Sleep and type 2 diabetes mellitus

It is increasingly clear that sleep duration and quality are important in the prevention and management of a number of cardiovascular and metabolic conditions, including type 2 diabetes.

Emer Brady and Andrew Hall examine the evidence in relation to sleep and diabetes, and highlight the clinical implications.

Man has always had a fascination with sleep; ancient philosophers considered it to be a state somewhere between life and death, though were more fascinated by dreams and their interpretation. We all know when we have had a good or bad night’s sleep and recognise that feeling of tiredness when sleep is required. However, it is easy to imagine sleep as a period of simple dormancy, the quiescent part of our daily lives, analogous to putting one’s computer or television in a standby mode.

The neurological characteristics of sleep were not properly examined and described until the 1960s. We now understand it to be a dynamic process essential for life and health. Recently, it has become apparent that sleep quality and quantity can impact upon a number of metabolic, immune and hormonal processes including energy regulation and glycaemic control.2–5

What is normal sleep?
Sleep is characterised by reduced consciousness, relatively suspended sensory activity, and inactivity of nearly all voluntary muscles. Numerous complex physiological processes occur that are different from those in the ‘awake resting’ state. It comprises a highly organised sequence of events that follow a regular, cyclic programme categorised into rapid eye movement (REM) sleep and non-REM sleep (of which there are four stages). Dreaming is thought to occur largely during REM sleep. These sleep stages display characteristic electroencephalographic (EEG), electro-oculographic (EOG) and electro-myographic (EMG) activity. Broadly speaking, during non-REM sleep, the overall EEG signal shows a lower frequency and greater amplitude with increased depth of sleep. Stages 1 and 2 non-REM sleep are considered to be light sleep whereas 3 and 4 (commonly today grouped together as Stage N3) are described as deep (or slow wave) sleep. During REM sleep the EEG pattern more closely resembles that of wakefulness, though with the intermittent but characteristic occurrence of rapid eye movements and also a significant reduction in muscle tone; a mechanism to prevent the physical acting out of dreamt movements.

In healthy adults, sleep onset occurs via non-REM Stage 1 or 2. It is recognised that normal sleep generally consists of four to five ‘sleep cycles’ across a typical 7 hour night. Each cycle of approximately 60–90 minutes consists of, firstly, a long period of deeper slow wave sleep, followed by lighter sleep and a brief episode of REM sleep. Ensuing sleep cycles tend to be less deep and followed by longer periods of REM sleep such that in the later part of the night, non-REM sleep is shallow, shorter and followed by longer periods of the REM sleep.6 Sleep is ‘scored’ by dividing sleep time into consecutive 30-second epochs and assigning to each a label representing the predominant sleep stage contained. The results can be displayed as a ‘hypnogram’ showing the progress of sleep stages across the night. Figure 1 shows a stylised representation of a hypnogram in a healthy young adult.

How much sleep do we need?
In answer to this question, Napoleon Bonaparte is said to have stated ‘6 hours for a man, 7 for a woman and 8 for a fool’. More recent expert guidance addressing this question has been published. The US National Sleep Foundation (NSF) multidisciplinary expert panel examined the evidence and not surprisingly reported a large variation in sleep needs across age groups. For example, new-borns require considerably more sleep per day (14–17 hours) than the older adult (7–8 hours). However, even within age bands, the recognised healthy range was wide. In the adult group aged 26–64, the recommended range was 7–9 hours and further broadened by recognising that as little as 6 hours or as many as 10 may be appropriate.7

Interestingly, over the last two decades, evidence of a ‘U’-shaped relationship between daily sleep duration and all-cause mortality has emerged. A similar relationship between sleep duration and the incidence of obesity, cardiovascular disease (CVD), hypertension and type 2 diabetes (T2DM) has also

![Figure 1. Representation of a hypnogram in a young adult](image-url)
been found. Both long and short sleep duration pose potential risks of obesity, metabolic dysfunction and CVD.8–10

Cappuccio et al. reported a systematic review and meta-analysis11 that found a relative risk for all-cause mortality of 1.12 for short sleepers (<6 hours/day, [95% CI 1.06–1.18; p<0.01]). Furthermore, they found that long sleep (>9 hours/day) was associated with a relative risk of 1.3 (95% CI 1.22–1.38; p<0.0001) with an effect more pronounced in older individuals and in East Asian cohorts. Additionally, short and long sleep duration is associated with greater risk of developing or dying of stroke (RR 1.15 [1.00–1.31; p=0.047] and 1.65 [1.45–1.87; p<0.0001], respectively).12 More recently, Leng et al. observed a J-shaped relationship between daily sleep duration and 9.5-year stroke risk in an older (42–82 years) British population.13 Short sleep and long sleep were associated with 18% and 46% increase in stroke risk, respectively.

There are a myriad of potential causes for short sleep including lifestyle choice, societal pressures and shift work. Additionally, there are a variety of comorbid conditions with various pathologies that are known to disturb sleep such as obstructive sleep apnoea (OSA). OSA is a sleep disorder characterised by the recurrent collapse of the upper airway and cessation (apnoea) or reduction of airflow (hypopnoea) which lead to brief arousals from sleep to reinitiate breathing. The recurrent arousals result in sleep fragmentation and thus overall reduction in sleep duration that is further compounded by the associated intermittent hypoxaemia. This particular sleep disorder is more prevalent in those with T2DM14 and commonly co-aggregates with CVD.15 Indeed, the co-occurrence of both OSA and the metabolic syndrome have been recognised as its own condition: Syndrome-Z.16,17

Short sleep (<6 hours/day) has reported associations with obesity, T2DM, hypertension, CVD and the incidence of work-place and road traffic accidents.18–28 The physiological and metabolic pathways connecting poor sleep to CVD and T2DM are well described and were recently articulated by Neurakul and Van Cauter.29 Essentially, short sleep duration, sleep fragmentation and intermittent hypoxia are physiological stressors that contribute to an overall increase in sympathetic activity, altered levels of hormones such as cortisol and growth hormone and activation of inflammatory markers. The mechanisms involved in the detrimental effects of long sleep (>9 hours/day) are less clear and all the more fascinating since a greater effect seems apparent in longer sleeping cohorts as described above. It is plausible that in those patients there may be poorer sleep quality and sleep disturbance leading to a longer apparent sleep period. Long sleep may be a result of poorer health rather than the cause. However, there are many potential confounders, including unemployment, lower socio-economic class, less physical activity and fatigue associated with other conditions such as depression, chronic fatigue syndrome and cancers that increase the complexity of identifying mechanisms relating long sleep duration with adverse health outcomes.

Sleep restriction studies

There have been a number of well-controlled, laboratory-based sleep restriction and extension studies investigating the short-term effect of sleep restriction and/or extension in healthy volunteers. In 1999, Spiegel and colleagues3 investigated the effect of sleep deprivation on metabolic and endocrine function limiting subjects to 4 hours/night for six consecutive nights. This was followed by six nights of sleep recovery where sleep was extended to up to 12 hours/night. They conducted intravenous glucose tolerance tests at 09.00 on day 5 of sleep restriction and day 5 of the recovery period. On the sixth day of each phase they took blood samples every 10–30 minutes to measure glucose and hormone concentrations. The cohort comprised healthy white males aged 18–27 years. Sleep deprivation resulted in a reduction in glucose effectiveness (glucose disposal independent of insulin) that is equivalent to that reported between groups of white male patients with T2DM and normoglycaemia (1.4 vs 2.6%/min).30 Furthermore, the acute insulin response, an early indicator of T2DM, was 30% lower in the sleep restricted condition. This work is supported by a review conducted by Lucassen and colleagues31 who examined the evidence around the mechanisms linking sleep with metabolism. They report, from the some 38 studies reviewed, that sleep restriction in most cases results in a reduction in peripheral glucose tolerance and a reduced cerebral glucose uptake with no compensatory rise in plasma insulin secondary to increased insulin resistance. Furthermore, other short-term studies have been able to demonstrate that sleep restriction leads to an increased energy intake and net weight gain along with increased hepatic insulin resistance and decreased peripheral insulin sensitivity. Little or no change in energy expenditure has been reported. Disappointingly, there does not appear to be a consistent response in terms of leptin or ghrelin levels.32–35

Metabolic syndrome and type 2 diabetes

The metabolic syndrome has a global prevalence between <10% to 84%, depending on the region, urban or rural environment, composition (sex, age, race, and ethnicity) of the population, and the definition of the syndrome used.36,37 It is a clustering of CVD risk factors that together increase the risk of incidence of CVD and T2DM and includes visceral adiposity, dyslipidaemia, hypertension and dysglycaemia. Recently, Xi and colleagues conducted a systematic review and meta-analysis specifically looking at the effect of sleep duration upon the risk of metabolic syndrome.38 They concluded that short sleep duration was associated with increased risk with an OR of 1.27 (95% CI 1.09–1.47; p<0.002). They found no association of long sleep with the incidence of metabolic syndrome. More recently, Shan et al. sought to investigate sleep duration and the risk of T2DM with a prospective study designed to determine how many hours of sleep are associated with the lowest risk of T2DM and to investigate the ‘dose relationship’ between sleep duration and risk of T2DM.39 Their meta-analysis ran to
March 2014 and included 482,509 individuals of whom 18,443 had T2DM. Patients were followed up between 2.5–16 years. Again a ‘U’ shaped relationship was reported between sleep duration and a relative risk of T2DM. The lowest risk was observed at 7–8 hours sleep with a relative risk of 1.09 (95% CI 1.04–1.15) for each hour of shorter sleep and a relative risk of 1.14 (95% CI 1.05–1.26) for each hour of longer sleep.

**Circadian mal-alignment**

Overall sleep duration is clearly important. However, sleep may be more readily obtained and also be of better quality at particular times across the 24-hour day. One’s urge to sleep can be broadly thought of as relating to the overlap of two simultaneous processes. On the one hand, a period of prolonged wakefulness leads to an accumulating sleep need that can only be discharged through sleep itself. In addition, there is an underlying background rhythm which, for most individuals, makes sleep more readily obtainable during the night time hours and dissipates in the small hours of the morning, even if little or no sleep has been obtained. There is, of course, the addition of the early afternoon dip which makes daytime napping more common at that time. We all differ slightly in the preferred timing of our natural sleep period.

In 1976, Horne and Ostberg devised their ‘Morningness–Eveningness Questionnaire’ which described five different ‘chronotypes’. At the one extreme, ‘Morning Types’ are those individuals who get up very easily at a relatively early time but are more inclined to be early to bed in the evening. At the other end of the spectrum, ‘Evening Types’ will be more naturally later to bed but struggle with early starts. Merikanto et al. found that Evening Types were two-fold more likely to develop T2DM compared to Morning Types. Reutrakul and colleagues examined 194 non-shift workers, all with established T2DM. They analysed these individuals by chronotype, assessing their mid-sleep time on free days. Individuals were then grouped into quartiles moving from Morning Types to the Evening Types. The median HbA1c in the latter group was found to be 8.3%, significantly higher than that of individuals in the first quartile, 7%. The weekend wake time for the Morning Type individuals tended to still be quite early at around 05.35. The Evening Type individuals had a wake time at around 10.00 thus suggesting that this chronotype are more likely to spend their weekdays in a state of relative sleep deprivation, struggling to get up for work following a shorter sleep period and thus catching up at the weekend; therefore the morning chronotype are less sleep deprived.

This idea is further supported by work from Vetter and colleagues from the Nurses’ Health Study II. They examined the association of chronotype with T2DM and how rotating night shift work may modulate these associations. Their questionnaire-based study categorised individuals by chronotype and by their number of years of rotating night shift work (≥3 shifts/month in addition to daytime and evening shifts).

Their key findings included decreasing levels of physical activity and increasing BMI when moving from early through intermediate to late chronotype. Risk estimates for developing T2DM increased with increasing duration of shift work exposure in early chronotypes (p trend=0.02) and decreased for late chronotypes with increasing shift work exposure. Late chronotypes without any history of rotating night shift work had a 1.5-fold increased risk of T2DM; the early chronotypes had a lower risk of T2DM when not exposed to night shift. The risk of T2DM in early chronotypes increased if they worked longer durations of night shifts.

Cumulatively, these findings indicate a chronotype-dependant association between work hours and metabolic disease risk, and generate a wealth of public health questions. For example, should we be chronotyping our workforce and altering shift patterns accordingly? Furthermore this raises the question: can we change our chronotype? Certainly, individuals with training and strict sleep hygiene can at least partially adjust to an earlier or later sleep period. However, reversion is likely if discipline is not maintained. Exogenous melatonin is used in the management of circadian rhythm disorders and may phase delay or phase advance an individual’s rhythm, depending upon the timing of administration. It has yet to be determined whether any such strategy can impact upon the metabolic risk described above.

**Do improved sleep duration and quality reduce diabetes risk?**

Epidemiological studies of sleep duration and studies of shift workers certainly would suggest that good sleep hygiene, sleeping at night and consistently sufficient sleep across the whole week rather than catch up sleep in the day time or at weekends are associated with reduced risk of metabolic dysfunction. However, the treatment of OSA also provides a useful model whereby the benefits of a more controlled and immediate reduction in sleep disturbance can be assessed. Guest and colleagues recently reported a case-controlled study using patients recruited from the ‘THIN’ database whereby 150 continuous positive airway pressure (CPAP) treated patients with OSA and T2DM were randomly selected and matched with 150 subjects with OSA and T2DM that were not treated with CPAP. Total NHS costs and outcomes were measured over five years. They found that at five years, CPAP use was associated with a lower blood pressure and progressively lower HbA1c. At five years, HbA1c in the CPAP-treated group was 8.2% versus 12.1% among controls (p≤0.03). This was associated with an increase of 0.27 QALYs (p≤0.001) at a cost of £4141 per patient over five years and thus representing a cost per QALY gained with CPAP of £15,337.

**Clinical implications**

It is thus increasingly clear that sleep duration and sleep quality are important in the prevention and management of a number of cardiovascular and metabolic conditions, including T2DM. The International Diabetes Federation has already made clear recommendations about...
the need to consider OSA as a likely comorbid condition in subjects with T2DM and similarly that all individuals with known OSA should be screened for diabetes. Questions about sleep quality and duration should be commonplace in the diabetes clinic. Perhaps also questions about chronotype, shift work and sleep pattern.

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Acknowledgement
The authors acknowledge support from the National Institute for Health Research Collaboration for Leadership in Applied Health Research and Care - East Midlands (NIHR CLAHRC - EM) and the NIHR Leicester - Loughborough Diet, Lifestyle and Physical Activity Biomedical Research Unit, which is a partnership between University Hospitals of Leicester NHS Trust, Loughborough University and the University of Leicester. The views expressed as those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

References