Sleep epidemiology—a rapidly growing field

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Introduction

The human body has adapted to daily changes in light such that it anticipates periods of sleep and activity. Deviations from the circadian rhythm come with functional consequences. Thus, 17 h of sustained wakefulness in adults leads to a decrease in performance equivalent to a blood alcohol level of 0.05%;1 the legal limit for driving in many countries.2 Rats deprived of sleep die after a month or so,3 and sleep deprivation is used as a common form of torture.4

Given the readily observable effects of sleep in everyday life, it is unsurprising that there has been scholarly interest in sleep since the beginning of recorded history.5 Sleep Epidemiology as a subject in its own right has a recognizable history of just over 30 years,6 with the first modern epidemiological studies of sleep disturbances appearing around 1980.7,8 Nevertheless, a PubMed search on the terms ‘sleep/insomnia’ and ‘epidemiology’ shows the cumulative number of papers on the subject over the past 10 years is already about 10,000. Although this is less for standard risk factors, such as obesity (more than 60,000) and smoking (50,000) (Figure 1), the annual number of papers on Sleep Epidemiology is rising rapidly (Figure 2). This issue of the IJE includes a review9 of the first comprehensive textbook of Sleep Epidemiology,10 and the purpose of our Editorial is to give the reader an idea why the coming years are likely to see an increasing interest in sleep studies.

Why the upsurge in interest?

Several reasons underlie the increasing interest in sleep. First, sleep problems are associated with accidents and human errors. By 2020, the number of people killed in motor-vehicle crashes is expected to double to 2.3 million worldwide, of which approximately 230,000–345,000 will be due to sleepiness or fatigue.11 Similarly, disturbed sleep has been shown to double the risk of a fatal accident at work over a 20-year period.12

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Figure 1 Exposures and epidemiology 2000–10

Figure 2 Sleep/insomnia and osteoporosis/bone density by year (PubMed search October 2011)
Secondly, sleep problems are common. Population studies show that sleep deprivation and disorders affect many more people worldwide than previously thought. Insomnia is the most common sleep disorder, with ‘some insomnia problems over the past year’ reported by ~30% of adults, and chronic insomnia by ~10%.[14] Prevalence of obstructive sleep apnoea, characterized by respiratory difficulties during sleep, is also high with estimates of 9–21% in women and 24–31% in men.[14,15]

Thirdly, 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 means adequate uninterrupted sleep may become increasingly compromised. Some data suggest a decline in sleep duration of up to 18 min per night over the past 30 years.[16,17] Complaints of sleeping problems have increased substantially over the same period, with short sleep (<6 h/night) in full-time workers becoming more prevalent.[17,18] As more shift work is required to service 24/7 societies, the proportion of workers exposed to circadian rhythm disorders and their effects on health and performance is likely to rise. Similarly, as the proportion of elderly people and the prevalence of obesity in populations across the world increases, sleep disorders, more common in both groups, will rise in lower as well as high-income countries.[14,19]

Fourthly, there is increasing awareness of the association between sleep problems and health. 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.

**Sleep, mortality and chronic conditions**

The association between sleep and mortality, as well as many diseases and disease risk factors, is often U-shaped,[20] suggesting an optimal sleep duration between 7 and 8 h. Two recent meta-analyses provide strong support for associations between premature all-cause mortality and both shorter (<7 h) and longer sleep (>8 h).[21,22] In part, the excess mortality observed in short and long sleepers will be due to individual differences in health and health-risk factors, although U-shaped associations have remained in recent studies that have taken account of socio-demographic factors, health-related behaviours, health status, and disease history.[21] However, this does not exclude the potential for residual confounding due to unmeasured factors, including prodromal disease in ‘healthy’ participants, or measurement error. Thus, the debate about whether sleep is a risk factor or risk marker continues.

The commonest cause of premature mortality in adults is cardiovascular disease and a new meta-analysis suggests that both short and long sleep are associated with increased risk of coronary heart disease and stroke.[23] So, mechanisms involving cardiovascular risk factors provide potential explanations for the associations between sleep and mortality.

Firstly, short and long sleep are associated with an increased prevalence of hypertension.[24] 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 apnoea, have produced only modest antihypertensive effects.[25]

Experimental studies in animals and humans provide evidence of associations between sleep and inflammatory markers. Although the findings are complex, there is compelling evidence that sleep restriction in humans is associated with increases in inflammatory markers, with some evidence of bidirectional effects (Figure 3),[26,27] and that inflammatory responses are increased in people with obstructive sleep apnoea.[28] Results from observational studies additionally show that treatment of sleep disorders reduces levels of inflammatory markers, although evidence from randomized controlled trials remains equivocal.[29]

Major sleep disorders are more prevalent among the obese. A meta-analysis has suggested an association between short sleep and obesity,[30] although prospective evidence is inconsistent.[31,32] In the general population an extra 1 h of sleep is associated with a lower body mass index (0.35 U).[30] Although this may seem unimportant at the individual level it has greater significance at the population level.[33] For example, based on prevalence data from published studies it has been estimated that 3–5% of the overall proportion of obesity in adults could be attributable to short sleep.[34]

There is an interesting literature linking sleep with the release of hormones and disrupted endocrine function.[35] Many cross-sectional studies have also observed associations between short sleep and diabetes. A meta-analysis of prospective studies using 3586 incident cases of type 2 diabetes confirmed the risk of incident diabetes in those reporting short sleep and suggested some associations also with long sleep and insomnia symptoms (Figure 4).[36] Laboratory studies, which have shown sleep restriction and poor sleep quality 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,[37] indicate pathways to diabetes via insulin resistance and the metabolic syndrome.[38,39]
Finally, common mental disorders, in particular depression, are the most prevalent conditions associated with problematic 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 past decade show insomnia to be a separate condition; although one that has high co-morbidity with depression. Insomnia may lead to depression, alternately common causes such as heightened arousal could underlie the two disorders. A review of studies that simultaneously examined the effects of sleep and depression on cardiometabolic disease showed sleep to be associated with disease independent of depression. Less attention has been paid to the association between sleep and anxiety. Findings resemble those for depression, with a shift from the assumption that the association is unidirectional (anxiety to insomnia), to an appreciation of bidirectional effects, and evidence of insomnia as a risk factor for anxiety.

**Figure 3** Sleep, inflammation, and cardiovascular disease outcomes (from reference with permission)

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

**Progress in assessment and 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 that, in general, do not ask respondents to differentiate time asleep from time in bed. Obtaining data using polysomnography (a comprehensive recording of biophysiological changes that occur during sleep) is expensive and time consuming and is rarely considered feasible in large-scale epidemiologic studies. However, actigraphy, a less expensive objective measure, is now increasingly being introduced on a larger scale. The actigraph,
generally worn on the wrist, can measure movements in three directions 24 h a day for up to 9 days. It appears to be a reliable and valid measure of sleep duration and quality, and measurements 1 year apart have produced consistent results.45

For large-scale observational studies, a number of well-validated questionnaires for insomnia are appropriate for self-completion. However, individuals suffering from sleep-disordered breathing disorders and parasomnias may be unaware of symptoms other than daytime sleepiness. 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 studies. Unattended home polysomnography using portable digital recorders is an emerging and reliable method of recording sleep.46,47 Although still relatively expensive compared with 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 continue apace, it will undoubtedly be some years before reliable repeat recorded data on large numbers of individuals are available. At present there are probably more data available for the simple 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 studies with repeat data for this measure. Assessments of sleep duration and preliminary diagnoses of sleep disorders in the primary health-care setting rely on self-reported data from patients and it is important to recognize that self-reported sleep duration and disorders are strongly associated with objectively ascertained health outcomes.

Large population-based studies of associations between sleep and health in twin and sibling pairs remain relatively rare, but can be informative. In a study of sleep and obesity in 612 twin pairs, an association between short sleep duration and elevated body mass index was observed after accounting for genetics and the shared environment. The authors suggest that voluntary change in habitual sleep duration is the environmental factor most likely to account for the association.48 Similarly, in a recent study of over 1500 twin and sibling pairs, associations between sleep and symptoms of anxiety and depression were not explained by genes but were attributed to non-shared environmental factors.49 Sibling discordance methods are increasingly being used in epidemiology.50 Application of these methods to the effects of pre-natal maternal smoking on health have shown associations observed in population studies to be inflated by confounding.51 As a strategy that substantially reduces the potential for confounding, such sibling discordance studies are of particular relevance to resolution of the risk factor/risk marker debate in Sleep Epidemiology. Such analyses are currently underway using data from India (S Ebrahim, personal communication).

Sleep patterns and sleep genetics—new areas of interest

Several new lines of research are emerging in Sleep Epidemiology. For example, not only sleep duration and sleep disturbances, but also change in these parameters over time is relevant to subsequent health. In a cohort of over 25 000 Finnish employees, for example, repeated measurements of sleep disturbances, compared with a single measurement, improved prediction of future work disability by >10%.52 Corresponding findings have been obtained for sleep duration in relation to mortality53,54 and cognitive function.55 In the Whitehall II study a reduction in sleep duration among participants who regularly slept 6, 7 or 8 h at baseline was associated with an increased risk of mortality, mainly due to cardiovascular deaths. Conversely, an increase in sleep duration from 7 to 8 h at baseline was associated with an increased risk of mortality, mainly due to non-cardiovascular deaths.55 A further study using Whitehall II data examined change in sleep duration over a 5-year period and cognitive function in late middle age. The findings suggest that people who begin sleeping more or less than 6–8 h per night are subject to an accelerated cognitive decline equivalent to 4–7 years of ageing.56

Authors of a recent review that detected similarities between age-related and insomnia-related cognitive and brain changes suggested at least part of what is regarded as age-related change may, in fact, be due to poor sleep.56 However, given the strong association between age and sleep over the life course (Figure 5), distinct effects for sleep and ageing may be difficult to disentangle in observation studies. In laboratory settings sleep deprivation has been shown to predict contiguously measured cognitive performance,57 and poor sleep is a feature of dementia.58 However, we do not yet know whether long-term sleep problems truly increase the risk of dementia.

Most recently, genetic studies support the notion that there are likely to be common pathways that underlie circadian rhythm and health outcomes. Overlapping pathways have been particularly noted in genome-wide association studies of metabolic markers and disease. Thus risk variants from genes that have traditionally been related to sleep regulation, such as melatonin receptor 1 B, brain-derived neurotrophic factor (BDNF) and a circadian pacemaker gene cryptochrome 2, have now been found to be associated with markers of glycaemic homeostasis, obesity and type 2 diabetes.60–63 BDNF encodes brain-derived nerve growth factor and has also been thought to underpin associations of sleep, learning and memory.64 A particularly interesting finding
relates to a suggested positive association between phosphodiesterase 4D (PDE4D) and ‘sleepiness’. A PDE4-specific inhibitor, rolipram, has antidepressant effects in patients with major depression, indicating 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. Identification of these genetic markers would make it possible to address the causal relation of sleep behaviours and outcomes of interest with methods akin to an approach recently employed using genome-wide determinants of obesity [FTO (16q12.2) and MC4R (18q21.32)] to examine the relationship between adiposity and hypertension.

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