

## Sleep epidemiology - a rapidly growing field

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### Introduction

The human body has adapted to daily changes in dark and light such that it anticipates periods of sleep and activity. Deviations from this circadian rhythm come with functional consequences. Thus, 17 hours of sustained wakefulness in adults leads to a decrease in performance equivalent to a blood alcohol-level of 0.05%;<sup>1</sup> the legal level for drink driving in many countries.<sup>2</sup> Rats deprived of sleep die after 32 days,<sup>3</sup> and, with longer periods of sleep deprivation, this would also be the case in human beings. Indeed, sleep deprivation is a common form of torture.<sup>4</sup>

Given the readily observable effects of sleep in everyday life, it is not surprising that there has been scholarly interest in sleep since the beginning of recorded history.<sup>5</sup> Sleep epidemiology as a subject in its own right has a recognisable history of just over 30 years,<sup>6</sup> with the first modern epidemiological studies of sleep disturbances appearing around 1980.<sup>7;8</sup> Nevertheless, a PubMed search for terms "sleep/insomnia" and "epidemiology" shows that the cumulative number of papers on the subject over the past 10 years is already about 10,000. Although this is less than for standard risk factors, such as obesity (>60,000) and smoking (50,000)(Figure 1), the annual number of papers on sleep epidemiology is rising rapidly (Figure 2). This issue of *IJE* includes a review<sup>9</sup> of the first comprehensive textbook of Sleep Epidemiology,<sup>10</sup> and the purpose of our Editorial is further to highlight recent developments to give the reader an idea why the coming years are likely to see an increasing interest in sleep studies.

Figure 1: Exposures AND Epidemiology 2000-2010

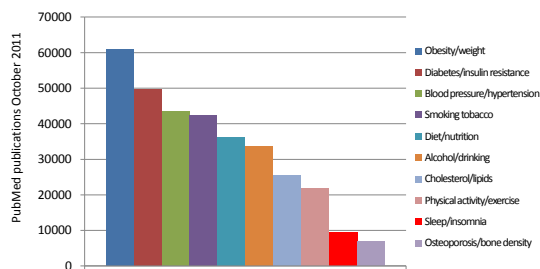
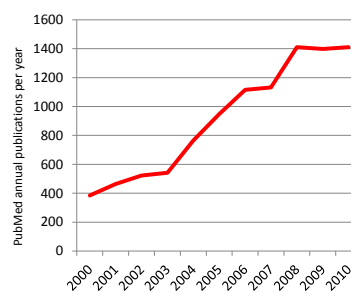


Figure 2: Sleep/insomnia AND Epidemiology by year



### Why the upsurge in interest?

There are several reasons for an increase in interest in sleep from an epidemiological perspective. First, sleep problems are associated with accidents and human errors. It has been estimated that 10-15% of fatal motor-vehicle crashes are due to sleepiness or driver fatigue. Furthermore, by 2020 the number of people killed in motor-vehicle crashes is expected to double to 2.3 million deaths worldwide, of which approximately 230,000-345,000 will be due to sleepiness or fatigue.<sup>11</sup> It has been estimated that nearly 100,000 deaths occur each year in US hospitals due to medical errors and sleep deprivation have been shown to make a significant contribution.<sup>12</sup> Similarly, in a national

sample in Sweden of over 50,000 people interviewed over 20 years disturbed sleep almost doubled the risk of a fatal accident at work.<sup>13</sup>

Second, sleep problems are common. Population studies show that sleep deprivation and disorders affect many more people worldwide than had been previously thought. A recent study found 20% of 25-45 year-olds slept “90 minutes less than they needed to be in good shape”.<sup>14</sup> Insomnia is the most common specific sleep disorder, with ‘some insomnia problems over the past year’ reported by approximately 30% of adults and chronic insomnia by approximately 10%.<sup>15</sup> Prevalence of obstructive sleep apnoea, characterized by respiratory difficulties during sleep, is also very high with estimates of 9-21% in women and 24-31% in men.<sup>16,17</sup>

Third, sleep problems are likely to increase. The rapid advent of the 24/7 society involving round-the-clock activities and increasing night time use of TV, internet and mobile phones mean that adequate sleep durations may become increasingly compromised. Some data suggest a decline in sleep duration of up to 18 minutes per night over the past 30 years.<sup>18,19</sup> Complaints of sleeping problems have increased substantially over the same period, with short sleep (<6 hours/night) in full-time workers becoming more prevalent.<sup>19,20</sup> As more shift work is required to service 24/7 societies the proportion of workers exposed to circadian rhythm disorders, such as shift work sleep disorder, and their effects on health and performance is likely to rise. Sleep architecture is known to change with age; slow-wave (or deep) sleep decreases and lighter sleep increases. Other changes include increases in nocturnal sleep disruption and daytime sleepiness. As the proportion of elderly people in populations across the world increases, these changing sleep patterns will raise the prevalence of sleep disorders. Similarly, the increasing worldwide obesity epidemic and the prevalence of obstructive sleep apnoea, which is over double among the obese, ensure sleep disorders will be of increasing public health importance in lower as well as high income countries.<sup>16,21</sup>

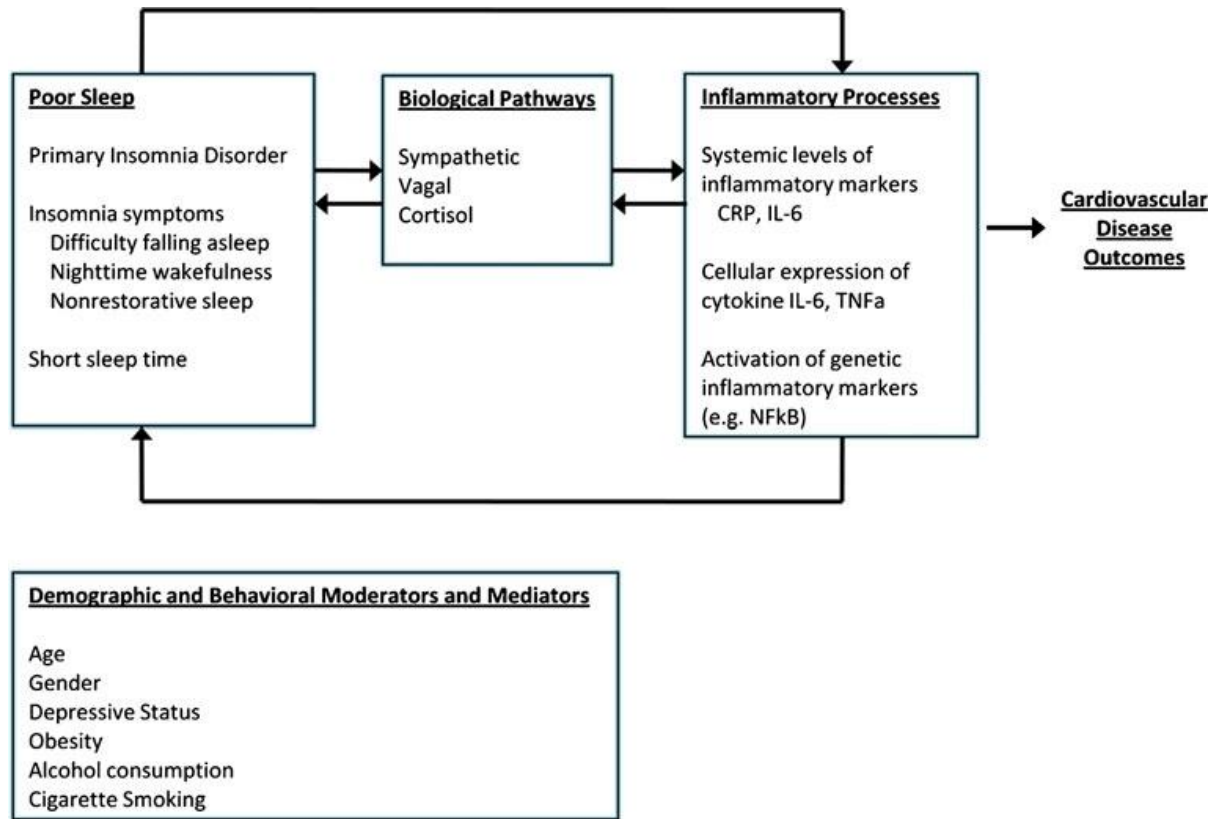
Fourth, sleep problems are associated with short and long-term effects on health and well-being. Immediate effects at the individual level relate to well-being, performance, daytime sleepiness and fatigue. Longer term, evidence has accumulated of associations between sleep deprivation and sleep disorders and numerous health outcomes including premature mortality, cardiovascular disease, hypertension, inflammation, obesity, diabetes and impaired glucose tolerance, and psychiatric disorders, such as anxiety and depression. As this evidence represents the core of Sleep Epidemiology, we provide below a snapshot on key findings.

### **Sleep as a risk factor for mortality and chronic conditions**

Two recent meta-analyses confirm associations between premature all-cause mortality and both shorter (less than 7 hours) and longer sleep (more than 8 hours),<sup>22,23</sup> although not all studies show this association to be U-shaped.<sup>24</sup> Another meta-analysis also suggests that both short and long sleep are associated with increased risk of coronary heart disease and stroke.<sup>25</sup> Potential explanations of these associations are provided by evidence of the impact of sleep on an array of disease risk factors, in particular cardiovascular disease. First, short and long sleep are associated with an increased prevalence of hypertension,<sup>26</sup> with some evidence of sex-specific effects.<sup>27,28</sup> Insomnia and obstructive sleep apnoea have also been linked to higher rates of hypertension.

However, intervention studies of continuous positive airway pressure, the recommended treatment for obstructive sleep apnoea, have produced only modest antihypertensive effects.<sup>29</sup>

Figure 3: Sleep, inflammation, and cardiovascular disease outcomes (from reference<sup>30</sup> with permission)



Second, experimental studies in animal and humans provide evidence that sleep loss affects inflammatory markers. Although the findings are complex, there is compelling evidence that in humans sleep restriction is associated with increases in inflammatory markers with some evidence of bidirectional effects – Figure 3,<sup>30;31</sup> and that inflammatory responses are increased in people with obstructive sleep apnoea.<sup>32</sup> Results from observational studies also show that treatment of sleep disorders reduces levels of inflammatory markers, but evidence from randomised controlled trials remains equivocal.<sup>33</sup>

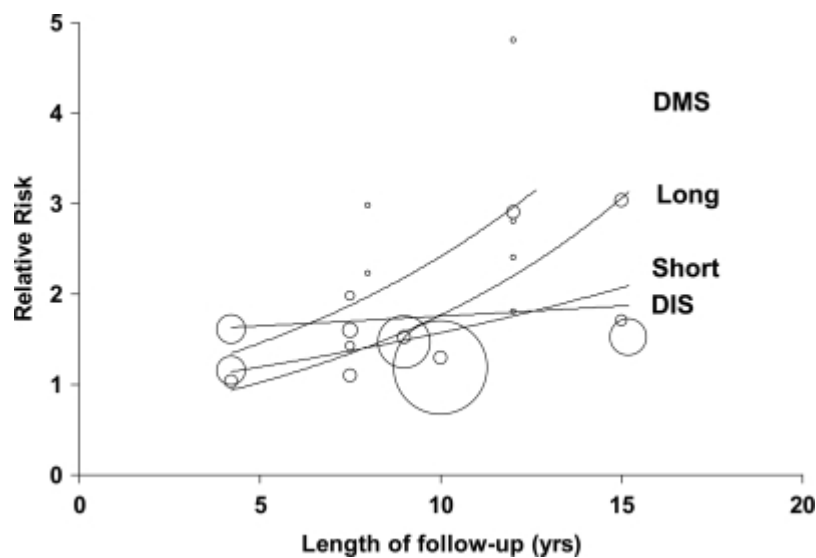
Third, major sleep disorders are more prevalent among the obese, a meta-analysis has suggested an association between short sleep and obesity,<sup>34</sup> although results from prospective studies do not provide consistent evidence that short sleep predicts the future development of obesity.<sup>35;36</sup> In the general population one extra hour of sleep is associated with a lower body mass index (0.35 units).<sup>34</sup> While unimportant at the individual level this will have greater significance at the population level.<sup>37</sup> For example, based on prevalence data from published studies it has been calculated that 3–5% of the overall proportion of obesity in adults could be attributable to short sleep.<sup>38</sup>

Fourth, sleep plays an important role in the release of many hormones and has the potential to disrupt endocrine function. Many cross-sectional studies have observed significant associations between short sleep and diabetes. A meta-analysis of prospective studies that included 3,586

incident cases of type 2 diabetes confirmed the risk of incident diabetes associated with short sleep and suggested some associations also with long sleep and insomnia symptoms – Figure 4.<sup>39</sup>

Laboratory studies, which have shown sleep restriction and poor quality sleep to be linked to glucose dysregulation and increases in hunger and appetite via down-regulation of the satiety hormone, leptin, and up-regulation of the appetite-stimulating hormone, ghrelin,<sup>40</sup> indicate pathways to diabetes via insulin resistance and the metabolic syndrome.<sup>41;42</sup>

Figure 4: Meta-regression of the risk of developing type 2 diabetes by duration of follow-up according to type of sleep disturbance. The size of circles is proportional to the weight of the study. DIS, difficulty in initiating sleep; DMS, difficulty in maintaining sleep. Reference group is those free of the particular sleep problem. (from reference<sup>39</sup> with permission)



Finally, the common mental disorders, in particular depression, are the most prevalent of the conditions associated with problem sleep. With insomnia included in the diagnostic criteria for depression the assumption tended to be that insomnia was a symptom of depression. However, studies over the last 10 years have provided evidence that insomnia could be a separate condition, albeit one that shows high co-morbidity with depression, that insomnia could lead to depression, or common causes, such as a heightened level of arousal, could underlie the two disorders.<sup>43</sup> A review of studies that simultaneously examined the effects of sleep and depression on cardiometabolic disease showed sleep to be associated with cardiometabolic diseases, independent of depression. However, it was unclear if the effects of depression were independent of sleep duration.<sup>44</sup> Less attention has been paid to the association between sleep and anxiety. Findings generally resemble those for depression, again with evidence of a shift from the assumption that the association is unidirectional, from anxiety to insomnia, to an appreciation of bidirectional effects,<sup>45</sup> and evidence of insomnia as a risk factor for the development of anxiety.<sup>46</sup>

### Progress in methodology

Sleep epidemiology in the future will be strengthened by recent methodological developments in the assessment of sleep. A limitation common to most studies of sleep duration is reliance on self-report measures, in which response categories are frequently hourly intervals and which, in general,

do not ask respondents to differentiate time asleep from time in bed. Obtaining data using polysomnography (a comprehensive recording of the biophysiological changes that occur during sleep) is expensive and time consuming and therefore has not yet been considered feasible in large-scale epidemiologic studies. However, actigraphy, a less expensive objective measure, is now increasingly being introduced on a larger scale.<sup>47</sup> The actigraph, generally worn on the wrist, can measure movements in 3 directions 24 hours a day for up to several days. It appears to be a reliable and valid measure of sleep duration and quality, and measurements one year apart have produced consistent results.<sup>48</sup>

Similar problems pertain to the ascertainment of sleeping problems and disorders in observational epidemiological studies. A number of well validated questionnaires for the ascertainment of insomnia are available and are appropriate for self-completion. However, individuals suffering from sleep-disordered breathing disorders and parasomnias may be unaware of symptoms other than daytime sleepiness, which can be due to a range of factors. Due to the strong association between snoring and apnoea, self-reported or partner-reported snoring is often used as a proxy measure of apnoea in population-based studies. Unattended home polysomnography using portable digital recorders is an emerging and reliable method of recording sleep.<sup>49;50</sup> Although still relatively expensive compared to actigraphy, home polysomnography is much cheaper, more naturalistic and representative of usual sleep, and less subject to first-night effects than laboratory recording.

Although technological developments in relation to actigraphy and polysomnography continue apace, it will undoubtedly be some years before repeat recorded data on large numbers of individuals are available. At present there are probably more data available for the simple self-reported question 'how many hours do you sleep on an average night?' than for any other measure of sleep and much useful work can be achieved using large cohort studies in which there are repeat data for this measure. Assessments of sleep duration and preliminary diagnoses of sleep disorders in the primary healthcare setting also rely on self-reported data from patients and it is important to highlight the finding that self-reported sleep duration and disorders are strongly associated with health outcomes.

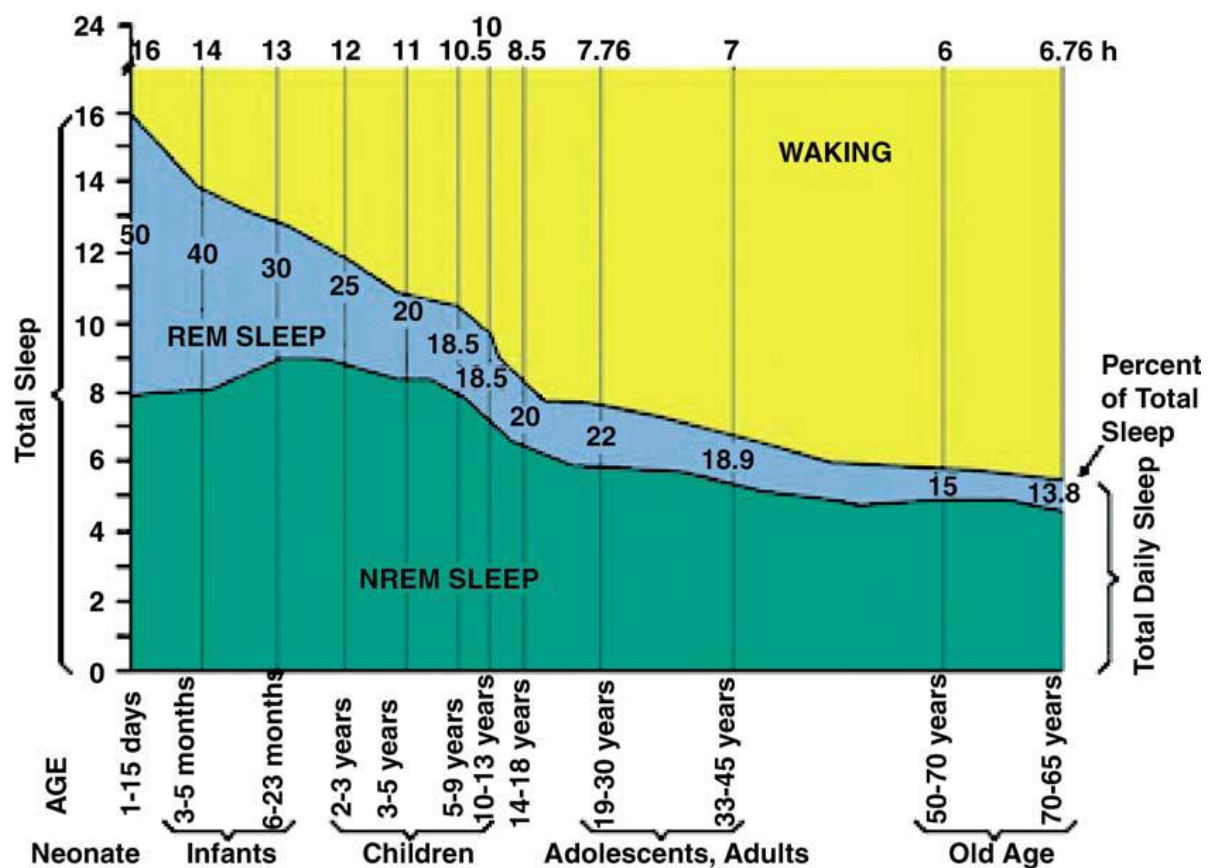
### **New and developing areas of interest**

What will be the next steps in sleep epidemiology? There several new lines of research are emerging. One is increasing recognition that it is not only sleep duration and presence of sleep disturbances but also *change* in these parameters over time that is of relevance to future health. In a cohort of over 25,000 Finnish employees, for example, repeated measurements of sleep disturbances, compared to a single measurement, improved prediction of future work disability by over 10%.<sup>51</sup> An increase in sleep disturbances was associated with greater risk of disability due to depressive disorders whereas disabling injuries were best predicted by continuous severe sleep problems. Corresponding findings have been obtained for sleep duration in relation to mortality<sup>52;53</sup> and cognitive function.<sup>54</sup> In the Whitehall II study a reduction in sleep duration among participants who regularly slept 6, 7 or 8 hours at baseline was associated with an increased risk of mortality, mainly due to cardiovascular deaths. An increase in usual sleep duration from 7 or 8 hours at baseline, in turn, was associated with an increased risk of mortality, mainly due to non-cardiovascular deaths.<sup>52</sup> A further study using Whitehall II data examined how change in sleep duration occurring over a five-year period in late middle age was associated with cognitive function

in later life. The findings suggest that women and men who begin sleeping more or less than 6 to 8 hours per night are subject to an accelerated cognitive decline that is equivalent to four to seven years of ageing.<sup>54</sup>

Authors of a recent review that detected similarities between age-related and insomnia-related cognitive and brain changes suggested that at least part of what is regarded as age-related change may, in fact, be due to poor sleep.<sup>55</sup> However, given the strong association between age and sleep over the lifecourse (Figure 5) distinct effects for sleep and ageing may be difficult to disentangle in observation studies. The age-related changes in sleep architecture are well known. In addition, the prevalence of many primary sleep disorders and daytime sleepiness increases with age.<sup>56;57</sup> These factors, combined with an increasing proportion of elderly in most populations worldwide mean that the role of sleep as a potential risk factor for adverse ageing outcomes is likely to attract increasing attention. For example, in laboratory settings sleep deprivation has been shown to have adverse consequences for contiguously measured cognitive performance,<sup>58</sup> and poor sleep is a feature of dementia,<sup>59</sup> although we do not yet know whether long-term sleep problems actually increase the risk of dementia.

Figure 5: Sleep becomes shorter with age (from reference<sup>57</sup> with permission)



Finally, genetics provides a new way to address the regulation, function and consequence of sleep. Recent data from genetic studies support the notion that there are common pathways that underlie

circadian rhythm and health outcomes. Overlapping pathways have been particularly noted in genome-wide association studies (GWAS) of metabolic markers and disease. Thus risk variants from genes that have traditionally been related to sleep regulation, such as melatonin receptor 1 B (MTNR1B), brain-derived neurotrophic factor (BDNF) and a circadian pacemaker gene cryptochrome 2 (CRY2), have now been found to be associated with markers of glycaemic homeostasis, obesity and type 2 diabetes.<sup>60-65</sup> BDNF encodes brain-derived nerve growth factor and has also been thought to underpin associations of sleep, learning and memory.<sup>66</sup> A particularly interesting finding relates to a suggested positive association between phosphodiesterase 4D (PDE4D) and 'sleepiness'.<sup>67</sup> A PDE4-specific inhibitor, rolipram, has antidepressant effects in patients with major depression,<sup>68</sup> pointing to common pathways between some aspects of sleep and depression. Thus, genetic data point to a number of pathways linking sleep, circadian rhythm, metabolism, functioning and disease. We anticipate further insights from genetics to sleep epidemiology in the near future as studies are underway that seek to examine genome wide determinants of sleep duration.<sup>69</sup>

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