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Review Article

Sleep disturbances and insulin resistance

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Abstract

The causes and risk factors of insulin resistance remain insufficiently understood. After taking into account the important roles of adiposity, age, sex and race/ethnicity, up to 50% of the individual variability in insulin resistance remains unexplained. In recent years, evidence has accumulated to support a role for sleep disturbances, including insufficient sleep, poor sleep quality and insomnia, and obstructive sleep apnoea, as independent risk factors for the development and exacerbation of insulin resistance. The present review summarizes the evidence. We will start with a brief introduction to sleep and its disorders and then examine in succession the role of the three major types of sleep disturbances of modern society, namely insufficient sleep, poor sleep quality and/or insomnia and obstructive sleep apnoea. Insulin resistance is a hallmark of the polycystic ovary syndrome, the most common endocrine pathology in women, and the last section of this review will discuss the role of obstructive sleep apnoea in the insulin resistance and metabolic disturbances of polycystic ovary syndrome.

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Keywords insulin resistance, sleep apnoea

Abbreviations HOMA-IR, homeostasis model assessment of insulin resistance; PCOS, polycystic ovary syndrome; REM, rapid eye movement; SWS, slow-wave sleep

An introduction to sleep and sleep disturbances

The temporal organization of sleeping and waking over the 24-h cycle is controlled in part by an internal circadian clock and in part by a homeostatic mechanism that increases the pressure for sleep in proportion to the duration of prior wakefulness. Sleep itself oscillates between two separate states of markedly different brain activity, known respectively as rapid eye movement (REM) sleep and non-REM sleep. Normal sleep is characterized by 90-min oscillations between non-REM and REM stages; this pattern is repeated throughout the night, usually 4–6 times per night. Non-REM sleep is further divided into stages I to IV, each representing a deeper sleep from which it becomes increasingly difficult to wake up. Stages III and IV of non-REM sleep are termed slow-wave sleep (SWS), a reference to the characteristic period and wave shape of electro-encephalographic activity during this phase. In contrast, REM sleep has an electro-encephalographic activity that is similar to wakefulness. During REM sleep, muscle tone is inhibited and eye movements that follow the visual imagery of dreams are prominent.

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The gold standard method for assessing sleep is polysomnography, which combines an all-night recording of the electro-encephalographic with measures of muscle tone and eye movements. Polysomnography recordings are visually scored in stages I, II, III, IV, REM and Wake over 30-s intervals using standardized criteria. In young healthy subjects, approximately 50% of the night is spent in stages I and II of non-REM sleep; 20–25% is spent in SWS; 25% is spent in REM sleep and approximately 5% of the night is spent being awake. With ageing, the percentages of time spent in each phase change: adults over 60 years of age will typically spend less than10% of their night in SWS and sleep is more fragmented by awakenings.

Objective estimations of sleep duration and sleep fragmentation may be obtained under ambulatory conditions by wrist actigraphy monitoring. Wrist actigraphy has been validated against polysomnography, demonstrating a correlation for sleep duration between 0.82 in insomniacs and 0.97 in healthy subjects [1]. Wrist actigraphy does not differentiate REM sleep from non-REM sleep.

Lastly, a number of validated questionnaires to assess subjective sleep duration and quality have been developed. Subjective sleep duration often overestimates the total sleep duration. Estimations of the number and duration of awakenings are notoriously unreliable.

The most common form of sleep disturbance may well be insufficient sleep because of behavioural bedtime curtailment, an endemic condition in modern society. Self-reported sleep duration in Americans has decreased by 1.5–2 h between 1960 and today in order to meet the demands and opportunities of the 24-h society [2]. More than 30% of US adults between 21 and 65 years of age report sleep durations under 6 h per night [3]. This curtailment of sleep may be considered as a sleep disorder because it produces both daytime and night-time alterations of neurobehavioural and physiological systems.

Insomnia is clinically defined as a subjective complaint that persists for at least 1 month of difficulty falling asleep, or difficulty maintaining sleep, or waking up too early in the morning, or unrefreshing sleep. When sleep is assessed by polysomnography in insomniacs, reduced total sleep time is not a universal finding. Insomnia is a syndrome of physiological and cognitive hyperarousal associated with elevations in sympathetic tone and hypothalamo–pituitary–adrenal axis activity [4,5]. Thus, the metabolic consequences of insomnia may differ from those of sleep loss attributable to bedtime curtailment. Insomnia currently affects at least 15% of the population, reflecting in part the ageing of the population, but the stressful lifestyle of modern times is often cited as another culprit. Insomnia is frequently associated with chronic medical illness and psychological disorders.

The current epidemic of obesity is logically followed by an epidemic of obstructive sleep apnoea, as adiposity is the most important risk factor for obstructive sleep apnoea. Obstructive sleep apnoea involves repetitive upper airway closures (apnoeas) or partial collapses (hypopnoeas). These respiratory disturbances have several consequences: (1) intermittent hypoxia; (2) transient arousals, which restore airflow but lead to sleep fragmentation and poor sleep quality with disruption of the normal REM–non-REM cycle; and (3) reduced amounts of SWS. Total sleep time is often reduced as well. Clinically, obstructive sleep apnoea is diagnosed when the number of apnoeas and hypopnoeas per hour [apnoea–hypopnoea index (AHI)] is ≥ 5. Estimations of the prevalence of obstructive sleep apnoea in obese individuals have ranged from 33 to 77% in men and from 11 to 46% in women [6]. The treatment of choice for obstructive sleep apnoea is the administration of continuous positive airway pressure, a non-pharmacological intervention that is highly efficacious in essentially eliminating all obstructive events. The major drawback of continuous positive airway pressure is poor patient compliance, with as many as 50% of patients not using their continuous positive airway pressure device or using it for only a few hours per night.

Insufficient sleep: impact on insulin resistance and diabetes risk

Causative evidence linking insufficient sleep to reduced insulin sensitivity has been obtained in several well-controlled laboratory studies where healthy adults were submitted to partial sleep restriction (restricting bedtimes to 4–5.5 h in bed) under carefully controlled conditions over a number of consecutive nights. We will limit our review to studies where sleep restriction was enforced for at least two consecutive nights and where insulin sensitivity was assessed via a frequently sampled intravenous glucose tolerance test and/or the euglycaemic hyperinsulinaemic clamp. Figure 1 illustrates the findings from three such independent studies [7–10]. Irrespective of the methodology, sleep restriction was associated with a consistent reduction in insulin sensitivity. In all three studies, there was no adequate compensation by increased insulin release and therefore diabetes risk was increased.

Epidemiologic evidence linking insufficient sleep and insulin resistance is minimal. Further, the assessment of insulin sensitivity usually relied on insulin and glucose levels measured on a single blood sample, presumed to have been taken under fasting conditions, and sleep duration was assessed by self-report. There is, however, abundant evidence linking short sleep (usually

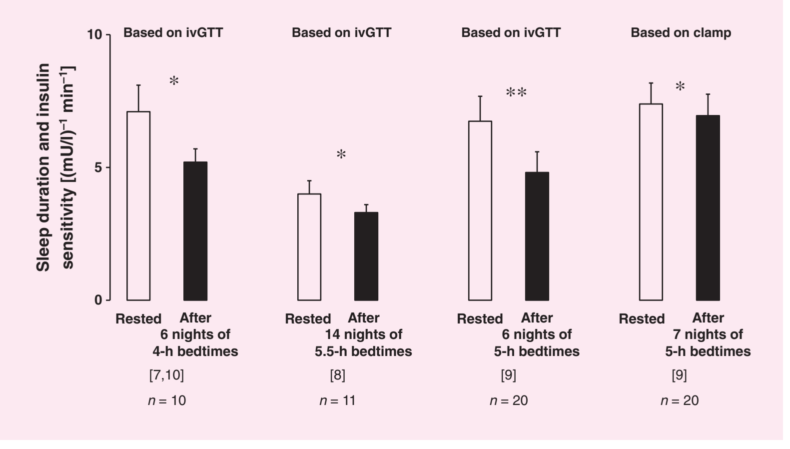

FIGURE 1 Summary of findings from studies that have examined the impact of experimental recurrent sleep restriction under controlled laboratory conditions on insulin sensitivity. **P* at least < 0.05; ***P* at least < 0.01. Data from Spiegel *et al.* [7], Nedeltcheva *et al.* [8], Buxton *et al.* [9] and Leproult and Van Cauter [10].

less than 6 h per night) and an increased risk of incident diabetes and we may infer that, as is generally the case, diabetes onset occurred as a result of insulin resistance without adequate compensation by increased insulin release. To date (August 2011), we were able to identify nine prospective studies [11–20], with six of those studies [11,13,15,17–19] reporting a significantly higher relative risk of diabetes in short sleepers. All analyses controlled for major risk factors for Type 2 diabetes, including age, BMI or other measures of adiposity, but also for multiple other risk factors. A recent meta-analysis [21] that included seven of these nine prospective studies found that the pooled relative risk of developing diabetes was 1.28 (1.03–1.60) in short sleepers. A recent study [20] demonstrated an increased risk of incident pre-diabetes in short sleepers.

Much work remains to be carried out to elucidate the intermediate pathways linking insufficient sleep and insulin resistance. Among the plausible pathways supported by experimental evidence, we can list: (1) increased release of counter-regulatory hormones, including epinephrine and cortisol; (2) increased sympathetic nervous activity with elevated levels of norepinephrine; (3) inflammation, with elevations of interleukin 1 beta (IL-1β), tumour necrosis factor alpha (TNF-α), IL-6 and C-reactive protein (CRP); (4) increased risk of weight gain and obesity, a major risk factor for insulin resistance. There is indeed an abundant literature linking short sleep and the prevalence or incidence of obesity (for a recent review, see Knutson [22]).

Poor sleep quality and insomnia

Two independent laboratory studies have shown that experimentally induced reductions of sleep quality in healthy young adults result in a rapid and robust decrease of insulin sensitivity. The first study examined the impact of selective suppression of SWS in young healthy adults in a randomized crossover design [23]. Older age, even in healthy adults, is a major cause of reduced or absent SWS and is also associated with insulin resistance. Suppression of SWS was achieved by delivering acoustic stimuli to the bedside. The stimuli were continuously calibrated to replace SWS by shallow sleep without inducing full arousals. As compared with undisturbed sleep, this intervention decreased the amount of SWS by nearly 90%, similar to that which occurs over the course of four decades of ageing, without decreasing total sleep duration or the amount of REM sleep. Findings from the intravenous glucose tolerance test performed after either undisturbed sleep or 3 nights of SWS suppression [23] indicated that SWS suppression resulted in an approximate 25% decrease in insulin sensitivity (Fig. 2, left panel). Similar to studies of experimental sleep restriction, the increased insulin resistance was not compensated by an increase in insulin release. A second study examined the impact of fragmentation of sleep across all sleep stages for two consecutive nights in healthy young volunteers [24]. Both auditory tones and mechanical vibrations were used to induce approximately 30 microarousals per hour of sleep, a degree of fragmentation typical of moderate to severe obstructive sleep apnoea. As illustrated in Fig. 2 (middle panel), after just 2 nights of sleep fragmentation, the insulin sensitivity index decreased by ± 25%.

Population studies linking poor sleep quality by subjective report with measures of insulin resistance are lacking, but there is an increasing body of evidence from prospective epidemiologic studies linking sleep difficulties with an increased risk of Type 2 diabetes. A recent meta-analysis combined the results of prospective studies where the participants reported either difficulties initiating sleep or difficulties maintaining sleep [21]. For difficulties initiating sleep, the combined relative risk for

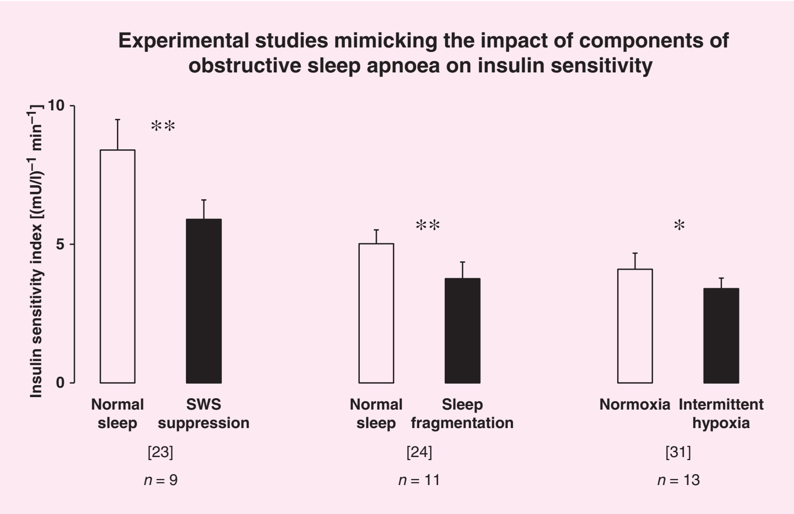

FIGURE 2 Summary of findings from studies that have examined the impact on insulin sensitivity of experimental conditions designed to simulate components of obstructive sleep apnoea under controlled laboratory conditions. *P at least < 0.05; *P at least < 0.01. Data from Tasali *et al*. [23], Stamatakis and Punjabi [24] and Louis and Punjabi [31]. SWS, short-wave sleep.

incident diabetes was 1.57 (1.25–1.97), while, for difficulties maintaining sleep, the combined relative risk was even larger at 1.84 (1.39–2.43). Two additional prospective studies supporting an increased risk of incident diabetes in individuals with sleep complaints have appeared since the meta-analysis was published [25,26].

In a cross-sectional study of 210 healthy adults, participants who reported difficulty initiating sleep on one or more nights per week had a higher level of insulin resistance as measured by the homeostasis model assessment of insulin resistance (HOMA-IR) than those who had no problem falling asleep [27]. Another cross-sectional study of 1714 adults living in Central Pennsylvania who used polysomnography in addition to subjective report revealed that, relative to adults without insomnia who slept 6 h or more, those who had chronic insomnia as well as an objective sleep duration < 5 h were nearly three times more likely to have diabetes after controlling for age, race, obesity, alcohol consumption, smoking, depression and the presence of other sleep disorders [28].

The pathways linking poor sleep quality, clinically defined insomnia and alterations of glucose metabolism are poorly defined, but likely to overlap those putatively involved in the relationship between insufficient sleep, insulin resistance and diabetes risk. There is emerging evidence to suggest that insomnia without objectively defined reduced total sleep duration may have fewer adverse cardio-metabolic consequences than insomnia with reduced sleep duration.

Obstructive sleep apnoea

While some of the components of obstructive sleep apnoea (low SWS, sleep fragmentation, reduced total sleep time) were mimicked in the studies of experimentally reduced sleep disturbances summarized in the previous two sections of this review, breathing and oxyhaemoglobin saturation were not affected. There is a substantial body of evidence from rodent models showing adverse effects of intermittent hypoxia on insulin resistance and glucose metabolism, whether induced during wake or during the sleep period [29,30]. Only one study has addressed the impact of exposure to intermittent hypoxia on glucose metabolism in humans, and the intervention was performed during wakefulness, not during sleep [31]. The healthy young participants in this randomized crossover study were subjected to intermittent hypoxia (resulting in an average of 24 drops in oxyhaemoglobin saturation per hour, similar to the hypoxic effect of moderate to severe obstructive sleep apnoea) or normoxia for a 5-h period of wakefulness in a semi-recumbent position, followed by an intravenous glucose tolerance test. The findings are illustrated in Fig. 2. Insulin sensitivity decreased by 15–20%, without compensation by increased β-cell release. Taken together, the findings of the studies summarized in Figs 1 and 2 provide strong evidence that each of the abnormalities present in obstructive sleep apnoea can cause insulin resistance, and there is also evidence for this direction of causality from prospective epidemiologic studies that have linked the presence of obstructive sleep apnoea with an increased risk of incident diabetes. Disappointingly, studies that have examined the impact of continuous positive airway pressure treatment on insulin sensitivity have had mixed results, with more than half of the studies reporting no beneficial effect of continuous positive airway pressure (reviewed in Pamidi *et al.* [32]). Negative findings could be because of poor compliance with continuous positive airway pressure treatment, which often averaged less than 4 h per night.

The 'candidate' pathways linking reduced sleep duration and/or quality with adverse metabolic outcomes, including elevated activity of the sympathetic nervous system and hypothalamo–pituitary axis and release of proinflammatory cytokines, are likely to be involved in the association of insulin resistance and obstructive sleep apnoea. There is strong evidence that the intermittent hypoxia associated with obstructive sleep apnoea increases the production of reactive oxygen species, and simultaneously impairs insulin release and action [33,34]. Intermittent hypoxia may also induce dysregulation of lipid metabolism and promote hyperlipidaemia [34].

Numerous cross-sectional studies have found a robust association between the presence and severity of obstructive sleep apnoea and insulin resistance, independent of BMI or other measures of adiposity (see recent reviews [35–37]). The most commonly used markers of severity of obstructive sleep apnoea were the apnoea–hypopnea index and the frequency and the degree of intermittent hypoxia. To estimate insulin sensitivity, the majority of the studies used fasting insulin levels and/or the homeostatic model assessment (HOMA) index, i.e. the normalized product of fasting glucose and insulin. We will briefly review the studies that derived measures of insulin sensitivity from an oral or intravenous glucose tolerance test. In a 2003 report, increasing severity of obstructive sleep apnoea assessed in 595 men who were referred to a sleep clinic was associated with an increased degree of insulin resistance, independently of age and BMI [38]. Analyses of the Sleep Heart Healthy Study also showed that the severity of obstructive sleep apnoea (as measured by the apnoea–hypopnoea index and the frequency of oxygen desaturations) was independently associated with both fasting and glucose levels 2 h after oral glucose administration [39]. In a population-based sample of 400 females, those with severe obstructive sleep apnoea had significantly lower insulin sensitivity than those without obstructive sleep apnoea, and the apnoea–hypopnoea index was associated with increasing fasting and 2-h post-load insulin levels during an oral glucose tolerance test, after controlling for age, waist–hip ratio and other confounders [40]. A large clinical research study provided important insights regarding the pathophysiological mechanisms underlying the association between obstructive sleep apnoea and increased diabetes risk [41]. A total of 118 subjects without diabetes underwent polysomnography, body composition measurements and an intravenous glucose tolerance test. Insulin sensitivity and the acute insulin response to glucose were derived to estimate insulin action, β-cell responsiveness and diabetes risk. All analyses were

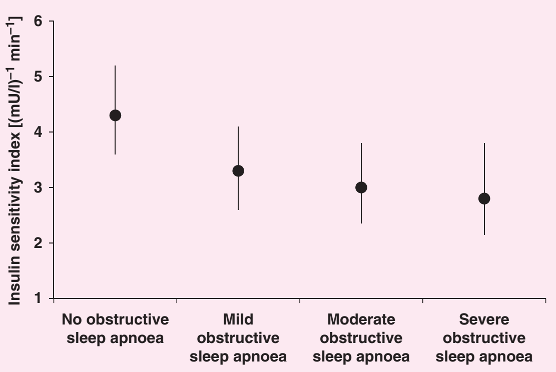

FIGURE 3 Cross-sectional associations between the insulin sensitivity index (derived from minimal model analysis of frequently sampled intravenous glucose tolerance tests) and the presence and severity of obstructive sleep apnoea. No obstructive sleep apnoea: apnoea–hypopnoea index (AHI) < 5/h; mild obstructive sleep apnoea 5 ≥ AHI < 15; moderate obstructive sleep apnoea: 15 ≥ AHI < 30; severe obstructive sleep apnoea: AHI ≥ 30. Adapted from Punjabi and Beaver [41].

controlled for age, sex, race and per cent body fat. Figure 3 illustrates the highly significant graded relationship between the adjusted insulin sensitivity and the presence and severity of obstructive sleep apnoea as assessed by the apnoea–hypopnoea index. The acute insulin response to glucose did not increase across obstructive sleep apnoea categories. Thus, the increased diabetes risk of obstructive sleep apnoea appears associated with increased insulin resistance without adequate compensation by β-cell release, consistent with the laboratory studies that attempted to mimic some of the components of obstructive sleep apnoea.

The polycystic ovary syndrome: role of obstructive sleep apnoea in metabolic disturbances

Polycystic ovary syndrome (PCOS) affects approximately 5–8% of women in the USA and typically manifests at the time of puberty with menstrual irregularity, hirsutism, elevated free testosterone levels and obesity. Insulin resistance is considered a hallmark of the syndrome. Women with PCOS have a high risk of early-onset impaired glucose tolerance and Type 2 diabetes, as well as an increased risk for hypertension, dyslipidaemia and cardiovascular disorders [42].

Women with PCOS frequently complain of poor sleep quality [43]. The risk for obstructive sleep apnoea is at least fivefold higher, and perhaps as much as 30-fold higher in PCOS, than in similarly obese women [44,45]. This high prevalence of obstructive sleep apnoea is particularly striking for young pre-menopausal women, as male sex is one of the major risk factors for obstructive sleep apnoea. Recent results suggest that there may in fact be two ‘subtypes’ of women with PCOS—those with obstructive sleep apnoea and those without obstructive sleep apnoea—and that these two subtypes may be associated with distinct metabolic and endocrine alterations [45]. Because nearly all published studies characterizing metabolic abnormalities in PCOS have not controlled for the potential impact of obstructive sleep apnoea and other sleep disturbances, the precise role of obstructive sleep apnoea in the insulin resistance of PCOS is not yet known.

In a study that examined this relationship [45], 52 pre-menopausal women with PCOS and 21 women without PCOS of similar age and BMI were submitted to overnight polysomnography and a 75-g oral glucose tolerance test. Fifty-six per cent of women with PCOS had obstructive sleep apnoea compared with 19% of control women (adjusted odds ratio 7.1). After controlling for age, BMI and ethnicity, the severity of obstructive sleep apnoea was a highly significant predictor of the fasting concentrations of glucose and insulin, as well as the 2-h glucose concentration and HOMA index (Fig. 4). In contrast, no significant association between apnoea–hypopnoea index and free testosterone levels was detected. Thus, the assumption that the high prevalence of obstructive sleep apnoea in women with PCOS is caused by the hyperandrogenism is not supported by this study. When the microarousal index (number of microarousals per hour) was substituted for the apnoea–hypopnoea index in the analyses of severity of metabolic disturbances, results similar to those illustrated in Fig. 4 were found. In contrast, the minimum oxygen saturation was not a significant predictor of any of the metabolic variables. Thus, the degree of sleep fragmentation, rather than the severity of hypoxia, appeared to be related to the severity of insulin resistance and glucose intolerance in PCOS.

In a recent study in obese women with PCOS, continuous positive airway pressure treatment modestly improved insulin sensitivity (assessed via an intravenous glucose tolerance test) after controlling for BMI [46]. The change in insulin sensitivity correlated positively with hours of nightly continuous positive airway pressure use and negatively with BMI. The predicted improvement in the insulin sensitivity index for an overweight (but not obese) woman using continuous positive airway pressure 6 h per night was nearly 30%. Daytime and night-time norepinephrine levels were decreased after continuous positive airway pressure and the reductions were greater in the women with better compliance [46].

Conclusions

The findings from the six independent experimental studies summarized in Figs 1 and 2 are remarkably consistent in indicating that sleep disturbances result in decreased insulin sensitivity. All these studies involved short-term interventions and the robust decreases in insulin sensitivity occurred independently of changes in adiposity. Insulin action is thus rapidly and markedly affected by sleep disturbances. Findings of increased risk of incident diabetes in individuals with sleep disturbances in prospective epidemiologic studies are consistent with this direction of causality. Nonetheless, the reverse direction of causality, namely that hyperinsulinaemia and insulin resistance, once they are established, promote sleep disturbances, including

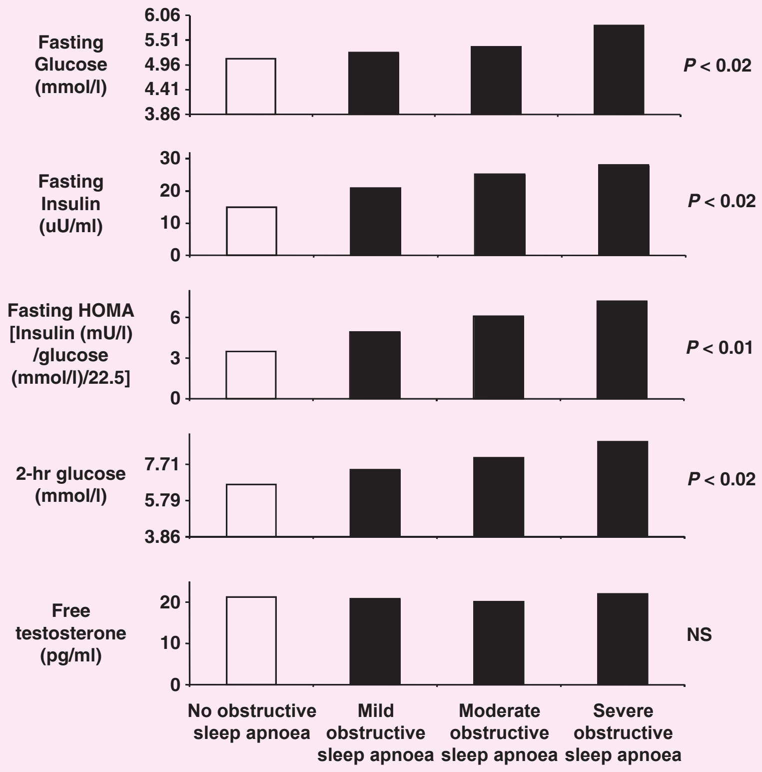

FIGURE 4 Relationships between the severity of obstructive sleep apnoea (as assessed by the apnoea–hypopnoea index) in women with polycystic ovary syndrome (PCOS) and fasting levels of glucose, insulin and homeostatis model assessment (HOMA) index, as well as 2-h post-challenge glucose concentration and free testosterone concentrations. Adapted from Tasali *et al*. [45]. NS, not significant.

obstructive sleep apnoea, is plausible, but has been poorly investigated so far. A recent prospective epidemiologic study [47] reported for the first time that fasting hyperinsulinaemia and insulin resistance (as assessed by the HOMA-IR index) preceded incident 'observed apnoeas' over a 6-year follow-up period. After controlling for age and adiposity, individuals who had higher insulin levels or HOMA-IR indices at baseline had a 31% increase in the risk of having their bed partner report that they stopped breathing during their sleep. The authors suggested that hyperinsulinaemia and insulin resistance may promote obstructive sleep apnoea via a reduction in the activity of the pharyngeal dilator muscle or inflammatory mechanisms. If confirmed, these findings could have important clinical implications for the prevention of diabetes and cardiovascular disease in obese, insulin-resistant individuals with obstructive sleep apnoea.

With the alarming increase in overweight and obesity, insulin resistance has become an endemic condition which plays a pivotal role in the rise in diabetes prevalence. The obesity epidemic has resulted in an increased prevalence of obstructive sleep apnoea. Five independent studies have shown that obstructive sleep apnoea is a frequent co-morbidity of diabetes, with a prevalence averaging a staggering 68%. It is therefore important to be aware of the diagnosis of sleep disturbances in both those people at high risk of diabetes and with established diabetes, as this may have an impact on insulin sensitivity. Nonetheless, clinical trials are required to answer whether treatment of sleep disorders might be an additional strategy to prevent diabetes and improve glycaemic control in established diabetes.

Competing interests

Nothing to declare.

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References

1 Jean-Louis G, von Gizycki H, Zizi F, Spielman A, Hauri P, Taub H. The actigraph data analysis software: I. A novel approach to scoring and interpreting sleep–wake activity. *Percept Mot Skills* 1997; **85**: 207–216.

2 Knutson KL, Spiegel K, Penev P, Van Cauter E. The metabolic consequences of sleep deprivation. *Sleep Med Rev* 2007; **11**: 163–178.

3 National Center for Health Statistics. QuickStats: percentage of adults who reported an average of ≤ 6 h of sleep per 24-h period, by sex and age group – United States, 1x985 and 2004. *MMWR Morb Mortal Wkly Rep* 2005; **54**: 933.
4 Bonnet MH, Arand DL. Insomnia, metabolic rate and sleep restoration. *J Intern Med* 2003; **254**: 23–31.
5 Vgontzas AN, Bixler EO, Lin HM, Prolo P, Mastorakos G, Vela-Bueno A *et al.* Chronic insomnia is associated with nyctohemeral activation of the hypothalamic–pituitary–adrenal axis: clinical implications. *J Clin Endocrinol Metabol* 2001; **86**: 3787–3794.
6 Young T, Peppard PE, Taheri S. Excess weight and sleep-disordered breathing. *J Appl Physiol* 2005; **99**: 1592–1599.
7 Spiegel K, Leproult R, Van Cauter E. Impact of sleep debt on metabolic and endocrine function. *Lancet* 1999; **354**: 1435–1439.
8 Nedeltcheva AV, Kessler L, Imperial J, Penev PD. Exposure to recurrent sleep restriction in the setting of high caloric intake and physical inactivity results in increased insulin resistance and reduced glucose tolerance. *J Clin Endocrinol Metab* 2009; **94**: 3242–3250.
9 Buxton OM, Pavlova M, Reid EW, Wang W, Simonson DC, Adler GK. Sleep restriction for 1 week reduces insulin sensitivity in healthy men. *Diabetes* 2010; **59**: 2126–2133.
10 Leproult R, Van Cauter E. Role of sleep and sleep loss in hormonal release and metabolism. *Endocr Dev* 2010; **17**: 11–21.
11 Ayas NT, White DP, Al-Delaimy WK, Manson JE, Stampfer MJ, Speizer FE *et al.* A prospective study of self-reported sleep duration and incident diabetes in women. *Diabetes Care* 2003; **26**: 380–384.
12 Bjorkelund C, Bondyr-Carlsson D, Lapidus L, Lissner L, Mansson J, Skoog I *et al.* Sleep disturbances in midlife unrelated to 32-year diabetes incidence: the prospective population study of women in Gothenburg. *Diabetes Care* 2005; **28**: 2739–2744.
13 Mallon L, Broman JE, Hetta J. High incidence of diabetes in men with sleep complaints or short sleep duration: a 12-year follow-up study of a middle-aged population. *Diabetes Care* 2005; **28**: 2762–2767.
14 Yaggi HK, Araujo AB, McKinlay JB. Sleep duration as a risk factor for the development of type 2 diabetes. *Diabetes Care* 2006; **29**: 657–661.
15 Gangwisch JE, Heymsfield SB, Boden-Albala B, Buijs R, Kreier F, Pickering TG *et al.* Sleep duration as a risk factor for diabetes incidence in a large US sample. *Sleep* 2007; **30**: 1667–1673.
16 Hayashino Y, Fukuhara S, Suzukamo Y, Okamura T, Tanaka T, Ueshima H. Relation between sleep quality and quantity, quality of life, and risk of developing diabetes in healthy workers in Japan: the High-risk and Population Strategy for Occupational Health Promotion (HIPOP-OHP) Study. *BMC Public Health* 2007; **7**: 129.
17 Chaput JP, Despres JP, Bouchard C, Astrup A, Tremblay A. Sleep duration as a risk factor for the development of type 2 diabetes or impaired glucose tolerance: analyses of the Quebec Family Study. *Sleep Med* 2009; **10**: 919–924.
18 Beihl DA, Liese AD, Haffner SM. Sleep duration as a risk factor for incident type 2 diabetes in a multiethnic cohort. *Ann Epidemiol* 2009; **19**: 351–357.
19 Xu Q, Song Y, Hollenbeck A, Blair A, Schatzkin A, Chen H. Day napping and short night sleeping are associated with higher risk of diabetes in older adults. *Diabetes Care* 2010; **33**: 78–83.
20 Rafalson L, Donahue RP, Stranges S, Lamonte MJ, Dmochowski J, Dorn J *et al.* Short sleep duration is associated with the development of impaired fasting glucose: the Western New York Health Study. *Ann Epidemiol* **20**: 883–889.
21 Cappuccio FP, D'Elia L, Strazzullo P, Miller MA. Quantity and quality of sleep and incidence of type 2 diabetes: a systematic review and meta-analysis. *Diabetes Care* 2010; **33**: 414–420.
22 Knutson KL. Sleep duration and cardiometabolic risk: a review of the epidemiologic evidence. *Best Pract Res Clin Endocrinol Metab* 2010; **24**: 731–743.
23 Tasali E, Leproult R, Ehrmann DA, Van Cauter E. Slow-wave sleep and the risk of type 2 diabetes in humans. *Proc Natl Acad Sci U S A* 2008; **105**: 1044–1049.
24 Stamatakis KA, Punjabi NM. Effects of sleep fragmentation on glucose metabolism in normal subjects. *Chest* 2010; **137**: 95–101.
25 Eriksson AK, Ekbom A, Granath F, Hilding A, Efendic S, Ostenson CG. Psychological distress and risk of pre-diabetes and Type 2 diabetes in a prospective study of Swedish middle-aged men and women. *Diabet Med* 2008; **25**: 834–842.
26 Rod NH, Vahtera J, Westerlund H, Kivimaki M, Zins M, Goldberg M *et al.* Sleep disturbances and cause-specific mortality: results from the GAZEL cohort study. *Am J Epidemiol* 2010; **173**: 300–309.
27 Suarez EC. Self-reported symptoms of sleep disturbance and inflammation, coagulation, insulin resistance and psychosocial distress: evidence for gender disparity. *Brain Behav Immun* 2008; **22**: 960–968.
28 Vgontzas AN, Liao D, Pejovic S, Calhoun S, Karataraki M, Bixler EO. Insomnia with objective short sleep duration is associated with type 2 diabetes: a population-based study. *Diabetes Care* 2009; **32**: 1980–1985.
29 Polotsky VY, Li J, Punjabi NM, Rubin AE, Smith PL, Schwartz AR *et al.* Intermittent hypoxia increases insulin resistance in genetically obese mice. *J Physiol* 2003; **552**: 253–264.
30 O'Donnell CP. Metabolic consequences of intermittent hypoxia. *Adv Exp Med Biol* 2007; **618**: 41–49.
31 Louis M, Punjabi NM. Effects of acute intermittent hypoxia on glucose metabolism in awake healthy volunteers. *J Appl Physiol* 2009; **106**: 1538–1544.
32 Pamidi S, Aronsohn RS, Tasali E. Obstructive sleep apnea: role in the risk and severity of diabetes. *Best Pract Res Clin Endocrinol Metab* 2010; **24**: 703–715.
33 Xu J, Long YS, Gozal D, Epstein PN. Beta-cell death and proliferation after intermittent hypoxia: role of oxidative stress. *Free Radic Biol Med* 2009; **46**: 783–790.
34 Drager LF, Jun J, Polotsky VY. Obstructive sleep apnea and dyslipidemia: implications for atherosclerosis. *Curr Opin Endocrinol Diabetes Obes* 2010; **17**: 161–165.
35 Tasali E, Mokhlesi B, Van Cauter E. Obstructive sleep apnea and type 2 diabetes: interacting epidemics. *Chest* 2008; **133**: 496–506.
36 Punjabi NM, Polotsky VY. Disorders of glucose metabolism in sleep apnea. *J Appl Physiol* 2005; **99**: 1998–2007.
37 Levy P, Bonsignore MR, Eckel J. Sleep, sleep-disordered breathing and metabolic consequences. *Eur Respir J* 2009; **34**: 243–260.
38 Meslier N, Gagnadoux F, Giraud P, Person C, Ouksel H, Urban T *et al.* Impaired glucose-insulin metabolism in males with obstructive sleep apnoea syndrome. *Eur Respir J* 2003; **22**: 156–160.
39 Punjabi NM, Shahar E, Redline S, Gottlieb DJ, Givelber R, Resnick HE. Sleep-disordered breathing, glucose intolerance, and insulin resistance: the Sleep Heart Health Study. *Am J Epidemiol* 2004; **160**: 521–530.
40 Theorell-Haglow J, Berne C, Janson C, Lindberg E. Obstructive sleep apnoea is associated with decreased insulin sensitivity in females. *Eur Respir J* 2008; **31**: 1054–1060.
41 Punjabi NM, Beamer BA. Alterations in glucose disposal in sleep-disordered breathing. *Am J Respir Crit Care Med* 2009; **179**: 235–240.
42 Nitsche K, Ehrmann DA. Obstructive sleep apnea and metabolic dysfunction in polycystic ovary syndrome. *Best Pract Res Clin Endocrinol Metab* 2010; **24**: 717–730.

43 Tasali E, Van Cauter E, Ehrmann DA. Relationships between sleep disordered breathing and glucose metabolism in polycystic ovary syndrome. *J Clin Endocrinol Metab* 2006; **91**: 36–42.
44 Vgontzas AN, Legro RS, Bixler EO, Grayev A, Kales A, Chrousos GP. Polycystic ovary syndrome is associated with obstructive sleep apnea and daytime sleepiness: role of insulin resistance. *J Clin Endocrinol Metabol* 2001; **86**: 517–520.
45 Tasali E, Van Cauter E, Hoffman L, Ehrmann DA. Impact of obstructive sleep apnea on insulin resistance and glucose tolerance in women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 2008; **93**: 3878–3884.
46 Tasali E, Chapotot F, Leproult R, Whitmore H, Ehrmann DA. Treatment of obstructive sleep apnea improves cardiometabolic function in young obese women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 2011; **96**: 365–374.
47 Balkau B, Vol S, Loko S, Andriamboavonjy T, Lantieri O, Gusto G *et al*. High baseline insulin levels associated with 6-year incident observed sleep apnea. *Diabetes Care* 2010; **33**: 1044–1049.