OSAS in clinical practice is overnight polysomnography (PSG), preferably carried out in a technician-attended sleep laboratory [101]. Because laboratory-based PSG is expensive, labor-intensive, may be experienced as disturbing by the individual subjected to the sleep study, and of limited access, alternative methods to diagnose OSAS have been developed. One such alternative to PSG is portable monitoring, which refers to a spectrum of devices that record as many parameters as PSG or a minimum of one [102]. Home sleep studies with portable monitoring have been proposed as a useful strategy to reduce costs and overall simplify the diagnostic process among individuals suspected of having sleep apnea [103]. In Europe, for instance, modified portable sleep apnea testing, or portable cardiorespiratory monitoring, is the

diagnostic method of choice in 67% of patients with suspected OSAS [104]. To further simplify diagnostic processes and accommodate increasing demands for OSAS testing, simple screening or diagnostic tools have been created. Among these tools are questionnaires assessing common symptoms of the disease [105, 106]. The notion is that such tests can form the basis for triaging decisions or further objective testing of OSAS.

2.8 A NOTE ON SLEEP QUALITY

Dissatisfaction with sleep quality is a key feature of insomnia [107]. It would therefore be reasonable to assume that there is a standardized definition of this concept which is so commonly used for both clinical and research purposes, but there is none [108].

Sleep quality may be viewed as a construct including both quantitative and subjective aspects of sleep. Sleep duration, sleep latency, number of awakenings, total wake time, and sleep efficiency are examples of quantitative aspects. Subjectively oriented aspects include depth of sleep, restfulness of sleep, overall subjective sleep quality (with no definition in terms of specific sleep complaints), and feelings of refreshment upon awakening [109]. Many times, however, sleep quality is regarded a characteristic of sleep independent of, or contrasting with, sleep quantity.

Objective equivalents of the quantitative aspects of sleep quality can be derived from PSG, and thus include measures of total sleep time, sleep latency, number of awakenings, wake time after sleep onset, sleep efficiency, and so on. Measures of the architecture of sleep (*i.e.*, the percentage or amount of time spent in different sleep stages) have no obvious self-report equivalents, but are sometimes also used as indicators of sleep quality [108]. Subjective components of sleep quality are by definition more challenging to describe and measure objectively, and it should be kept in mind that the makeup of sleep quality may well vary across individuals [108, 109]. Nevertheless, comparisons of sleep quality ratings with physiologically assessed sleep may prove valuable because they allow for an improved understanding of the subjective experience of sleep.

3 AIMS

The overall aim of this thesis was to expand knowledge about self-reported habitual sleep and its implications for health and correspondence with objective sleep measures.

More specifically, the aims were the following:

Study I: to compare the distribution of body mass index among subjects with different sleep patterns in terms of duration and quality indicators of sleep.

Study II: to examine sleep duration and insomnia symptoms separately and jointly in relation to the risk of cardiovascular events.

Study III: to examine if subjects with and without obstructive sleep apnea syndrome may be accurately distinguished from each other using self-report measures of apneas/snoring and sleepiness compared with diagnostic testing based on overnight cardiorespiratory monitoring.

Study IV: to examine the association between self-reported ratings of sleep quality and restoration from sleep, respectively, and sleep recorded by polysomnography.

4 METHODS

The papers included in this thesis cover four study designs and three settings (Table 1). The Karolinska Sleep Questionnaire (KSQ) was the common denominator and used throughout all papers. The KSQ is a self-administered tool which asks about habitual sleep duration, quality and disturbances, and possible daytime consequences of too little or disturbed sleep. The KSQ was developed during the 1980's, and the reliability and validity of the questionnaire scores have been tested with various Swedish populations [41, 110-112].

Table 1. Overview of studies included in thesis.

Characteristic	Study I	Study II	Study III	Study IV
Design	Cross-sectional	Cohort	Diagnostic test accuracy	Validation
Population				
Number	40,197	41,192	103	33
Age range, y	18–94	18–94	30–66	28–69
Female sex, %	64	65	31	61
Data from KSQ (exposure variables)	Sleep duration Sleep quality (index) Restorative power of sleep (index) Daytime sleepiness	Sleep duration Difficulty falling asleep Difficulty maintaining sleep Early morning awakening Nonrestorative sleep	Apnea/snoring (index) Sleepiness (index)[a]	Sleep quality (index) Restoration from sleep (index)[b]
Outcome variable(s)	Body mass index	(1) Overall and (2) specific cardiovascular events	Obstructive sleep apnea syndrome[c]	Standard polysomnography parameters[d]
Primary analytical method	Quantile regression	Cox proportional hazards regression	Calculation of accuracy estimates, e.g., sensitivity and specificity	Linear regression

[a] The indices were the index tests used to identify obstructive sleep apnea syndrome.
[b] The indices constituted the outcome variables of interest.
[c] Rather than the outcome variable, obstructive sleep apnea syndrome was the target condition under study.
[d] Polysomnography parameters constituted the predictor variables.

4.1 STUDY DESIGNS AND POPULATIONS

4.1.1 The National March Cohort

Studies I and II are based on the same study population, the National March Cohort. It was established between September 10 and 14 in 1997 when a walk for cancer, "Riksmarschen" (*i.e.,* the National March), was organized by the Swedish Cancer Society in 3,600 places throughout Sweden. The aim of the walk (1–10 km in distance) and accompanying events ("meet the professor," microscope imaging stations, etc.) was to raise funds for cancer research and promote a healthy lifestyle. The target group was the entire Swedish population. For a group of researchers at the Karolinska Institutet, the National March was an opportunity to collect high-quality and detailed exposure data from a large number of presumably motivated people. The overall purpose was to study the role of lifestyle factors, physical activity especially, in the development of chronic conditions. Cancer was a main focus among those conditions, although the cohort design allowed for examination of several other endpoints, e.g., cardiovascular disease.

Adult participants in the National March were invited to complete a 36-page questionnaire. It covered 13 areas of lifestyle and health, among them physical activity, body weight, dietary habits, and sleep habits. Thus, the KSQ was part of the overall study questionnaire, which was distributed at each starting place of the walk, local libraries, grocery stores, etc. Taking part in the walk for cancer was not a prerequisite for study participation. In the questionnaire, subjects provided their personal identity number (PIN) [113], a unique identifier enabling multiple register linkages for prospective follow-ups of the cohort.

The total number of participants in the National March could not be assessed and therefore the response rate to the questionnaire is unknown. A total of 43,880 subjects completed and returned the questionnaire. Of these, 35,806 reported that they had participated in the walk for cancer.

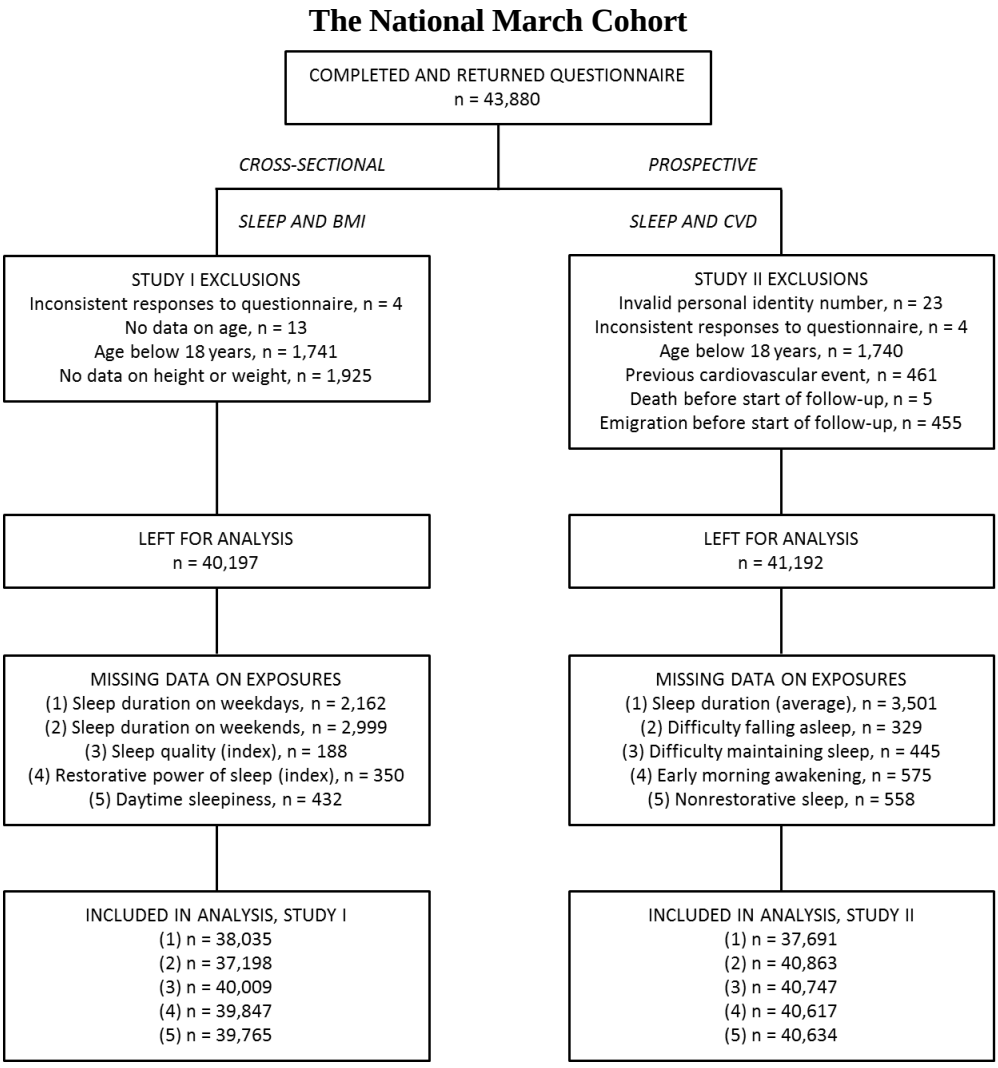

Figure 2. Flow of subjects in studies I and II. Exclusion criteria are not necessarily mutually exclusive; the exclusions are listed in the sequence they were carried out. Note that missing information on age is not the same as an PIN. Thus, one individual aged below 18 years provided an invalid PIN. Missing values on the exposure variables further reduced the number of individuals included in analyses.

Figure 2 depicts the flow of subjects through studies I and II. The former study was based solely on data collected at baseline, and thus used a cross-sectional design to examine the relationship between sleep habits and BMI. In the latter study, subjects were followed prospectively for the occurrence of cardiovascular disease associated with sleep habits; it was a cohort study.

As seen in the figure, some of the subjects with an invalid PIN were excluded from study II but not study I. An invalid PIN would prevent follow-up in Swedish registers, but is not necessarily a problem in a cross-sectional study where a group of people is studied at a single point in time. Subjects with invalid PINs provided a fully reasonable date of birth. Also, their three-digit sex-specific birth number [113] was consistent with answers to sex-specific questions in the study questionnaire. We therefore assumed that subjects who stated they were men indeed were men and that those who stated they were women in fact were women. They were kept in the database for analysis in study I.

4.1.2 Patients at a sleep clinic

In study III we examined, for the first time, the diagnostic ability of the KSQ for OSAS. The key concept of a so-called diagnostic test accuracy study is to compare results of an index test with those of a reference standard. Here, the KSQ was the index test. The reference standard should be a method that accurately identifies patients with the condition under study, preferably the diagnostic "gold standard." In our study, the reference was the method used routinely by the sleep clinic to establish presence or absence of OSAS. This method includes overnight unattended portable cardiorespiratory monitoring and a clinical evaluation, *i.e.*, a follow-up visit to the clinic to review the monitoring results in light of the patient's symptoms of OSAS.

Study subjects were prospectively recruited among patients referred to a large sleep clinic in Stockholm for the evaluation of OSAS. In other words, subjects' status with respect to the target condition was not known at the time of enrolment. It required us to determine the sample size such that the sample with high probability (we chose 95%) would include sufficient numbers of subjects with and without the condition to accurately estimate the diagnostic ability of the KSQ. As the condition to be tested (OSAS) had a binary outcome (yes/no), sample size determination was based on the binomial distribution [114]. According to the clinic's records, the prevalence of OSAS in the target population was likely to exceed 50%. We expected that questionnaire specificity would be 0.85 and wanted the lower 95% confidence limit to fall somewhere between 0.55 and

0.65. Based on these parameters, the sample size calculation gave that 137 to 255 subjects would suffice. Because of the high patient flow through the clinic (>100 patients/week), we expected that the adequate number of subjects would be reached within 1 month.

Eligible subjects were selected from patients scheduled for overnight unattended portable cardiorespiratory monitoring between September 17 and October 19, 2012 (n = 493). Subjects were excluded if they were already diagnosed with or receiving treatment for OSAS (*i.e.*, were aware of their OSAS status), or if the reason for referral turned out to be an indication other than OSAS. Insufficient knowledge of Swedish and residence outside Stockholm or neighboring counties also qualified for exclusion. Hence, study invitations including the KSQ were mailed to 400 patients approximately three weeks before their scheduled sleep study. Patients were instructed to return the completed questionnaire to the clinic on the day they came to collect the portable monitor for testing of OSAS in their homes. We did not administer the KSQ at the clinic (which might have promoted a higher response rate) because the invitation also included the Karolinska Sleep Diary and the Karolinska Sleepiness Scale. Subjects were asked to complete those tools on seven consecutive days. Apart from completion of the three Karolinska tools, study participation meant no extra procedures beyond clinical practice. Thus, completing and returning the KSQ to the clinic was considered informed consent.

Among the 400 patients invited, 99 canceled or rescheduled their visit to the clinic and 22 did not receive the study invitation (invitation letters were returned to us as undeliverable). In total, 103 subjects completed and returned the KSQ. Non-participating subjects (n = 176) were slightly younger than those participating (49 y vs. 53 y), but the proportion of men was similar across groups (68% vs. 69%). A chart over the flow of subjects through the study is presented in paper III (Figure 1).

4.1.3 Adults with no documented sleep problems

Study IV used data from the investigation "Sleep and Health." It was set up with the purpose to monitor the interconnection between objectively measured sleep, self-reported sleep, and health-related measures in a real-world environment. The data collection took place between 1998 and 2000, and healthy adult men and women were targeted. The specific aim of study IV was to examine the association between habitual sleep reported in the KSQ and physiological sleep, *i.e.*, sleep measured using PSG.

Fifty-two individuals were approached via advertisements and personal contacts, 46 accepted participation and 33 completed the study. The reasons for noncompletion (n = 13) were illness, travel, work schedules, etc., which interfered with participation. Study subjects underwent a medical examination to ensure that they were healthy and did not complain of sleep disturbances. They filled out the KSQ and, starting approximately two months later, underwent multiple objective sleep recordings using PSG. All subjects received a cash payment of 1,200 SEK (equivalent to 180 USD) as compensation for participation.

4.2 ETHICS APPROVAL

The institutional review board at the Karolinska Institutet granted ethics approval for all studies: I and II, dnr 97-205; III, dnr 2012/973-31/3; and IV, dnr 98-411.

4.3 ASSESSMENT OF EXPOSURE VARIABLES AND SUBJECTIVE SLEEP MEASURES

This section deals with data obtained from the KSQ and how they were used across the papers. Readers will notice that the definitions of medium-/normal-length sleep and long sleep differ between papers I and II. In papers I and IV, slightly different wordings were used for the same construct relating to the (non)restorative feeling of sleep experienced upon awakening. This construct was termed *restorative power of sleep* in paper I, and *restoration from sleep* in paper IV. While these inconsistencies may be confusing and reduce comparability across studies, they also reflect the lack of a standardized

definition and terminology of the concepts used. In addition, the research question at hand in each study has directed the choices made.

4.3.1 Sleep duration and sleep quality indicators

In studies I and II, subjects reported their usual sleep duration per 24 hours as shown in Figure 3 below. We used two separate categorical sleep duration variables in study I to examine if the pattern of association with BMI differed between weekday and weekend sleep. Sleep duration was classified as short (≤5 h), medium-length (6–8 h; reference category), and long (≥9 h). In study II, we calculated the weighted average sleep duration across both questions by assigning weekdays a weight of 5/7 and weekends a weight of 2/7. The open-ended response alternatives (<5 hours and ≥9 hours) were assigned a value of 3.5 and 10, respectively, to enable that calculation. The resulting duration variable was then classified as short (≤5 h), normal-length (6–7 h, with 7 h as reference category), and long (≥8 h). Note that 6 h and 7 h comprised separate categories.

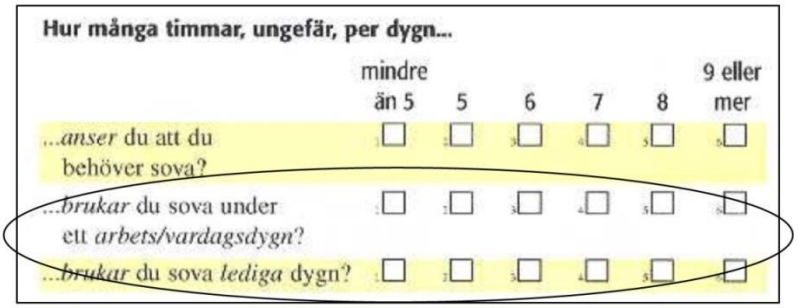

Figure 3. Assessment of usual sleep duration on weekdays ("arbets/vardagsdygn") and weekends ("lediga dygn") in the KSQ version used in studies I and II. We used two variables to reflect sleep duration separately for weekdays and weekends in study I. In study II, we computed the weighted average sleep duration.

Sleep duration was not a variable of primary interest in study IV; however, it was assessed and included in the paper mainly for description. Subjects reported usual bedtime (putting the lights out), rise time, and sleep latency (time in minutes to falling asleep after lights out) separately for weekdays and weekends. We calculated sleep duration as the difference between rise time and bedtime, subtracting sleep latency. Again, responses were averaged across the two

questions, and a weighted sleep duration variable was created by assigning weekday sleep a weight of 5/7 and weekend sleep a weight of 2/7.

Sleep problems were assessed using 13 items with a five-point categorical response scale reflecting the frequency of problems in studies I and II (Figure 4). In study I, we combined sets of items into two indices reflecting different aspects of sleep quality. According to KSQ practice, four items on sleep disturbances indicative of insomnia (see which in the figure) comprised the *sleep quality* index. Three items (see figure) were combined to form the *restorative power of sleep* index. We categorized each index such that responding mostly or always to at least one item qualified as "poor" sleep quality or restorative power of sleep, sometimes to all items as "moderate," and otherwise as "good" (reference category). A single item (see figure) was used to reflect *daytime sleepiness*. It was classified as "yes" if subjects responded mostly or always, and otherwise as "no" (reference category). In total, we used five variables derived from the KSQ to examine the relation between habitual sleep and BMI in study I; sleep duration on weekdays and sleep quality were the exposures of primary interest.

In study II, three of the items used to create the sleep quality index represented separate exposure variables. Those variables were *difficulty falling asleep*, *difficulty maintaining sleep*, and *early morning awakening* (DFA, DMS, and EMA, respectively, in the figure). A single item reflected *nonrestorative sleep* (NRS in the figure). Thus, insomnia symptoms were in focus in this study, too. For analysis, we used the original categorical response scale for all variables, with mostly and always merged into one category; never was the reference category. In the analysis of the joint association of sleep duration and insomnia symptoms with cardiovascular events we instead dichotomized each symptom variable. Insomnia symptoms were classified as "frequent" if subjects responded sometimes, mostly or always, and otherwise as "infrequent."

In study IV, we focused, again, on the indices for sleep quality and restoration from sleep, but this time as outcome variables. The same items as in study I were used to create each of the indices. All items were assessed on the same five-point response scale as in study I, but subjects were asked to report their sleep habits

for the past six, not 12, months. We assigned the responses a value between 1 (always) and 5 (never) and calculated the index scores by averaging responses across the respective set of items. A higher score thus indicated less frequently occurring problems – or for simplicity, better *sleep quality* or *restoration from sleep*.

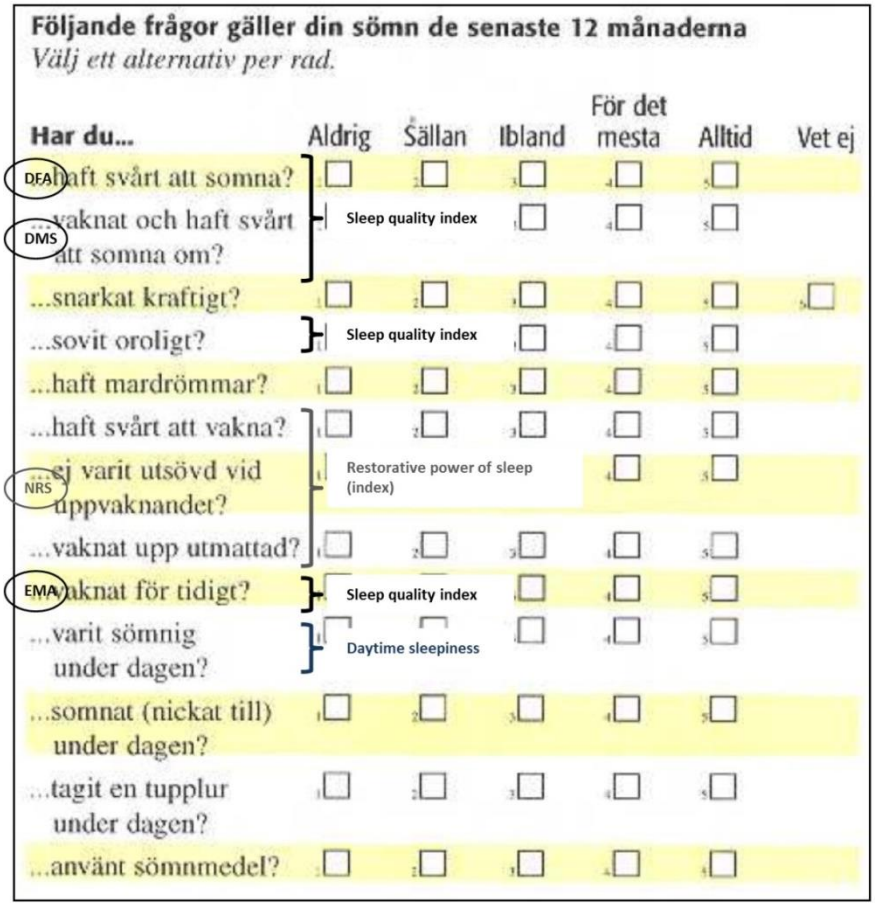

Figure 4. Assessment of sleep problems in the KSQ version used in studies I and II. Subjects were asked with which frequency (never, rarely, sometimes, mostly, or always; and do not know for snoring) they had experienced problems the past 12 months. Four items were combined into the *sleep quality* index used in study I: difficulty falling asleep (labeled DFA), difficulty maintaining sleep (DMS), restless sleep, and early morning awakening (EMA). Three items created the *restorative power of sleep* index, which was also used in study I: difficulty waking up, waking up feeling unrested, and waking up feeling exhausted. One item reflected *daytime sleepiness* in study I: feeling sleepy during the day. In study II, three of the items in the sleep quality index represented separate exposure variables: *DFA*, *DMS*, and *EMA*. One item reflected *nonrestorative sleep* in study II: waking up feeling unrested (NRS).

4.3.2 Symptoms of OSAS

Study III focused on two different KSQ indices. The *apnea/snoring* index was based on three items, as shown in Figure 5. The *sleepiness* index consisted of five items, also indicated in the figure. In this later version of the KSQ, problems were assessed on a six-point response scale where the alternative "often" had been added. For the apnea/snoring items there was an additional "do not know" response alternative. We classified subjects as test positive, *i.e.*, symptomatic of OSAS, if they responded mostly or always to at least one item in the respective index. Missing or indeterminate answers (do not know) were coded as never. We also examined the impact of *overall sleep quality* on diagnostic ability. Responding "moderately poor" or "very poor" counted as poor overall sleep quality. Subjects were classified as test positive if they were symptomatic according to the apnea/snoring index *or* the sleepiness index *or* had poor overall sleep quality.

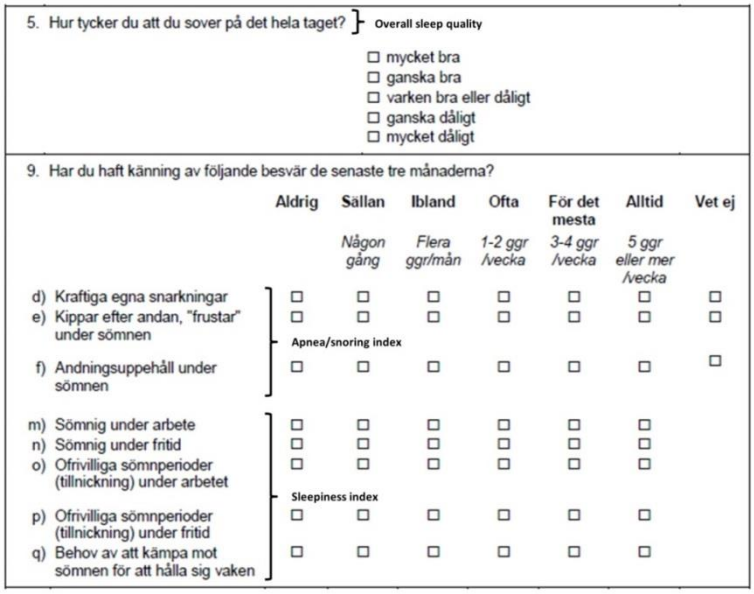

Figure 5. Assessment of *overall sleep quality*, and *apnea/snoring* and *sleepiness* complaints in the KSQ version used in study III. For sleep quality, subjects were asked "On average, how do you sleep?" with response alternatives very well, moderately well, neither well nor poorly, moderately poorly, and very poorly. They were also asked with which frequency they had experienced a number of specific sleep problems (only those relevant for the study shown here) the past 3 months. Three items comprised the apnea/snoring index: heavy snoring (d), gasping for breath during sleep (e), and breathing cessations during sleep (f).Five items comprised the sleepiness index: sleepiness during work (m) and leisure time (n), involuntary sleep episodes during work (o) and leisure time (p), and need to fight off sleep to stay awake (q).

4.4 ASSESSMENT OF OUTCOME VARIABLES AND OBJECTIVE SLEEP MEASURES

This section covers the ascertainment of outcome variables in studies I and II, and the sleep measures *not* assessed by the KSQ in studies III and IV.

4.4.1 Body mass index

BMI was the outcome of interest in study I. Participants reported height and weight in the study questionnaire. BMI was calculated as weight in kg divided by height in meters squared, and used as a continuous numerical variable in the primary analysis (quantile regression).

4.4.2 Cardiovascular events

In study II, the primary outcome of interest was a composite variable of incident (i.e., new cases of) cardiovascular events and death from cardiovascular disease. We also examined the diagnosis-specific outcomes used to create the overall variable: acute myocardial infarction, heart failure, stroke, and death from all cardiovascular diseases.

Nonfatal events were ascertained in the inpatient portion of the Patient Register (also known as the Hospital Discharge Register) [115]. It contains information on all inpatient care for the whole of Sweden since 1987. Register variables include, e.g., the PIN, dates of admission and discharge, one primary and several contributory diagnoses recorded at the end of the hospital stay, *i.e.* the discharge. The diagnoses are coded using the Swedish adaptation of the *International Classification of Diseases* (ICD) system.

Fatal events were ascertained in the Cause of Death Register [116]. Since 1961 it covers all deceased individuals who were Swedish residents at the time of death, regardless of whether death occurred in Sweden or not. The PIN, date of death, underlying and contributory causes of death (coded using the ICD) are examples of register variables.

We classified myocardial infarction and stroke as events regardless of whether they were recorded as primary or contributory diagnoses, and heart failure only if

recorded as primary diagnosis. The admissiono date was considered the event date. We considered only those fatal events where any cardiovascular disease was recorded as the underlying cause of death. Table 2 reports the ICD codes used to identify nonfatal and fatal events in the registers.

Table 2. Diagnostic events in study II classified according to ICD-9 and -10.

Diagnostic event	ICD-9 code	ICD-10 code
Acute myocardial infarction	410	I21
Heart failure	428	I11.0, I50
Stroke	430, 433, 434, 436	I60, I61, I63.0–I63.5, I63.8–I63.9, I64
Death from all cardiovascular diseases	390–459	I00–I99

In study II, cardiovascular events were identified in the Swedish National Patient Register (acute myocardial infarction, heart failure, stroke) and the Swedish Cause of Death Register (death from cardiovascular disease) using ICD-9 and ICD-10 codes.

Study subjects were followed from October 1, 1997 until the date of an incident cardiovascular event, emigration, death from causes other than cardiovascular disease, or the end of follow-up on December 31, 2010, whichever came first. "Incident" was defined as having no record of any of the (nonfatal) events under study in the Patient Register 10 years before start of follow-up.

4.4.3 Diagnosis of OSAS

In study III, subjects underwent unattended overnight cardiorespiratory monitoring in their homes for estimation of the AHI. OSAS was defined as an AHI of 5 or more with symptoms indicative of disease, such as excessive daytime sleepiness and impaired concentration [86]. Symptoms were mainly verbally evaluated at the subjects' follow-up visit to the clinic, but also reported in the clinic's standard questionnaire, which did not include the KSQ. The diagnosis was coded as G47.3 (sleep apnea syndrome in ICD-10) in the sleep clinic's records. OSAS was classified as mild (AHI, ≥5–<15), moderate (≥15–30), or severe (≥30). For detailed information on technology and event scoring criteria used in the cardiorespiratory monitoring, please see paper III.

4.4.4 Sleep measured by polysomnography

In order to obtain a representative estimate of habitual physiological sleep in study IV, subjects underwent multiple unattended PSG recordings in their homes on nonconsecutive nights. The median number of days between the first and last recording was 26 (interquartile range, 18–31 days; range, 7–83 days). The majority of subjects (n = 23) completed four unattended PSG recordings. The rest completed five (n = 2), three (n = 6), or two (n = 2) recordings.

Standard PSG-derived parameters, as termed and defined by Rechtschaffen and Kales [9], were considered in the analysis: sleep efficiency, total sleep time, sleep latency (to stage 1 sleep), stage 1 sleep, stage 2 sleep, slow-wave sleep (*i.e.*, stages 3 + 4), REM sleep, wake time after sleep onset, and number of awakenings. Sleep efficiency was defined as percentage total sleep time of time in bed after lights out. Except for number of awakenings, the parameters were considered in minutes; sleep stages were also summarized as percentage total sleep time. In each subject, all PSG measures were averaged across the number of recordings completed. For details on technology and sleep scoring criteria used, please refer to paper IV.

4.5 STATISTICAL ANALYSES

Below is a summary of the most relevant statistical methods used and analyses performed.

4.5.1 Study I

The primary method of analysis in study I was quantile regression. It is an extension of the ordinary linear regression model which allows for multiple points of examination in the distribution of an outcome variable and not only at the mean. Quantile regression therefore offers an opportunity to establish a more complete picture of the relationship between predictor and outcome variables. Quantile regression does not require any assumption about the distribution of the regression residuals and is not influenced by outliers or skewness in the distribution of the outcome variable.

We estimated the 5^{th}, 10^{th}, 25^{th}, 50^{th}, 75^{th}, 90^{th}, and 95^{th} percentiles of BMI, conditional on the values of each of the sleep variables and possible confounding factors. Quantile regression parameters are interpreted as follows: the estimated parameter denotes the change in the value at the modeled percentile of the outcome variable for each unit change in the predictor variable. With reference to our study, a parameter estimate of 0.80 for ≤5 h of sleep in the 90^{th} percentile model suggests that the 90^{th} percentile of BMI is 0.80 kg/m^2 higher among short sleepers relative to medium-length sleepers (6–8 h). In this example, the 90^{th} percentile represents the BMI value below which 90% of the observations fall within each sleep duration category.

Ninety-five percent confidence intervals (CI) were estimated with 500 bootstrap samples for each modeled BMI percentile. Based on subject matter knowledge about potential confounding factors of the relation between sleep habits and body weight, we adjusted data for age, educational level, physical exercise, smoking status, alcohol consumption, and work schedule. Because of appreciable differences across sexes in the association of sleep duration on weekdays with the considered BMI percentiles, men and women were analyzed separately. We assessed the robustness of our findings by restricting the analyses to subjects with no reported depressive symptoms or treatment of cancer, diabetes, myocardial infarction, rheumatoid arthritis, Crohn's disease, or ulcerative colitis (2,888 men and 5,880 women excluded from analysis).

In all analyses, subjects with missing values on any of the covariates entered into the model were excluded. Depending on the exposure variable, a complete-case fully adjusted analysis included 78–82% of the initial sample.

4.5.2 Study II

In this time-to-event, or survival, analysis, we used the Cox proportional hazards model to compare the occurrence of cardiovascular events between exposed and unexposed subjects. Hazard ratios (HRs) with corresponding 95% CIs were estimated with attained age as the underlying time scale. All models were stratified on sex to allow for separate baseline hazards among men and women.

We checked that the proportional hazards assumption, stating that the HR is constant over time, was satisfied by using scaled Schoenfeld residuals. There was no evidence of departure from this assumption.

The selection of potential confounding factors was based on subject matter knowledge and assisted by the use of directed acyclic graphs [117]. Consequently, data were adjusted for age, sex, educational level, employment status, smoking status, and work schedule in a parsimonious model. Depressive symptoms, self-rated health, physical activity, BMI (obesity), diabetes, lipid disturbance, and hypertension were left out of this model because they could be on the causal pathway between unfavorable sleep habits and cardiovascular disease. Given that the data on all predictor variables were collected at baseline only, we additionally controlled for those variables in a next step. To obtain a slightly more nuanced view of how all variables selected for analysis influenced the relationship between sleep habits and cardiovascular events, we regrouped them into four separate sets of confounders. Education, employment status, and work schedule comprised one set (socio-demographics); alcohol consumption, smoking, and physical activity another (life-style related behaviors); self-rated health and depressive symptoms a third (mental/physical ill health); and BMI, snoring, diabetes, lipid disturbance, and hypertension a fourth (risk factors for CVD).

We included multiplicative interaction terms between sleep duration and each of the insomnia symptoms and sex (with model stratification removed), and age at baseline (dichotomized at age 50; the median was 53 y), respectively. Interaction terms were also included between sleep duration and each of the insomnia symptoms (dichotomized and defined as frequent vs. infrequent). This was done to examine the presence of effect measure modification, *i.e.*, whether the effect of sleep habits on the outcome differed across levels of a third variable. For each interaction examined, we compared the model with the interaction term with the corresponding main effects model using a likelihood ratio test; significance level was set at 0.05.

Using main effects models only, HRs were estimated for myocardial infarction, stroke, heart failure, and death from all cardiovascular disease in separate cohorts. Subjects with a baseline history of the specific (nonfatal) outcome under study were excluded from analysis; a history of any of the other (nonfatal) outcomes did not warrant exclusion.

In an attempt to address potential reverse causation, *i.e.*, that any observed association would be due to cardiovascular disease giving rise to disrupted sleep, we excluded the first 2 years of follow-up and reran the analyses.

Finally, multiple imputation by chained equations [118, 119] was used to assess the influence of missing values on the observed associations. Five imputed datasets were created, and the HRs were pooled into a single estimate using Rubin's formula for standard errors [120].

4.5.3 Study III

To assess the diagnostic performance of the apnea/snoring and sleepiness indices, and their combination with overall sleep quality, we calculated sensitivities, specificities, positive predictive values (PPVs) and negative predictive values (NPVs) across severity levels of OSAS. Under the assumption of a binomial distribution, 95% CIs were computed.

Sensitivity is defined as the proportion of people *with* the target condition that are correctly identified by the test, *i.e.*, who has a positive test result. Specificity is the proportion of people *without* the target condition that are correctly identified by the test, *i.e.*, who was a negative test result. The PPV is defined as the proportion of people with a positive test result who are correctly diagnosed as having the target condition. The NPV is the proportion of people with a negative test result who are correctly diagnosed as *not* having the target condition. The predictive values of a test are highly dependent on the prevalence of the target condition in the study population. This can be nicely demonstrated by a condition like OSAS. With increasing severity of the disease (as defined by the AHI), "prevalence" decreases. Consequently, across AHI thresholds, the NPV will become higher, and the PPV lower. This is because the rarer the condition,

the higher the probability that a negative test result truly reflects absence of the disease, and the less likely that a positive test results truly reflects its presence.

To estimate the extent of possible bias from missing values or indeterminate answers (*i.e.*, symptom unawareness), we excluded 20 subjects who could not be classified as test positive or negative according to the apnea/snoring index. These 20 subjects had missing or indeterminate answers to all items in the index. Missingness affected only a minor percentage of answers to the sleepiness items; no one had missing answers to all five items.

4.5.4 Study IV

Differences in sleep efficiency and sleep duration between self-report and PSG measures were tested using the Wilcoxon matched-pairs signed rank test; the significance level was set at 0.05. We used linear regression analysis to model the relationship between self-reported habitual sleep quality and restoration from sleep with PSG parameters. Each index was modeled separately as a function of the PSG parameters, which were entered as single or simultaneous multiple predictors. Total sleep time was relatively strongly correlated with most other PSG parameters. Obviously, there was also a strong correlation between sleep efficiency and wake time after sleep onset. For these reasons, total sleep time and sleep efficiency were not included in the multiple regression models. Had we included them, we would have been prevented from estimating the relationship between self-reported sleep and important indicators of sleep architecture due to multicollinearity issues. We chose to keep as many PSG parameters as possible in the multi-predictor model. For any consistent associations observed across simple and multiple regression models, we explored the potential impact of age. In other words, only those PSG parameters that appeared to be robustly associated with habitual sleep quality or restoration from sleep were included as predictors. One observation exerted undue influence on the estimated regression coefficients and was therefore excluded. Because another subject had missing values on the self-reported sleep variables, a total of 31 subjects were included in the analyses. We observed no violations to the model assumptions.

5 MAIN FINDINGS

5.1 SLEEP AND THE DISTRIBUTION OF BMI (STUDY I)

Among men and women respectively, 8.7% and 7.8% reported having short sleep (≤5 h), and 1.9% and 2.4% reported long sleep (≥9 h) on weekdays. As for sleep quality, 16.1% of men and 18.6% of women were classified as poor sleepers. Below, the results on these main exposures are reported.

Men and women with short sleep on weekdays differed from medium-length sleepers (6–8 h) by 0.46–1.46 kg/m^2 in the upper part of the BMI distribution (≥50th percentile in men; ≥75th percentile in women) (Figure 6). The difference between sleep duration groups generally grew larger with each advancing BMI percentile, so that they were most evident at the tail of the distribution (90th and 95th percentiles). Thus, BMI was extended towards higher values among short sleepers relative to medium-length sleepers. A similar pattern of association was evident among women with long sleep. In contrast, men with long sleep differed from medium-length sleepers primarily in the lower tail of the BMI distribution (5th and 10th percentiles), displaying smaller values by 0.79–0.84 kg/m^2.

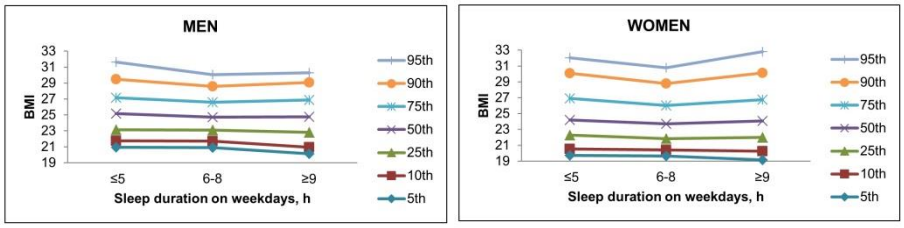

Figure 6. Predicted values at seven percentiles of BMI, by sleep duration on weekdays in men and women. Data adjusted for age, education, physical exercise, smoking, alcohol consumption, and work schedule. Adapted from Westerlund et al. *Sleep Med.* 2014. doi:10.1016/j.sleep.2014.06.012.

Differences across sleep quality groups were more pronounced in women than men (Figure 7). Notably, in the upper tail of the distribution, women with poor sleep showed higher BMI values by 0.82–1.08 kg/m^2 compared with good sleepers. The medians differed little. Among men with poor sleep, the shift towards higher BMI values in the upper tail was 0.39–0.48 kg/m^2.

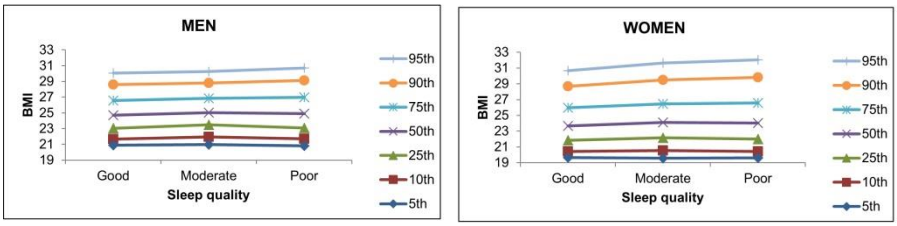

Figure 7. Predicted values at seven percentiles of BMI, by sleep qualityin men and women. Data adjusted for age, education, physical exercise, smoking, alcohol consumption, and work schedule. Adapted from Westerlund et al. *Sleep Med.* 2014. doi:10.1016/j.sleep.2014.06.012.

Restricting the analysis to subjects without depressive symptoms and history of treatment of cancer, diabetes, myocardial infarction, rheumatoid arthritis, Crohn's disease, or ulcerative colitis reduced power and attenuated the observed differences across sleep pattern groups somewhat. Overall, the patterns of associations for short, long and poor sleep were the same as in the full sample.

5.2 SLEEP AND RISK OF CARDIOVASCULAR EVENTS (STUDY II)

Among all subjects, 4.7% reported short sleep (≤5 h) and 24.1% reported long sleep (≥8 h). A total of 5.5% reported having difficulty falling asleep mostly or always. Corresponding figures for difficulty maintaining sleep, early morning awakening, and nonrestorative sleep were 7.3%, 8.7%, and 14.3%, respectively.

The median follow-up time was 13.2 years. During this period, we identified 4,031 incident overall cardiovascular events. Compared with normal-length sleepers (7 h), the risk of developing or dying from a cardiovascular event was 24% higher among short sleepers in the parsimonious model adjusting for age, sex, education, employment status, smoking, alcohol consumption, snoring, and work schedule (Table 3). This association was attenuated in the full model additionally adjusting for depressive symptoms, self-rated health, physical activity, BMI, diabetes, lipid disturbance, and hypertension. To further explore which of these factors attenuated the relationship, we regrouped the confounders and reran the analysis. The risk increase was maintained on the same level as in models 1 and 2 in Table 3 with adjustments for education, employment status and work schedule; or alcohol, smoking, and physical activity. However, with control for self-rated health and depressive symptoms; or BMI, snoring, diabetes, lipid disturbance, and hypertension, the association with short sleep was

attenuated (HR ≈ 1.1 with both sets of confounders). We observed no excess risks of cardiovascular events for difficulty falling asleep, difficulty maintaining sleep, early morning awakening, and nonrestorative sleep (HRs = 0.91–1.10). Overall, the observed results did not differ between sexes or across age groups.

Table 3. Risk of overall cardiovascular events associated with sleep duration.

	Model 1	**Model 2**	**Model 3**
	HR (95% CI)	HR (95% CI)	HR (95% CI)
Sleep duration, h			
≤5	1.25 (1.10–1.42)	1.24 (1.06–1.44)	1.05 (0.88–1.26)
6	1.01 (0.92–1.10)	1.00 (0.89-1.11)	0.97 (0.86–1.09)
7	Reference	Reference	Reference
≥8	1.07 (0.97–1.16)	1.02 (0.92–1.14)	1.00 (0.89–1.13)

Model 1 adjustments: age and sex. Model 2 adjustments: model 1 + education, employment status, smoking, alcohol, snoring, and work schedule. Model 3 adjustments: model 2 + depressive symptoms, self-rated health, physical activity, BMI, diabetes, lipid disturbance, and hypertension. Adapted from Westerlund et al. *Eur J Epidemiol*. 2013;28:463-73.

We next considered sleep duration and insomnia symptoms jointly. Invariably, the majority of short sleepers experienced frequent, as opposed to infrequent, insomnia symptoms. The proportion with frequent symptoms varied between 65.6% (difficulty falling asleep) and 77.7% (difficulty maintaining sleep). As sleep duration grew longer, the percentage of subjects with frequent insomnia symptoms gradually decreased.

Subjects with short sleep and frequent insomnia symptoms showed increased risks of overall cardiovascular events in the parsimonious model. Using 7 h with infrequently occurring problems as reference, the HR associated with short sleep and frequent difficulty falling asleep was 1.39 (95% CI: 1.15–1.67). Corresponding figures for short sleep and frequent difficulty maintaining sleep, frequent early morning awakening, or frequent nonrestorative sleep were 1.31 (95% CI: 1.09–1.58), 1.26 (95% CI: 1.04–1.52), and 1.27 (95% CI: 1.04–1.54), respectively. Again, associations were attenuated in the fully adjusted model (HRs = 1.02–1.13). No statistically significant associations with cardiovascular events were observed among short sleepers with infrequent symptoms of any kind. Long sleep duration with frequent or infrequent insomnia symptoms was also unrelated to risk. Overall, the evidence of effect measure modification on

the multiplicative scale was weak regardless of the confounder adjustments made (all *p*-values >0.05).

When then examined each cardiovascular outcome separately. Short sleep was associated with an increased risk of myocardial infarction following adjustment for multiple confounders (HR = 1.42; 95% CI: 1.15–1.76). As before, the association was weakened in the fully adjusted model (HR = 1.19; 95% CI: 0.92–1.55). Corresponding risk estimates for long sleep were 1.16 (95% CI: 1.00–1.34) and 1.19 (95% CI: 1.00–1.41), respectively. No statistically significant associations were found between sleep duration and stroke, heart failure, or cardiovascular death. With the exception of some paradoxical associations between different levels of difficulty falling asleep and reduced risks of heart failure and cardiovascular death, insomnia symptoms were unrelated to the specific the outcomes.

In a sensitivity analysis addressing potential reverse causation, we excluded the first 2 years of follow-up. The risk increases of overall cardiovascular events and myocardial infarction associated with short sleep remained essentially the same (HR = 1.20; 95% CI: 1.02–1.42 and HR = 1.44; 95% CI: 1.14–1.82, respectively). The relation of long sleep with myocardial infarction reached statistical significance (HR = 1.21; 95% CI: 1.03–1.42) and also withstood full confounder adjustment (HR = 1.21; 95% CI: 1.01–1.46). Using multiple imputation to deal with missing values, said associations, although estimated for the complete follow-up period, moved closer to the null.

5.3 DIAGNOSTIC ACCURACY OF SELF-REPORTED SYMPTOMS FOR OSAS (STUDY III)

Among 103 study subjects, 62 (60.2%) were diagnosed with OSAS (threshold, AHI ≥5). The severity distribution was as follows: 47% mild, 15% moderate, and 39% severe disease. Forty-eight subjects (46.7%) had a positive score (were considered symptomatic for OSAS) on the apnea/snoring index, and 35 (34.0%) on the sleepiness index derived from the KSQ.

At an AHI of 5 events/h or more, the apnea/snoring and sleepiness indices performed with lower sensitivity than specificity (Figure 8). Among those diagnosed with OSAS, 56% and 37% were correctly identified by the apnea/snoring and sleepiness indices, respectively. Approximately 70% of those without OSAS were correctly identified as disease free by either index. According to the positive and negative predictive values, respectively, 66–73% of subjects with positive index scores were later diagnosed with OSAS, and 43–51% of those with negative index scores were deemed disease free. We relaxed the criteria for being considered symptomatic by allowing for endorsement of apnea/snoring symptoms, *or* sleepiness symptoms, *or* poor overall sleep quality. This resulted in an increase in sensitivity to 74% and a decrease in specificity to 39%. No material changes in PPV or NPV were observed. Based on the sensitivity and specificity estimates, 26%–63% of subjects diagnosed with OSAS were misclassified as false negatives and 29%–61% of those without the disease were misclassified as false positives according to the three KSQ measures.

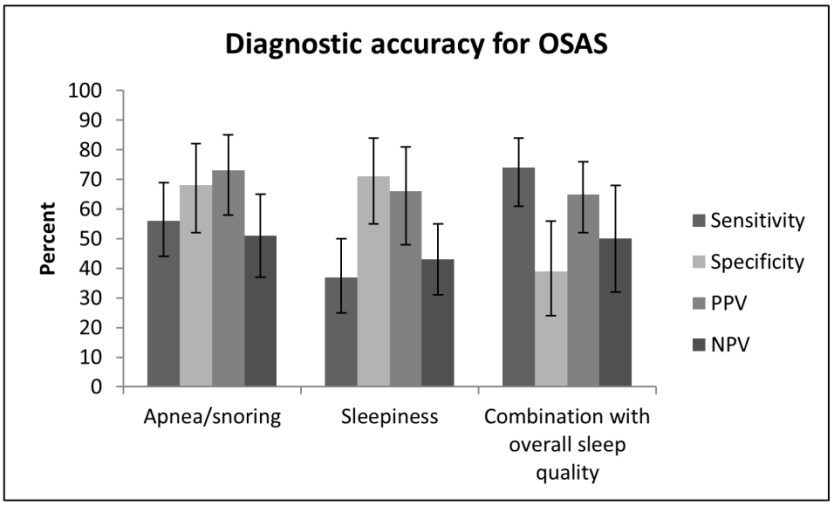

Figure 8. Diagnostic accuracy estimates of the apnea/snoring and sleepiness indices, and either of the indices combined with poor overall sleep quality. OSAS was defined as AHI ≥5 events/h. Bars indicate 95% confidence intervals. Adapted from Westerlund et al. *Clin Respir J*. 2014. doi: 10.1111/crj.12095.

With an increased AHI threshold (≥15 events/h) to define OSAS present, sensitivity of the apnea/snoring index improved to 0.72 (95% CI: 0.54–0.87),

while specificity was maintained (0.66; 95% CI: 0.53–0.77). Changes in sensitivity and specificity of the sleepiness index or the combination with sleep quality were negligible in comparison. For all three KSQ measures, the PPV decreased (0.37–0.50) and the NPV (0.71–0.84) increased substantially. At an AHI greater than 30 events/h, overall performance of the apnea/snoring index or the other two composites did not change, although slight increases in NPV were observed across all measures. The highest percentage (68%) of overall correctly classified subjects was observed for the apnea/snoring index at an AHI threshold of 15 events/h or more.

Unawareness of apnea/snoring symptoms was high. Forty-four percent of subjects with OSAS and 61% without OSAS did not know whether they experienced breathing cessations. Corresponding figures for gasping for breath were 39% and 37%, and for snoring 15% and 27%. The differences across subjects with and without OSAS were statistically nonsignificant (all *p*-values >0.05).

We excluded 20 subjects with indeterminate or missing answers (coded as *never* in the previous analysis) to all items of the apnea/snoring index, and recalculated diagnostic accuracy estimates. At an AHI of 5 or more, sensitivity increased to 0.67 (95% CI: 0.53–0.80) and specificity decreased to 0.58 (95% CI: 0.39–0.75), leaving the overall impression of diagnostic performance unchanged.

5.4 HABITUAL SLEEP QUALITY AND POLYSOMNOGRAPHY (STUDY IV)

Scores on sleep quality and restoration from sleep were similar, 3.4 (range, 1.5–4.5) and 3.3 (range, 1.7–4.7), respectively. Compared with their polysomnographic equivalents, self-reported sleep duration was longer (443.0 minutes vs. 371.0 minutes; p <0.001) and sleep efficiency higher (97.8% vs. 86.8%; p <0.001). These discrepancies were partly due to the fact that wake time after sleep onset was not queried in the KSQ. Sleep latencies were comparable (KSQ, 10.0 minutes; PSG, 11.9 minutes; p = 0.52). Stage 1 sleep constituted 4.9%, stage 2 sleep 60.7%, slow-wave sleep 7.8%, and REM sleep 26.0% of polysomnographic total sleep time.

Across simple and multiple linear regression models, stage 2 and slow-wave sleep were the PSG parameters that appeared the most relevant predictors of self-reported sleep quality. Adjusting for the remainder of parameters (sleep latency, stage 1 sleep, REM sleep, wake time, and number of awakenings), stage 2 sleep was associated with worse sleep quality (β, -0.06; 95% CI: -0.10, -0.02; p <0.01). Slow-wave sleep was associated with better sleep quality (β, 0.05; 95% CI: 0.00, 0.10; p = 0.04). In the multi-predictor model, stage 1 sleep and wake time after sleep onset also became significantly related to better and worse sleep quality, respectively. Together, the PSG parameters explained 42% of the variance in sleep quality ratings. Adjustment for age did not affect the association of sleep quality with stage 2 and slow-wave sleep.

The PSG parameters explained less of the variance in ratings of restoration from sleep (19%). Slow-wave sleep was the only parameter consistently associated with restoration from sleep across simple and multiple regression models. In the multi-predictor model, slow-wave sleep predicted less restoration from sleep (β, -0.05; 95% CI: -0.10, -0.00; p = 0.03). This relationship was weakened with adjustment for age (β, -0.02; 95% CI: -0.07, 0.04; p = 0.54).

6 DISCUSSION

6.1 METHODOLOGICAL CONSIDERATIONS

6.1.1 Assessment of validity

Whether or not an epidemiological study is accurate in terms of its estimated exposure–outcome associations depends both on validity and precision. Biases and confounding affect the validity of a study; random errors its precision. If biases or confounding (collectively termed systematic errors) are judged not to explain the estimated exposure–outcome association, a study is considered *internally valid*. It means that the conclusions drawn from the study are valid within the study population. If a study lacks internal validity, it automatically lacks *external validity*. The latter type of validity refers to the *generalizability* of study findings to people outside the study population. This section covers threats to validity as they relate to the studies in this thesis. Studies III and IV are not typical epidemiological studies in the sense that the measures of association used are not between "exposure" and "outcome." Still, some of the concepts apply to those studies, and will be discussed accordingly.

6.1.1.1 Selection bias

Selection bias has been defined as "distortions that result from procedures used to select subjects and from factors that influence study participation" [121]. Due to such distortions, the relation between exposure and outcome will be different among the study subjects than it would have been for all theoretically eligible individuals.

An example of selection bias is when nonresponse or study participation is related to both exposure and outcome. It is usually considered more probable in case–control, cross-sectional and retrospective cohort studies than in prospective cohorts [122]. The reason is that both exposure and outcome have occurred by the time subjects are selected into the former types of study. The somewhat unorthodox procedure to select subjects in studies I and II may elicit questions about selection bias. The cancer and lifestyle theme of the National March likely

attracted generally health-conscious people. Although far-fetched, those who agreed to participate in the study by completing the questionnaire might have exhibited additional health-promoting factors which systematically distinguished them from the rest of the eligible individuals present at the National March. For instance, about 80% of study subjects reported walking the voluntary walk for cancer. (How many walkers there were among those who did not participate in the study can never be established, but it could have been a similar proportion.) The decision to walk presumably was influenced by some underlying health- and lifestyle-related factors. These factors could in turn have affected the level (*i.e.*, prevalence, severity and/or chronicity) of deviations from "normal" sleep, the distribution of body weight (study I), and the probability of developing cardiovascular disease (study II). We cannot rule out the possibility that the cohort is enriched in subjects healthier than the total pool of eligible individuals. This may have biased our findings downward.

Another, perhaps more important, source of selection bias in prospective cohort studies is loss to follow-up. Overall, tracing of subjects via the PIN in the Swedish health data registers ensured few losses to follow-up in study II. Competing risks may have been a more serious concern. A competing risk is an event that eliminates a subject from being at risk for the outcome under study. Death from cancer could be a competing risk in study II. The theme of the National March might have gathered people with cancer who wanted to make a contribution to cancer research by participating in the study. Sleep problems are common in cancer [123], and subjects with cancer could thus have been overrepresented among those with short, long, or disturbed sleep in our study. Differential elimination of subjects across exposure groups due to death from cancer might have resulted in falsely low cardiovascular event rates among the exposed. Consequently, HRs would have been biased toward the null. On the other hand, the activity-orientation of the sampling event likely prevented those with advanced cancer – with the highest likelihood of dying during follow-up – from participating, reducing their chance of selection into the study. Despite being theoretically appealing, selection bias due to death from cancer was likely not a major problem in study II.

Bias from self-selection is a possibility in study III due to the low response rate (37%). The decision to participate might have been influenced by the perceived severity of apnea/snoring and sleepiness symptoms. Given the widespread symptom unawareness, however, this appears unlikely. Furthermore, the presence of OSAS was not determined until *after* the subjects had agreed to participate, ruling out the possibility that disease status influenced that decision. In other words, selection bias seems implausible in study III.

6.1.1.2 Information bias

Information bias arises when subjects have entered the study, and is related to the collection of data. It will bias the association between exposure and outcome variables, and results from systematic measurement errors or *misclassification* (classification of an individual into a category other than the "true" one) [2, 122]. Misclassification may affect exposure, covariate, or outcome variables. *Nondifferential* misclassification occurs when the likelihood of misclassification is equal across comparison groups, *i.e.*, independent of exposure/covariate/ outcome status. *Differential* misclassification occurs when the likelihood of misclassification is dependent on such statuses. These types of misclassification can impact study results in different ways, as demonstrated below.

Misclassification of exposure (self-reported sleep) variables

Self-reports of sleep and other behaviors or factors collected through single-time point questionnaires were central components in all studies in this thesis. Self-report measures of behaviors are inherently prone to error because they rely on memory. For frequent behaviors, like sleep, people may not be able to recall details of many individual episodes. To provide an answer, people have to turn to extrapolation and estimation strategies rather than "recall-and-count" techniques, which may be used with less frequent behaviors [124]. The accuracy of self-reported habitual sleep will be affected by the cognitively challenging task posed to respondents by asking them to account for their usual sleep over some (un)specified period of time.

For comparisons with objective measures, as described below, it should be noted that measurement equipment and/or sleeping in a laboratory (for a single night) will influence an individual's sleep duration and quality to various degrees. Consequently, objective measures may not entirely reflect *habitual* sleep patterns.

Studies among individuals without sleep disturbances consistently show that both self-reported next-morning and habitual sleep duration, on average, is overestimated in comparison with objective sleep duration, whether obtained from a single night's PSG or several nights of actigraphy [125-128]. Overestimation is greatest among self-reported short sleepers, and diminishes as objective sleep duration increases [125, 127, 128]. Among individuals with longer objective sleep (≥6 h), over- and underestimation of self-reported sleep duration seem to occur to similar degrees. Overall, this boils down to a substantially higher proportion of accurately classified subjects among objective longer sleepers than short sleepers[127, 128], 60% vs. 16% in the study by Fernandez-Mendoza and colleagues [128]. In the same study it was further demonstrated that among individuals with chronic insomnia, the direction of misreports was dependent on objectively recorded sleep duration. Insomnia sufferers with longer objective sleep tended to underestimate habitual sleep duration, and insomnia sufferers with short objective sleep in general overestimated sleep duration although to a lower degree than short sleepers without sleep complaints [128].

Assuming that these complex misclassification patterns are applicable to the National March Cohort, a possible net effect on misclassification of habitual sleep duration in studies I and II is the following. There is likely an enrichment of subjects with insomnia symptoms among the reported short sleepers, some of which are true short sleepers and some of which belong higher up in the distribution of sleep duration. Among the so-called normal-length sleepers, there is probably quite a high number that should have been classified as short sleepers without accompanying insomnia symptoms. Overall, misclassification issues are likely less extensive in the upper half of the distribution, *i.e.*, among normal-

length and long sleepers, and the prevalence of short sleep (with or without insomnia symptoms) should have been higher.

In study I, misclassification of sleep duration might have been differential for the outcome, BMI. Obese individuals have been shown to overestimate habitual sleep duration to a lesser degree than nonobese individuals [125]. Consequently, the number of short sleepers misclassified as medium-length sleepers would have been higher at the middle and lower parts of the BMI distribution than at the upper tail. This could explain why differences in BMI across sleep groups were largely negligible at the middle part of the distribution.

In study II, misclassification of sleep duration was nondifferential for cardiovascular events because of the prospective design. A falsely low prevalence of short sleep might have biased observed HRs toward the null because true short sleepers misclassified as normal-length sleepers carried with them a (supposedly) higher disease risk, resulting in more similar comparison groups.

Misclassification of sleep quality/problems is harder to evaluate due to the lack of a standard definition and clear-cut objective sleep homologues. In study I, sleep quality was a composite measure of insomnia symptoms, which were considered separately in study II. Although actigraphy or PSG can be used in addition to self-reports to quantify symptoms of difficulty falling asleep or maintaining sleep, the diagnosis of insomnia is based on the subjective experience of sleep [107]. For this reason, the (level of) insomnia symptoms reported by the subjects in studies I and II at least are harder to question than the validity of reported sleep duration.

In study II, it should be noted that sleep habits could have changed during follow-up. In the Finnish Twin Cohort [129] and the British Whitehall II Study [130], the stability of sleep patterns over 6–7 years was assessed *before* follow-up for death from all causes or CVD started. Overall, increased mortality was seen among individuals with decreased and increased sleep durations [129, 130], as well

as in those with stable long and stable short sleep [129]. Thus, our single measurement of sleep may not have captured the whole story.

In study IV, there was a time lag of approximately two months between completion of the KSQ and the first PSG recording. It is possible that the subjective experience of sleep changed during those two months, although this risk was probably reduced by the fact that study subjects were "normal" sleepers. Relative to individuals complaining of insomnia symptoms or who have insomnia syndrome, those without sleep complaints have more stable self-reported sleep as assessed on a monthly basis over 1 year [131].

Misclassification of outcome variables

In comparison with direct measurements, self-reported height is generally overestimated and weight underestimated, biasing BMI calculated from self-reports downward [132]. However, misreports have been shown to differ across measured BMI groups, so that self-reported BMI is overestimated among underweight individuals and increasingly underestimated among the normal-weight, overweight and obese [133, 134], with the greatest discrepancies between measured and self-reported BMI seen among overweight or obese individuals [134]. The implication of these findings for study I is that the distribution of BMI probably is biased away from the tails, in particular the upper one, resulting in an overall narrower range of BMI values. We have no reason, however, to believe that misreports were dependent on sleep habits. What the effects of this nondifferential outcome misclassification would be in terms of bias of the outcome measure (absolute differences in BMI) are difficult to disentangle. Two scenarios appear plausible for the associations observed at the tails of the BMI distribution: no effect on the results or bias toward the null. However, coupled with the probable differential misclassification of sleep habits and the possibility of correlated errors in the measurements of BMI and sleep because they were both determined by questionnaire, matters become even more complicated. The net information bias effect remains elusive in study I.

Because BMI was included as a confounder in study II, it also serves as an example of the possibility of misclassification of covariate variables. Another example is physical activity, reports of which are also prone to error [135]. Undeniably, misclassification patterns in a given epidemiological study may be exceedingly complicated and difficult to fully embrace.

Further in regard to study II, and the quality of diagnoses of cardiovascular events, more than 99% of all hospital discharges are recorded in the National Patient Register [136]. In less than 1% of the records, the primary diagnosis is missing [137]. Previous validation studies with various reference standards for confirmation found that myocardial infarction diagnoses were correct in 98% of cases [138], heart failure primary diagnoses in 95% of cases [139], and stroke (including transient ischemic attacks) in 99% of cases [136]. Thus, a low number of false-positives (and false-negatives for cases not recorded in the register) likely had little effect on our results.

In the Cause of Death Register, the number of deaths lacking a death certificate, preventing the cause of death from being established, is low by international standards. However, this number has been increasing from 0.3% in the mid-nineties, to reach 1.9% in 2010 (end of follow-up in our study). Similarly, the percentage of records with an insufficiently specified cause of death went from 1.8% in 1997 to 3.0% in 2010 [140], a possible result of declining autopsy rates. Since the mid-70's, Swedish autopsy rates have dropped from 50% to 12% in 2010 ([140]). Whether the accuracy of the cause of death statistics has deteriorated because of this is not clear, as diagnostic procedures have been refined during the same period [141]. Similar to the nonfatal events, any misclassification of deaths probably had negligible consequences for the results from study II.

6.1.1.3 Validity of objective sleep measures

In study III, the reference standard for determining OSAS status was unattended overnight cardiorespiratory monitoring in subjects' homes using the portable Embletta monitor (Embla, Broomfield, CO, USA). The use of portable monitoring to detect OSAS has been debated because diagnostic accuracy may

not be equivalent to the "gold" standard, attended overnight PSG in the laboratory. For instance, type 3 monitors, such as the one used in this study, do not record sleep. As a result, self-reported sleep duration must be used to calculate the AHI. To reduce bias from over- or underestimation of sleep time in our study, self-reported next-morning sleep duration was combined with data on movements, snoring, and breathing patterns from the overnight recording.

A validation of the Embletta device among individuals with suspected OSAS showed that it performed with reasonably high sensitivity (0.92) and specificity (0.86) in comparison with standard PSG at an AHI threshold of ≥5 events/h [142]. Night-to-night variability in AHI may result in misclassification of subjects from one overnight recording regardless of whether PSG or portable monitors are used [143, 144]. Using a type 3 portable monitor to detect sleep apnea, approximately 90% of subjects referred for diagnostic testing of sleep apnea were classified congruently across 3 nights at AHI ≥5 events/h [144].

Unattended in-home portable monitoring may be recommended for the diagnosis of OSAS in place of standard PSG under certain conditions. For instance, portable monitoring should be accompanied by a comprehensive sleep evaluation; the clinical risk for OSA(S) should be high in those tested; patients should be educated in how to apply the monitoring sensors; and the device should allow for review of automated data or manual scoring [145]. All these conditions were met in our study. Shortcomings in terms of potential misclassification of subjects' disease status due to an imperfect reference standard should be acknowledged. However, the incentive for using another than the one in practice is low as the generalizability of findings to external populations would then be reduced.

As already touched upon, PSG measurements of sleep may not entirely reflect self-reported habitual sleep because they are typically recorded on a single night in the laboratory, which may give rise to impairments in sleep known as the first-night effect [146]. In study IV, these concerns were partly counteracted by multiple PSG recordings (4 in most subjects) conducted on nonconsecutive nights over a longer than usual period (median, 26 days) in the home environment, where first-

night effects are known to be absent [147]. However, some error in the PSG parameters is expected as estimates of habitual sleep quality and restoration from sleep referred to the past six months.

6.1.1.4 Confounding

As opposed to selection and information biases, a researcher is not at fault for confounding. It occurs as a result from characteristics being disproportionately distributed among study participants. The term "confounding" stems from *confundere* (Latin for "mixing up") and thus may be thought of as a mixing of the observed effect of an exposure on an outcome with effects from other factors, so-called confounders [121]. Importantly, this mixing up can occur even if the exposure has no effect on the outcome. Depending on the direction of the association between the confounders and the exposure, and between the confounders and the outcome, confounding can result in over- or underestimation of an apparent exposure–outcome association. A key characteristic of a confounder is that it should be associated with the occurrence of the outcome among the unexposed. If this is not the case, the confounder cannot explain why the occurrence among the exposed and unexposed is not the same, had it not been for the presence of the exposure among the exposed. A confounder also cannot be a consequence of the exposure or the disease; specifically, it cannot be in the causal pathway between exposure and outcome (a mediator) [121].

Confounding can be dealt with, or controlled, in different stages of an epidemiological study: the design stage, analysis stages, or a combination of the two [122]. Randomization, restriction, and matching are strategies to deal with confounding in the design stage. Thus, the restriction in study IV to adults without documented sleep complaints can be viewed as a way to control confounding from sleep disturbances. In the analysis stage, standardization, stratified analyses, matched analyses, and multiple regression analyses are methods to control confounding. In studies I and II, the collection of data on numerous pertinent factors in the study questionnaire allowed for adjustment for several potential confounding factors through regression modeling. Residual

confounding still cannot be ruled out. It can result from unmeasured confounding (confounding that remains because of imperfectly measured confounders or confounders for which data were not collected); or from an incorrect analysis (e.g., inappropriate categorization of a variable) [2]. Given that data on sleep and all other predictor variables were obtained through questionnaire, residual confounding is likely in studies I and II.

Modeling the long-term consequences of inadequate sleep habits is a complex undertaking, especially with baseline only data on potential confounding factors. There is a multitude of factors – including but not limited to lifestyle-related behaviors, societal influences, and working conditions – that could determine both the occurrence of inadequate sleep and the outcome of interest in study II, cardiovascular disease. We struggled with how to best model the (supposedly causal) relationship between sleep habits and cardiovascular disease. Several of the variables included in the analysis, e.g., BMI/obesity, hypertension, and self-rated health, could be argued to be either confounders or mediators. Because the time order of these variables relative to sleep habits could not be established, only assumed, we saw no choice but to specify two distinct models. (The confounder regrouping reported upon in this thesis should be seen as a complement to the initial analysis.) It is possible that the attenuation of the relationship between short sleep and cardiovascular events in the fully adjusted model represents overadjustment, *i.e.*, masking of the "true" effect of short sleep. If anything, the conflicting results from study II demonstrates the need for repeated assessments of exposure and other variables in future studies.

6.1.1.5 Generalizability

A high degree of generalizability is desirable in studies aimed at describing associations rather than analyzing them from a causal point of view. Representativeness – referred to as the similarity of the study subjects and study setting to an external population of interest – therefore is an essential feature in descriptive studies, but less important in analytical studies. Findings from an analytical (etiological) study may be generalized to external populations not entirely represented by the study sample. Such scientific inferences require

familiarity with subject matter and study-specific characteristics [2]. From this reasoning, the applicability of the findings from studies I and II to external groups may be different although the studies are based on the same population. Study I leans toward descriptive epidemiology due to its cross-sectional design; study II may be viewed as an etiological study. Representativeness is less of a requirement in study II. Therefore, generalizability issues resulting from the restriction of study subjects to presumably healthy volunteers sampled from the National March participants might be smaller in study II.

The low response rate in study III may not have resulted in selection bias. Still, the resulting sample could be suspected to be poorly representative of other populations in which the index test (the KSQ) could be applied, had it been diagnostically accurate. The subjects diagnosed with OSAS in study III can be conveniently compared with those recorded in SESAR, the Swedish Sleep Apnea Register. It includes some 1,500 subjects diagnosed with OSA (defined as AHI ≥5; presence of symptoms not required) at ten sleep clinics located mainly in the western part of Sweden. Among subjects recorded in SESAR through 2013, mean age was 56 years and mean BMI was 30 kg/m^2 *(data presented by Jan Hedner, who is on the steering committee for the register, at the annual meeting of the Swedish Sleep Research Society, Stockholm, May, 2014).* In our study, subjects with OSAS were 55 years old and had a BMI of 30 kg/m^2 (values are medians). These similarities appear reassuring in terms of the generalizability of the study findings. However, differences in relevant characteristics that have not been examined can never be ruled out, in any study.

Study IV targeted adults without documented sleep disturbances. This likely resulted in a narrower range of habitual sleep ratings and physiological sleep characteristics than what would have been obtained with a broader sampling frame. Findings from the study may not be easily generalizable to other groups. On the other hand, the restriction to "normal" sleepers may have reduced confounding from factors that could influence both the experience of sleep and its physiological characteristics, thereby enhancing the study's internal validity.

6.1.2 Evaluation of precision

When random error is low, precision is high. In an epidemiological study, random errors can arise from *measurement errors* when quantifying exposure, covariate or outcome variables. *Sampling variability* in the selection of subjects into a study is another source of random errors. Thus, an unrepresentative sample of the target population may be the result of 'chance.' Random errors can be reduced and precision improved by different strategies. Increasing the sample size is one common example, and repeated measurements within a study another. A study can have high precision but low internal validity, and vice versa [122].

As already described, subjects were nonrandomly sampled in studies I through IV, and as such, can be considered selected but not necessarily (selection-)biased samples. In all four studies, confidence intervals (CIs) were estimated as a measure of variability around the respective point estimates. The width of the CI depends on random error (from both measurement errors and sampling variability), and from an arbitrarily chosen certainty factor (commonly 95% as in our studies) [122]. It is obvious that the amount of random error by design was higher in studies III and IV due to their small sample sizes, which admittedly reduced their power to detect any "true" association. Study IV especially suffered from this, as indicated by the high variability around the linear regression coefficients. To some degree, however, random error was reduced by the repeated PSG recordings. Precision could be argued to be higher in study I than in study II, due to the analytical approach. For instance, relatively few subjects reported sleeping 9 h or more, resulting in wide CIs around the regression coefficients estimated in the tails of the BMI distribution.

With regard to study IV, it should be stressed that relative to the sample size, we estimated a large number of parameters. It is possible that the multi-predictor model was overfitted, and described random error rather than the underlying relationship between physiological and self-reported habitual sleep. For this reason, any associations that were not suggested in the single-predictor regressions should be interpreted with some caution. Our results require replication in a larger sample.

6.2 MAIN FINDINGS AND INTERPRETATION

6.2.1 Study I

In this cross-sectional study of approximately 40,000 Swedish men and women, subjects reporting short, long or poor-quality sleep differed from those with medium-length or good-quality sleep in the tails, but not the middle-part, of the BMI distribution. In the upper tail, BMI was shifted towards higher values among those with short, long (women only), or poor-quality sleep. In the lower tail, BMI was extended towards lower values among men with long sleep.

To our knowledge, only two previous studies have evaluated sleep patterns in relation to the entire distribution of BMI in adult populations [148, 149]. Among 10,007 residents in the Philadelphia area in the U.S., men who reported sleeping 5 h or less displayed a higher BMI relative to men sleeping more than 7 h from roughly the median and above [149]. As in our study, differences across sleep duration groups grew larger with advancing BMI percentile, culminating in a maximum of about 3 kg/m^2 in the upper tail. Women exhibited a similar pattern of association, but the effect sizes were smaller and overall statistically non-significant. Among the women, better sleep quality (more restful sleep) was associated with a lower BMI, albeit only by 0.2 kg/m^2, in the lower part of the distribution (30^{th}–40^{th} percentiles). A population-based Taiwanese study of 2,392 men and women also found that sleep duration was non-uniformly associated with BMI [148]. Again, the largest differences were observed in the upper tail of the BMI distribution, where men with longer self-reported sleep showed smaller values by approximately 2 kg/m^2. Differences among women did not reach statistical significance but were in the same direction.

Also in support of our results are a multitude of other cross-sectional investigations [150-159], including a meta-analysis [52] and a systematic review [160], which have related unfavorable sleep patterns to an increased average BMI or odds of obesity in various populations. Although most studies used self-reported sleep (in combination with measured height and weight), some provided evidence of an association between short sleep and increased adiposity based on actigraphy [158] or polysomnography [159]. Studies with a prospective design have

been relatively uncommon within the field so far, and show mixed findings [53, 54, 161-167].

All in all, study I has contributed refined evidence to the literature, suggesting that unfavorable sleep patterns and BMI are related primarily among the heaviest and the leanest subset of individuals. Given the cross-sectional design and the use of self-reported data, our findings need to be confirmed in prospective studies with objectively assessed sleep and body weight.

6.2.2 Study II

Our results on sleep duration and insomnia symptoms and the risk of later cardiovascular disease in a large cohort of Swedish men and women were inconclusive. Employing a parsimonious statistical model excluding factors that could be on the causal pathway between unfavorable sleep patterns and cardiovascular disease, short sleep – but not insomnia symptoms – was associated with a moderately increased risk of overall cardiovascular events. The diagnosis-specific analysis suggested that this association was driven by the excess risk of myocardial infarction observed with short sleep. When we additionally adjusted the data for BMI, hypertension, physical activity, and self-rated health (that is, treated those factors as confounders) said associations were attenuated. This pattern was repeated in the analysis of sleep duration and insomnia symptoms jointly in relation to the composite outcome variable. The joint analysis, however, provided some evidence that the excess risk of cardiovascular events associated with short sleep occurred mainly among those who also had frequent sleep problems. While unrelated to overall cardiovascular events, long sleep was associated with a small borderline-significant increased risk of myocardial infarction which was maintained in the fully adjusted model.

Several cohort studies have found a positive association between short [168-170] or long [171, 172] sleep, or both [173-175], and various cardiovascular outcomes in Asian, European, and U.S. populations, albeit with some differences in risk between sexes [169, 172, 174]. A U-shape association between sleep duration and risk of coronary heart disease, but not stroke or total CVD (more strongly and

significantly associated with long sleep only), was confirmed in a meta-analysis of 15 prospective studies including more than 474,000 men and women with no evidence of heterogeneity in effect between sexes [69]. For instance, the pooled relative risk of developing or dying from coronary heart disease associated with short sleep was 1.48 (95% CI: 1.22–1.80) and with long sleep 1.38 (1.15–1.66). All studies referred to above assessed sleep habits and potential confounding factors at a single point in time (baseline), as did we. Expectedly, there is variation in the confounders controlled for across studies. In most studies, associations were robust to adjustment for established risk factors for cardiovascular disease. The possible impact of self-rated health was usually not accounted for, though.

Although some studies have failed to demonstrate an independent association [168, 176], sleep problems have been prospectively linked to various cardiovascular outcomes whether considered alone [70, 177-180] or in combination with sleep duration [71, 168, 170, 181, 182]. Studies that examined sleep duration and sleep problems indicative of insomnia jointly were largely consistent, demonstrating that subjects from three European cohorts with both short and disturbed or nonrestorative sleep had the highest risk of cardiovascular disease or death [71, 168, 170, 181]. In contrast, among 3,430 Taiwanese adults, those with long sleep and frequent insomnia symptoms had the highest risk of a composite of coronary heart disease and stroke [182]. The evidence for interaction between sleep duration and sleep problems, however, was weak [71, 170] or not readily reported [168, 181, 182]. Consequently, Rod et al. [170] concluded that the risk increase observed in the joint analysis did not exceed the sum of the excess risks from short sleep and sleep problems alone.

Overall, baseline sleep duration and insomnia symptoms were not associated with development or death from cardiovascular events independently of known cardiovascular risk factors in the Swedish National March cohort. Our results therefore appear to contrast with the collected body of evidence within the field. The relation between sleep habits and self-rated health should be further characterized.

6.2.3 Study III

The diagnostic accuracy for OSAS of self-reported symptoms of apnea/snoring was poor and slightly worse for symptoms of sleepiness; significant numbers of patients were misclassified regardless of the AHI threshold used. A composite measure based on endorsement of apnea/snoring symptoms *or* sleepiness symptoms *or* poor overall sleep quality did not improve overall diagnostic accuracy. The overall best (least poor) performance was observed for the apnea/snoring index alone at an AHI of 15 events/h or more, with 68% of subjects correctly classified. A marked increase in NPV for all three KSQ measures was observed at this AHI threshold. Thus, among subjects with negative questionnaire scores, disease could be more – but not sufficiently – confidently excluded at the level of moderate or severe OSAS. This was of little practical relevance, however, because sensitivities remained modest. Clinical use of the apnea/snoring and sleepiness indices cannot be recommended.

The idea to be able to avoid costly objective testing of OSAS and/or to identify high-risk individuals by simple means clearly is attractive. Several tools, including questionnaires and clinical prediction rules, have been developed to this end. Among the most well-known tools are the Berlin questionnaire [106], STOP and STOP-Bang questionnaires [105], and the Epworth Sleepiness Scale (ESS) [183]. The Berlin (9 items) and STOP (4 items) questionnaires include similar questions relating to multiple features of OSAS: snoring, breathing cessations, sleepiness, and hypertension. With the "Bang" addition, STOP also asks about BMI, age, neck circumference, and sex (gender). The ESS quantifies sleepiness based on the likelihood of falling asleep in eight everyday situations, such as sitting and reading, watching TV, etc. Though it is not specific to OSAS, the ESS is extensively used for assessing daytime sleepiness in OSAS patients.

Diagnostic performance of these tools has been tested in various populations, including community samples, primary care patients, surgical patients, and sleep clinic patients. In the original publication of the STOP and STOP-Bang among elective surgery patients [105], results suggested that the Bang addition improved overall performance of the tool. At an AHI $\geq$5, the area under the receiver

operating characteristic (ROC) curve was 0.70 for STOP and 0.81 for STOP-Bang. Corresponding sensitivities and specificities were 0.66 and 0.60 (STOP) and 0.84 and 0.56 (STOP-Bang). At an AHI >30, sensitivity of the STOP-Bang increased to 1.0, while the area under the curve was similar. (Roughly speaking, an area under the ROC curve of 0.75 or less indicates that the test is not clinically useful in terms of its overall discriminatory power [184].) Among the same surgery patients, STOP was also compared with the Berlin questionnaire, which performed with similar discriminatory power (area under the ROC curve, 0.69), equivalent to a sensitivity of 0.69 and specificity of 0.56 for OSAS defined as AHI ≥5 [185]. In the original validation of the Berlin questionnaire among primary care patients, sensitivity was 0.89 and specificity 0.71 for the same disease definition [106, 186]. Performance of the Berlin questionnaire was worse in a diverse sleep clinic population, as indicated by a sensitivity of 0.68 and a specificity of 0.49 [187].

Similar to sleepiness reported in the KSQ, the ESS demonstrates poor discriminatory power for OSA(S). In a sleep clinic population, the ESS had a sensitivity of 0.66 and a specificity of 0.48 at an AHI of 5 or greater [188]. With a higher threshold to determine disease (AHI ≥15), the area under the ROC curve for the ESS was 0.67 among patients referred for snoring and suspected OSA [189]. Sil et al. [189] also performed a systematic literature review, and confirmed the weak correlations between ESS scores and the AHI previously reported [190-193]. Unsurprisingly, the ESS performed with the lowest diagnostic accuracy for moderate to severe OSA in a comparison with the STOP and STOP-Bang in the Sleep Heart Health Study [194] and with the STOP-Bang in a small sample referred for PSG evaluation of sleep [195]. The discriminatory power of the STOP-Bang, however, was only marginally better, with an area under the ROC curve of 0.6 in both studies. Based on these findings, a slightly better performance of the apnea/snoring relative to the sleepiness index was anticipated.

In the studies referred to above, subjects with missing or indeterminate (*i.e.*, "do not know") answers to the questionnaires were typically excluded from analysis, and the frequency of missing answers not reported. This poses two problems.

First, the usefulness of the test cannot be assessed, and second, bias might arise if missing answers are related to the true disease status [196]. The possibility that the diagnostic performance of tools like STOP-Bang and the Berlin questionnaire has been overestimated cannot be excluded.

With regard to the apnea/snoring index, unawareness of symptoms could partly be due to the question wording and frequency-based response format in the KSQ. In the STOP questionnaire, for instance, respondents are asked about *observed* breathing cessations and the response format is a simple "yes" or "no." The degree of unawareness we observed was somewhat unexpected given that subjects were referred for testing of OSAS. Nevertheless, it also demonstrates the inherent difficulty in answering questions about nocturnal breathing events: they occur when the individual is asleep.

No statistically significant difference in apnea/snoring symptom awareness was detected across subjects with and without OSAS. The results, however, were mildly suggestive of awareness of breathing cessations and snoring being higher among those with OSAS. Referral from specialist physicians and self-referral (Table 1, paper III) appeared more common among OSAS subjects, although again, numbers were small. Together, these findings are consistent with an overall higher awareness of disturbance of some aspect in life among the subjects who were later diagnosed with OSAS. What this aspect consists of remains speculative, but it could be related to a higher co-morbidity burden in OSAS subjects. Overall, a possible interpretation of our results is that the key features of OSAS were not necessarily what motivated the subjects in our study to seek care although they were referred on the suspicion of this disease. Improved understanding of care-seeking behavior in OSAS might help identify more accurate predictors for inclusion in simple diagnostic tools.

6.2.4 Study IV

In this study among adults without sleep complaints, we compared habitual sleep reported in the KSQ against PSG. Stage 2 and slow-wave sleep appeared to be the most important polysomnographic predictors of habitual sleep quality.

Specifically, stage 2 sleep was associated with worse sleep quality and slow-wave sleep with better; the stronger association was observed with stage 2 sleep. The negative relationship first observed between slow-wave sleep and habitual restoration from sleep was weakened with adjustment for age.

Comparisons of habitual sleep quality with PSG are rare in the literature. In fact, we are unaware of any study that has examined physiological sleep correlates of subjective sleep measurements adapted for epidemiological studies, such as the KSQ. However, parallels may be drawn to the original validation study of the Pittsburgh Sleep Quality Index (PSQI) [109]. The PSQI measures past-month sleep quality across seven domains, including but not limited to sleep duration, specific sleep problems and subjective sleep quality. It was designed to distinguish between "good" and "poor" sleepers in clinical populations. Scores from the separate domains are pooled to generate a global PSQI score, where a higher score reflects worse sleep quality.

In the original publication of the PSQI [109], healthy controls without sleep complaints were compared with patients suffering from depression, difficulty initiating or maintaining sleep, or excessive somnolence. Correlations of PSQI global and component scores with PSG measures were modest. Among all subjects and in depressed patients particularly, PSQI sleep latency (to stage 2 sleep) was positively correlated with PSG sleep latency (r = 0.33 and r = 0.37, respectively). The global PSQI score also correlated with objective sleep latency in all subjects (r = 0.20), with percentage REM sleep in controls (r = 0.34), and number of arousals in depressed patients (r = 0.47). No correlations were found between PSQI scores and the remaining polysomnographic measures (sleep efficiency, sleep duration, and percentage slow-wave sleep), which in addition to sleep latency and percentage REM had been selected beforehand as likely to correlate with subjective sleep quality.

In our study, sleep quality was a composite of difficulty initiating or maintaining sleep, early morning awakening, and restless sleep assessed over the past 6 months. In addition to slow-wave sleep, we hypothesized that the composite measure would be related to PSG indicators of sleep continuity because of its

quantitative nature. Associations with decreased sleep latency, wake time after sleep onset or number of awakenings, and thus to increased sleep efficiency, were expected. All but one of the objective sleep-continuity measures were unrelated to habitual sleep quality. The negative association with wake time after sleep onset observed in the multi-predictor regression model was in line with the hypothesis, but should be interpreted with some caution as it was not consistent across both regression models. Likewise, stage 1 sleep – an increased amount or percentage of which could be a sign of disrupted sleep [5] – became a significant positive predictor of sleep quality following adjustment for other PSG measures. Our sample appeared normal with respect to stage 1 percentage (4.9%). Also, in a study with a sleep diary-obtained measure of sleep quality, there was a negative correlation with stage 1 sleep [197]. Because our finding appears paradoxical, it requires confirmation in other samples.

The results on sleep quality and slow-wave sleep are supported by previous investigations of sleep quality ratings from the Karolinska Sleep Diary, which was compared with PSG measures under laboratory [198, 199] or naturalistic [200] settings. There was some heterogeneity in results across studies. However, subjective sleep quality as a single item or composite measure similar to the one derived from the KSQ was positively related to slow-wave sleep, total sleep time [199, 200], and sleep efficiency [198, 200]. A negative correlation to wake time after sleep onset also was demonstrated [200]. Slow-wave sleep is important in sleep homeostasis, as demonstrated by its sensitive response to prior wakefulness and sleep deprivation [201, 202]. Also, selective disruption of slow-wave sleep results in increased physiological and subjective sleepiness [203]. These data, and the finding that sleepiness is a determinant of subjective sleep quality [204], provide validity for our negative association between slow-wave sleep and habitual sleep quality ratings.

In the present study, there were no significant relations with sleep efficiency or total sleep time. Stage 2 sleep, however, is relatively strongly and positively correlated with total sleep time (stage 2 comprises the largest proportion of sleep in normal adults). Therefore, a speculative interpretation of the negative

association with stage 2 sleep is that longer sleep does not necessarily translate into better perceived habitual sleep quality. It is possible that the importance of sleep length differs between previous-night (*i.e.*, sleep diary) and habitual sleep quality ratings. Stage 2 and slow-wave sleep are inversely related; consequently, their inverse association with habitual sleep quality could be expected.

Habitual restoration from sleep was a combination of difficulty waking up, waking up feeling unrested, and waking up fatigued. As a result, this index may be viewed upon as a more subjective aspect of sleep quality. Because of its lack of apparent objective equivalents, the absence of any robust association with standard polysomnographic measures could be expected. The attenuation of the negative relation to slow-wave sleep was anticipated to some degree due to the young age dependence of ratings of ease of awakening, refreshment from sleep, and sufficient sleep previously reported [205], and the decrease in slow-wave sleep with age [6]. Median age in our sample was 44 years. Hence, the, on first impression, low percentage slow-wave sleep (7.8%) could partly be an age-related effect. Differences in sleep architecture between sexes may also have contributed [7].

In one of the examinations of the Karolinska Sleep Diary [199], a single item on ease of awakening was negatively associated with slow-wave sleep; the possible impact of age was not considered in that study. Among sleep clinic patients, ratings of refreshment of sleep for the past month were unrelated to most PSG measures. Controlling for age and total sleep time, the only correlation observed was with alpha EEG activity (r = -0.16) [206], a sign of arousal that has been associated with nonrestorative sleep [207]. Moreover, in a comparison of subjects complaining of nonrestorative sleep with healthy controls, those with nonrestorative sleep differed little from controls in the total amount or percentage of slow-wave sleep [208]. The *distribution* of time spent in slow-wave sleep across the night was, however, notably different between groups, with a reduction of about 20 minutes seen among those with nonrestorative sleep in the first hour of the night. Thus, the possibility that feelings of restoration from sleep

might not correlate strongly with the traditional summary measures of polysomnographic sleep should be considered.

In conclusion, this study in a nonclinical sample of adults found evidence in support of objective markers of habitual sleep quality reported in the KSQ. Polysomnographic stage 2 and slow-wave sleep predicted worse and better sleep quality, respectively. No robust associations were found with ratings of habitual restoration from sleep. Future studies should explore measures other than the conventional polysomnographic summaries for an increased understanding of the experience of sleep.

7 CONCLUSIONS

Study I

Differences in BMI between subjects with different habitual sleep patterns were heterogeneous across the BMI distribution. The slight extension of primarily the upper tail of the distribution among short, long or poor-quality sleepers suggested that unfavorable sleep patterns and BMI were associated only in a subset of people.

Study II

Sleep duration and insomnia symptoms were not independently associated with development of or death from cardiovascular events.

Study III

Subjects with and without OSAS could not be accurately distinguished using self-report measures of apnea/snoring and sleepiness symptoms. Subjects were highly unaware of whether they snored, had apneas, or gasped for breath during sleep. Clinical use of these self-report measures cannot be recommended.

Study IV

Among the polysomnographic measures considered, stage 2 sleep was associated with worse habitual sleep quality and slow-wave sleep with better habitual sleep quality. No robust associations with ratings of habitual restoration from sleep were found.

8 FUTURE DIRECTIONS

Sleep is a universal and potentially modifiable behavior. As such, it is an attractive target for disease-preventing, health-maintaining strategies. In order for epidemiology to aptly inform such strategies, well-designed observational studies are needed to further the understanding of the (causal) role of sleep in health and disease. Future studies should longitudinally and repeatedly measure sleep and other behaviors or factors potentially involved in the regulation of sleep and disease processes. To the extent possible, subjective measures of sleep and other variables should be accompanied by objective assessments. Sleep manipulation studies should also be considered for quantifying the effect of sleep on relevant outcomes and for assessing the feasibility of maintaining changes in sleep habits. Results from such intervention studies are starting to emerge [209, 210]. In this way, the causal network of which sleep patterns and health outcomes are part may be better outlined, and treatments or preventive strategies need not be in vain.

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