Sleep Apnoea & Hypertension: Physiological bases for a causal relation: Sleep and the metabolic syndrome

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Sleep and the metabolic syndrome

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The metabolic syndrome represents a clustering of several interrelated risk factors of metabolic origin that are thought to increase cardiovascular risk. It is still uncertain whether this clustering results from multiple underlying risk factors or whether it has a single cause. One metabolic abnormality that may underlie several clinical characteristics of the metabolic syndrome is insulin resistance. This review discusses the evidence that sleep disturbances (obstructive sleep apnoea, sleep deprivation and shift work) may independently lead to the development of both insulin resistance and individual clinical components of the metabolic syndrome. The converse may also be true, in that metabolic abnormalities associated with the metabolic syndrome and insulin resistance may potentially exacerbate sleep disorders. The notion that sleep disturbances exert detrimental metabolic effects may help explain the increasing prevalence of the metabolic syndrome and insulin resistance in the general population and may have important implications for population-based approaches to combat the increasing epidemic of metabolic and cardiovascular disease.

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The metabolic syndrome is not a well-defined pathophysiological entity and as such it escapes a simple mechanistic definition. According to the recommendations of the Adult Treatment Panel III (ATP III; Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol In Adults, 2001), the clinical diagnosis of the metabolic syndrome is made when three of the following five criteria are met: (i) abdominal obesity (increased waist circumference); (ii) elevated triglycerides; (iii) decreased high-density lipoprotein (HDL) cholesterol; (iv) high blood pressure; and (v) increased fasting glucose (Table 1). Other abnormalities have also been noted in individuals with the metabolic syndrome (including systemic inflammation, endothelial dysfunction, oxidative stress and hypercoagulability), although they are not included in the ATP III definition. Thus, the metabolic syndrome represents a clustering of several interrelated risk factors of metabolic origin that are thought to increase cardiovascular risk. Indeed, prospective population studies suggest that the metabolic syndrome confers an approximately twofold increase in relative risk for cardiovascular events and, in individuals without established type 2 diabetes, an approximately fivefold increase in risk for developing incident diabetes compared with individuals without the syndrome (Grundy *et al.* 2006).

In spite of ongoing efforts to elucidate the pathophysiological basis of the metabolic syndrome, it still remains unclear whether it has a single cause or whether it results from multiple underlying risk factors, which may be environmental, behavioural and genetic. Some of the predisposing risk factors include abdominal obesity, physical inactivity and insulin resistance. Importantly, although these factors appear to be interrelated and insulin resistance has been traditionally associated with obesity and physical inactivity, insulin resistance is not a simple function of these two factors. It has been suggested that differences in adiposity account for only 25% of the variability in insulin-mediated glucose disposal and physical fitness accounts only for another 25% (Reaven, 2006). Furthermore, even in the absence of overt diabetes, hyperinsulinaemia *per se* is associated with glucose intolerance, elevated triglycerides, lower HDL cholesterol, elevated blood pressure and endothelial dysfunction, as well as pro-coagulant and pro-inflammatory states, suggesting that insulin resistance may be at the core of the constellation of the risk factors that define

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Table 1. Adult Treatment Panel III definition of the metabolic syndrome

Metabolic syndrome comprises any three of the following:
Fasting glucose $\geq$ 6.1 mmol l^{-1} (110 mg dl^{-1})
Waist circumference:
Men > 102 cm (40 inches)
Women > 88 cm (35 inches)
Triacylglycerols $\geq$ 1.7 mmol l^{-1} (150 mg dl^{-1})
HDL cholesterol:
Men < 1.036 mmol l^{-1} (40 mg dl^{-1})
Women < 1.295 mmol l^{-1} (50 mg dl^{-1})
Blood pressure $\geq$ 130/85 mmHg

Reproduced from (Reaven, 2006), adapted from (Expert Panel, 2001).

the metabolic syndrome. This understanding of the metabolic syndrome is reflected in the original World Health Organization definition, in which the presence of glucose intolerance/insulin resistance is a necessary component for the diagnosis of the syndrome (Alberti & Zimmet, 1998; Reaven, 2006).

As indicated above, obesity and physical inactivity may account for only about 50% of the variability in insulin-mediated glucose disposal in healthy, non-diabetic, normotensive individuals (Reaven, 2006). Therefore, other contributors to the pathogenesis of insulin resistance need to be identified to explain the emerging epidemic of glucose intolerance and the metabolic syndrome. Recent data suggest that sleep disturbances may not only contribute to weight gain but also, in their own right, may lead to the development of insulin resistance. Thus, the high prevalence of qualitative and quantitative sleep disorders may help explain the high and rising population-wide prevalence of the metabolic syndrome and insulin resistance.

Obstructive sleep apnoea

Obstructive sleep apnoea (OSA) is a common condition characterized by recurrent episodes of cessation of respiratory airflow caused by upper airway inspiratory collapse during sleep, with a consequent hypoxaemia and decreases in oxygen saturation (to levels as low as 40–50%) as well as sleep fragmentation and deprivation. The presence and severity of OSA is assessed based on the number of apnoea/hypopnoea episodes per hour of sleep (apnoea/hypopnoea index, AHI) and the severity of oxygen desaturations. When defined as an AHI greater than 5, the incidence of OSA in the general population is estimated at 24 and 9% of middle-aged men and women, respectively (Young *et al.* 1993). OSA will be discussed below in the context of its implications for the development of individual components of the metabolic syndrome, including insulin resistance.

Abdominal obesity. OSA has been linked to visceral obesity, although the relationship between these two conditions is complex (Wolk *et al.* 2003). Obesity is a recognized risk factor for OSA. Total body weight, body mass index (BMI) and fat distribution all correlate with the odds of having OSA (Young *et al.* 2002). Every 10 kg increment in body weight increases OSA risk twofold. Every 6 kg m^{-2} increment in BMI increases OSA risk more than fourfold. An increase in waist or hip circumference by 13–15 cm also increases OSA risk approximately fourfold. Visceral fat especially predicts OSA and significantly correlates with AHI (Shinohara *et al.* 1997; Vgontzas *et al.* 2000). Furthermore, in a population-based prospective study of 690 randomly selected Wisconsin residents, a 10% weight gain was associated with a sixfold increase in the odds of developing sleep apnoea (Peppard *et al.* 2000*a*). In the same study, a 10% weight loss predicted a 26% decrease in the AHI.

There may be a reciprocal relationship between obesity and OSA, such that not only does obesity increase the risk of OSA, but also that sleep apnoea may predispose to weight gain and obesity. Indeed, patients with newly diagnosed OSA have difficulty losing weight and, in fact, are predisposed to excessive weight gain, far more than is evident in similarly obese control subjects proven to be free of OSA (Phillips *et al.* 1999*a*, 2000). In addition, OSA seems to have an independent effect on visceral fat distribution (Shinohara *et al.* 1997; Vgontzas *et al.* 2000; Schafer *et al.* 2002; Fig. 1). Chronic continuous positive airway pressure (CPAP) therapy has been shown to decrease visceral fat accumulation (assessed by computed tomography) in patients with OSA (Chin *et al.* 1999). Importantly, visceral

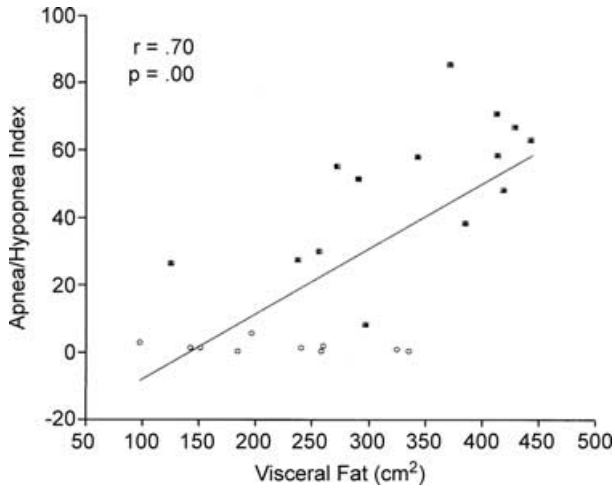

Figure 1. Correlation between visceral fat accumulation (measured by computed tomography) and OSA severity (apnoea/hypopnoea index, AHI)
■, OSA; ○, obese controls. Indices of OSA were positively correlated with visceral fat, but not with BMI or total or subcutaneous fat. Adapted and reproduced from Vgontzas *et al.* (2000), copyright 2000, The Endocrine Society.

fat decreased also in those OSA subjects who had no accompanying body weight reduction (Fig. 2), suggesting a pathophysiological link between OSA and excess visceral fat independent of overall body weight. Thus, the presence of OSA is conducive to accumulation of visceral fat and thereby contributes to the occurrence of this component of the metabolic syndrome.

Dyslipidaemia. Plasma lipid profiles have not been extensively studied in OSA, although lipid abnormalities have been reported in several clinical studies of OSA subjects. In the Sleep Heart Health Study of 6440 men and women, total cholesterol level did not vary across quartiles of AHI, but there was an inverse relationship between AHI and HDL cholesterol levels and a positive association between AHI and triglycerides, especially in younger subjects (Newman *et al.* 2001). In another study, fasting triglyceride levels as well as the percentage of subjects with elevated total cholesterol/HDL cholesterol ratio of > 5 were significantly higher in the OSA group (Ip *et al.* 2000*b*). Compared with non-OSA subjects, lower HDL, higher total cholesterol/HDL ratio and higher triglycerides were also observed in OSA subjects by Coughlin *et al.* (2004). In that study, triglycerides lost their statistical significance in regression analysis (after adjustment for age, BMI, smoking and alcohol consumption), but OSA remained independently associated with decreased HDL and increased total cholesterol/HDL ratio.

While further studies are needed to confirm these preliminary observations and to investigate whether the association between OSA and dyslipidaemia is causal and independent of other confounders (especially obesity), it is of note that decreases in total cholesterol (Robinson *et al.* 2004) and increases in HDL cholesterol levels (even in the absence of a significant change in body weight; Chin *et al.* 1999, 2000) have been reported after CPAP treatment, suggesting that OSA and dyslipidaemia may in fact be causally related. Further support for this hypothesis has been provided recently by experimental studies showing that intermittent hypoxia (a hallmark of OSA) causes an increase in the liver content of triglyceride and phospholipid, upregulates genes of lipid biosynthesis (Li *et al.* 2005*a*) and causes dyslipidaemia in lean mice (Li *et al.* 2005*b*). The changes observed in lipid profile included increased fasting total cholesterol, HDL cholesterol, phospholipids and triglycerides. While the elevated triglyceride levels in the mouse model are consistent with the observations in human subjects with OSA, elevations in HDL cholesterol are unlike those seen in OSA subjects (who usually have lower HDL), which suggests that there may be interspecies differences in cholesterol processing.

Notably, not only HDL levels, but possibly also HDL *function* can be affected by OSA. In a recent study of 128 OSA patients and 82 control subjects, despite similar concentrations of plasma lipids and apolipoproteins in the two groups, OSA subjects had greater HDL dysfunction (determined as the ability of HDL to inhibit low-density lipoprotein (LDL) oxidation *ex vivo*) and increased oxidized LDL levels (Tan *et al.* 2006). The AHI was the main

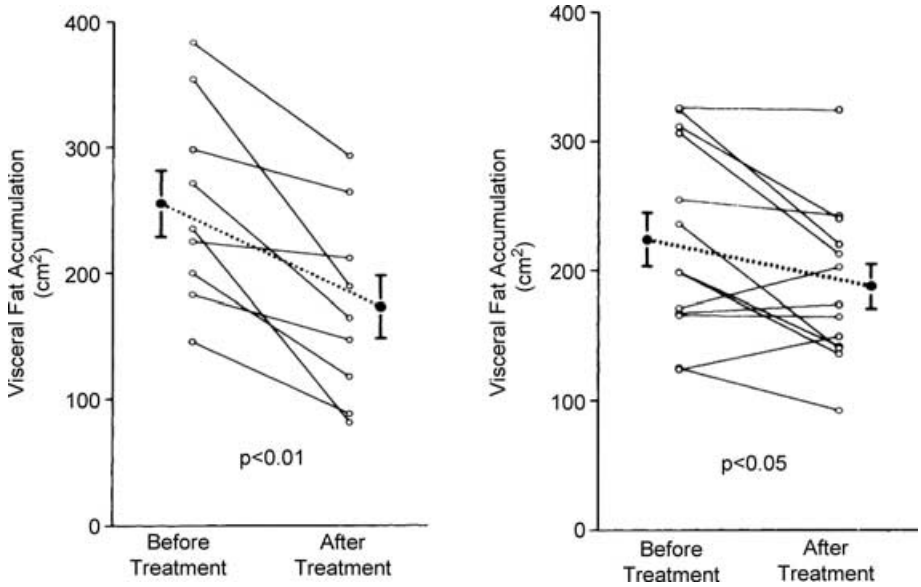

Figure 2. Changes in visceral fat after 6 months of CPAP therapy in OSA subjects with a concomitant decrease in body weight after the therapy (left panel) and in OSA subjects whose overall body weight was not reduced after CPAP (right panel)
Note that visceral fat accumulation was significantly reduced in both OSA groups. Reproduced and modified from Chin *et al.* (1999).

determinant of HDL dysfunction, accounting for 30% of its variance. Thus, OSA has the potential to induce not only quantitative, but also qualitative changes in plasma lipids.

High blood pressure. There is compelling evidence supporting the causal association between OSA and hypertension (Wolk *et al.* 2003). This evidence is based on numerous cross-sectional, longitudinal and treatment studies, all of which support the notion that the prevalence of hypertension is greater in patients with OSA, and vice versa, and that CPAP treatment leads to a decrease in both daytime and nighttime blood pressure. In one such benchmark prospective study (the Wisconsin Sleep Cohort Study), a dose–response relationship was demonstrated between sleep-disordered breathing at baseline and the presence of hypertension 4 years later (Peppard *et al.* 2000*b*). The odds ratios for the presence of incident hypertension at follow-up were 1.42, 2.03 and 2.89 for AHI of < 5, 5–15 and > 15 events h^{-1} at baseline, respectively (Fig. 3). This association was independent of other known risk factors, such as baseline hypertension, body mass and habitus, age, gender, and alcohol and cigarette use.

The pathophysiological mechanisms leading to sustained elevation of blood pressure in OSA are likely to be multifactorial. Abundant evidence supports the role of enhanced daytime sympathetic activity, which results not only from a carry-over effect from the nocturnal events, but may also be related to chemoreceptor resetting and tonic 'normoxic' chemoreceptor activation (Carlson *et al.* 1993; Somers *et al.* 1995; Narkiewicz *et al.* 1998*b*). Other potential contributing mechanisms that have been described in OSA include baroreflex (Narkiewicz *et al.* 1998*a*) and endothelial dysfunction (Carlson *et al.* 1996; Kato *et al.* 2000*b*). Irrespective of the exact mechanism of action, it appears that OSA can, in and of itself, lead to elevated blood pressure and thus contribute to yet another component of the metabolic syndrome.

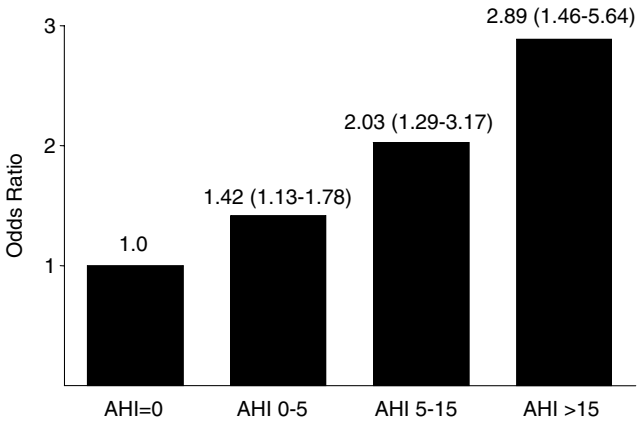

Figure 3. Odds ratios for the presence of incident hypertension at 4 year follow-up according to the apnoea/hypopnoea index (AHI) at baseline
The odds ratios are adjusted for baseline hypertension status, age, gender, body habitus (body mass index, waist and neck circumference), alcohol consumption and cigarette use. Data are shown as odds ratio (lower and upper 95% confidence interval). For trend, $P = 0.002$. Data from Peppard *et al.* (2000*b*); figure reproduced from Wolk *et al.* (2005*a*).

Glucose intolerance and insulin resistance. Subjects with OSA might intuitively be expected to have at least some degree of glucose intolerance and insulin resistance by virtue of their increased body weight and visceral obesity. Evidence has accumulated over the last few years, however, to support the concept that OSA may be directly related to insulin resistance, independent of obesity and other anthropometric measures, in both obese and non-obese subjects (Vgontzas *et al.* 2000; Ip *et al.* 2002; Punjabi *et al.* 2002; Tassone *et al.* 2003; Coughlin *et al.* 2004; Makino *et al.* 2006; Fig. 4). Several reports suggest that these metabolic abnormalities can be reversed by effective treatment of OSA with CPAP (Harsch *et al.* 2004*b*,*c*; Babu *et al.* 2005), lending further support to the notion that

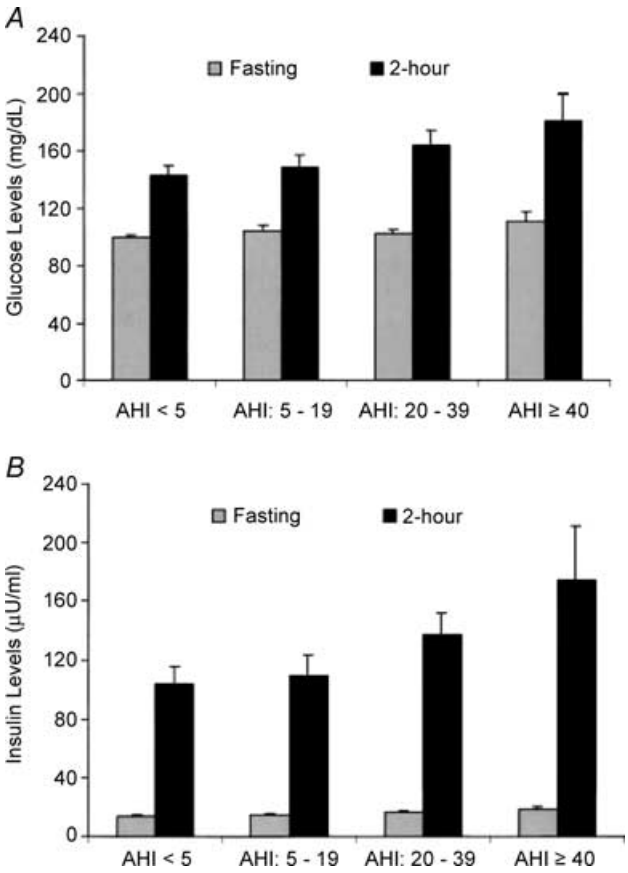

Figure 4. Fasting and 2 h (post glucose load) insulin and glucose levels (means ± s.e.m.) by apnoea/hypopnoea index (AHI) category
Significant trends ($P < 0.05$) were noted across AHI categories in the fasting insulin level and 2 h glucose and insulin levels. Reproduced from (Punjabi *et al.* 2002).

OSA and insulin resistance may be causally related. Earlier studies, however, provided somewhat conflicting results and did not consistently demonstrate an improvement in metabolic disturbances after CPAP treatment (Punjabi *et al.* 2003). Some of the differences in study outcomes can be attributed to different durations of CPAP therapy as well as to the fact that compliance with CPAP (and therefore any improvement in the severity of apnoea and hypoxic episodes) was not objectively assessed in most studies. Also, several studies employed relatively small sample sizes and did not have a control group.

While the exact mechanisms linking OSA to insulin resistance in humans have not been fully elucidated, several plausible explanations can be proposed. For example, physical inactivity (due to daytime somnolence) and sleep deprivation (see later) may be important contributing factors. Obstructive sleep apnoea is also characterized by a pro-inflammatory state and elevated cytokine levels (e.g. tumour necrosis factor-α, TNF-α) (Vgontzas *et al.* 1997, 2000; Ciftci *et al.* 2004; Minoguchi *et al.* 2004), which may lead to insulin resistance (Hotamisligil *et al.* 1993; Uysal *et al.* 1997). Furthermore, OSA may induce oxidative stress owing to repetitive episodes of intermittent hypoxia (Schulz *et al.* 2000*a*; Dyugovskaya *et al.* 2002), and increased oxidative stress has been shown to be an important pathogenic mechanism of insulin resistance (Matsuoka *et al.* 1997; Rudich *et al.* 1998; Maddux *et al.* 2001; Furukawa *et al.* 2004). Indeed, Polotsky *et al.* (2003) reported that leptin-deficient obese mice developed a time-dependent increase in fasting serum insulin levels and worsening glucose tolerance after long-term (12 week) exposure to intermittent hypoxia. However, whether oxidative stress can be consistently demonstrated in OSA is controversial (Svatikova *et al.* 2005).

Insulin resistance is also caused by increased lipolysis and fatty acid availability (Rebrin *et al.* 1996; Hertz *et al.* 1998; Kruszynska *et al.* 2002). OSA may act through this mechanism by virtue of its association with central adiposity (Chin *et al.* 1999) and sympathetic activation (Somers *et al.* 1995). Sympathetic activation raises circulating free fatty acids via stimulation of lipolysis and promotes insulin resistance (Kjeldsen *et al.* 1992). Several adipose tissue-derived hormones (such as leptin, adiponectin and resistin) have also been linked to the pathophysiology of insulin resistance (Segal *et al.* 1996; Vettor *et al.* 1997; Steppan *et al.* 2001; Weyer *et al.* 2001; Stefan *et al.* 2002, 2003; Rajala *et al.* 2003; Whitehead *et al.* 2006), and their plasma levels may be influenced by OSA (Ip *et al.* 2000*b*; Phillips *et al.* 2000; Vgontzas *et al.* 2000; Harsch *et al.* 2004*a*,*d*; Wolk *et al.* 2005*b*; Zhang *et al.* 2006). Finally, an important role may be played by monocyte chemoattractant protein-1 (MCP-1). That MCP-1 is involved in the regulation of glucose homeostasis is suggested by the observations that MCP-1 expression and secretion is insulin responsive, that circulating MCP-1 levels are elevated in subjects with type 2 diabetes and that MCP-1 levels are associated with measures of glycaemia and insulin resistance (Piemonti *et al.* 2003; Sartipy & Loskutoff, 2003; Simeoni *et al.* 2004). Preliminary data suggest that MCP-1 levels may be elevated in OSA (Ohga *et al.* 2003), raising the possibility that MCP-1 may be involved in the pathogenesis of insulin resistance in OSA.

Other abnormalities accompanying the metabolic syndrome. It is apparent from the discussion above that there may be a pathophysiological link between OSA and the individual components included in the clinical definition of the metabolic syndrome, such as abdominal obesity, elevated triglycerides, decreased HDL cholesterol, high blood pressure and glucose intolerance. However, there are other metabolic abnormalities that, although not included in the ATP III criteria, are also manifest in the metabolic phenotype of the syndrome. Examples of such abnormalities include systemic inflammation, oxidative stress, endothelial dysfunction and hypercoagulability. It is noteworthy that all of these other abnormalities have also been found in OSA.

Several studies are consistent in demonstrating that OSA can induce an inflammatory state. OSA is independently associated with elevation of C-reactive protein (Shamsuzzaman *et al.* 2002; Yokoe *et al.* 2003; Fig. 5), serum amyloid A (Svatikova *et al.* 2003) and various adhesion molecules, as well as increased expression of adhesion molecules on leucocytes and their adherence to endothelial cells (Chin *et al.* 2000; Dyugovskaya *et al.* 2002; El-Solh *et al.* 2002). Oxidative stress may be present in OSA (Schulz *et al.* 2000*a*; Dyugovskaya *et al.* 2002), as is impaired endothelium-dependent vasodilatation (Kato *et al.* 2000*b*) and hypercoagulability (Chin *et al.* 1996; Sanner *et al.* 2000; Wessendorf *et al.* 2000; Guardiola *et al.* 2001). Impaired

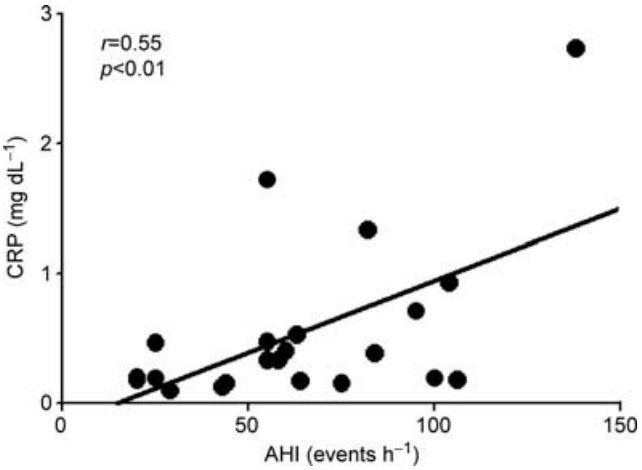

Figure 5. Regression of plasma C-reactive protein (CRP) levels *versus* apnoea/hypopnoea index (AHI) in OSA
Reproduced from Shamsuzzaman *et al.* (2002).

endothelial function in OSA probably has multiple contributing factors, such as hypertension, increased sympathetic tone, vascular inflammation, oxidative damage, etc. Specific abnormalities may be evident, including decreased nitric oxide production (Ip *et al.* 2000*a*; Schulz *et al.* 2000*b*) and increased endothelin (Saarelainen *et al.* 1997; Phillips *et al.* 1999*b*). OSA-related hypercoagulability may be related to increased platelet aggregability, increased haematocrit, elevated fibrinogen levels and increased blood viscosity (Chin *et al.* 1996; Sanner *et al.* 2000; Wessendorf *et al.* 2000; Guardiola *et al.* 2001).

Again, many of these inflammatory, oxidative, endothelial function and coagulation abnormalities in OSA may respond favourably to CPAP therapy (Chin *et al.* 1998, 2000; Ohga *et al.* 1999, 2003; Phillips *et al.* 1999*b*; Schulz *et al.* 2000*a*,*b*; El-Solh *et al.* 2002; Ohike *et al.* 2005), supporting their possible mechanistic link to the presence of OSA.

Effects of the metabolic syndrome on OSA. While there is experimental and clinical evidence to implicate OSA in the development of the metabolic syndrome, the evidence is often circumstantial, and the issue of causality still remains unproven. To this end, Vgontzas and co-workers have recently proposed that, rather than sleep apnoea being merely a cause of the metabolic syndrome, the latter may potentially be conducive to sleep apnoea (Vgontzas *et al.* 2003, 2005). This supposition is based on the following premises: (i) many sleep apnoeics do not have structural abnormalities in their upper airways and, vice versa, many patients with narrow upper airways owing to anatomical abnormalities do not have sleep apnoea; (ii) as discussed earlier, some early studies did not support any beneficial effect of CPAP on metabolic abnormalities in OSA (Punjabi *et al.* 2003); (iii) obesity (a component of the metabolic syndrome) increases the risk of OSA; (iv) sleep apnoea is very frequent in disorders in which insulin resistance is a primary pathophysiological abnormality, independent of obesity (an example of such a disorder is the polycystic ovary syndrome, in which insulin resistance is the strongest predictor of the presence of sleep apnoea); (v) insulin resistance, by releasing growth factors, may lead to soft tissue oedema and tissue proliferation in the neck; (vi) some metabolic abnormalities are associated with excessive daytime sleepiness; (vii) pro-inflammatory mediators (known to be elevated in OSA) are also independently associated with excessive daytime sleepiness; and (viii) anti-inflammatory interventions have the potential to decrease sleepiness and AHI in sleep apnoeics. With respect to this latter observation, in a pilot study of eight male obese apnoeics, administration of etanercept (which neutralizes TNF-α) resulted in a significant decrease in sleepiness and in the number of apnoeas/hypopnoeas per hour (Vgontzas *et al.* 2004). This suggests that pro-inflammatory cytokines may conceivably contribute to the pathogenesis of OSA, although this hypothesis remains to be proven.

The concept that the metabolic syndrome and insulin resistance may be conducive to sleep apnoea finds further support in the observation that diabetes may lead to a marked depression in ventilatory control mechanisms (Polotsky *et al.* 2001). In a model of streptozotocin-induced diabetes in C57BL/6J mice, diabetes resulted in depression of the hypercapnic ventilatory response and there was a strong association between the duration of hyperglycaemia, the decline in hypercapnic ventilatory response and increased glycosylation of the diaphragm. In another experimental study of streptozotocin-induced diabetes in rats, compared with normal rats, diabetic rats had a lower ventilatory response to CO_2 challenge and their sleep apnoea scores were markedly increased. Furthermore, metformin (known to reduce insulin resistance) returned sleep apnoea scores to their baseline levels, supporting the idea that insulin resistance is an important factor leading to the occurrence of apnoeas in this experimental model (Ramadan *et al.* 2006). While some clinical studies suggest that OSA patients have normal hypercapnic responses and CPAP treatment does not markedly affect hypercapnic chemosensitivity in OSA (Narkiewicz *et al.* 1999; Spicuzza *et al.* 2006), it should be noted that in those studies only 'healthy' and untreated OSA subjects were studied and diabetes was an exclusion criterion. Thus, whether or not ventilatory control is impaired by diabetes in humans with OSA needs to be established.

All this evidence notwithstanding, any claim that the metabolic syndrome may be a major cause of sleep apnoea is probably premature, although it is certainly an intriguing and conceivable hypothesis that may have important therapeutic consequences and therefore requires further studies. It is plausible that, in the setting of OSA and the metabolic syndrome, there may be a feedforward relationship between these two conditions, in that OSA predisposes to the metabolic syndrome, and the metabolic syndrome then impairs ventilatory control (by promoting obesity, inflammatory state, glucose intolerance, etc.), leading to progression of OSA with a consequent further deterioration in the metabolic syndrome. This reciprocal relationship between OSA and the metabolic syndrome may be more pronounced at the more advanced, diabetic stage.

Sleep duration and the metabolic syndrome

Altered sleep duration is an example of a quantitative sleep abnormality. While sleep deprivation is also characteristic of OSA, there is evidence to suggest that decreased sleep duration *per se* is not a benign phenomenon and can, in and of itself, exert important metabolic effects.

For example, a reduced amount of sleep is associated with overweight and obesity, such that obese subjects show a nearly inverse linear relationship between weight and sleep time (Gangwisch *et al.* 2005; Vorona *et al.* 2005). Several other reports also support the association between sleep duration and adiposity (Shigeta *et al.* 2001; Sekine *et al.* 2002). Although the exact mechanisms linking sleep deprivation to obesity remain to be established, preliminary data point to several neurohumoral consequences of sleep restriction, such as changes in sympathovagal balance, cortisol levels, thyrotropin concentration, growth hormone secretion patterns, or the diurnal rhythm and plasma levels of leptin (which regulates appetite and energy expenditure) (Spiegel *et al.* 1999, 2000, 2004).

In addition to visceral obesity, other components of the metabolic syndrome can also be affected by sleep duration. Sleep deprivation has been shown to raise blood pressure, may be independently associated with an increased risk for hypertension (Lusardi *et al.* 1996; Tochikubo *et al.* 1996; Kato *et al.* 2000*a*; Ogawa *et al.* 2003; Gangwisch *et al.* 2006), may activate systemic inflammatory processes (Vgontzas *et al.* 1999; Shearer *et al.* 2001; Meier-Ewert *et al.* 2004) and increase susceptibility to oxidative stress (Ramanathan *et al.* 2002; Everson *et al.* 2005), although this latter effect may be controversial and tissue specific (D'Almeida *et al.* 1998; Gopalakrishnan *et al.* 2004). Furthermore, in prospective studies, sleep deprivation has been suggested to be an independent risk factor for diabetes (Ayas *et al.* 2003; Yaggi *et al.* 2006), and evidence has recently emerged that sleep curtailment may be associated with glucose intolerance and insulin resistance, independent of obesity *per se*. For example, healthy subjects limited to 4 h of sleep for six consecutive nights demonstrated reduced glucose tolerance and a blunted insulin response to glucose (Spiegel *et al.* 1999). Decreased insulin sensitivity is observed with different durations of sleep deprivation (VanHelder *et al.* 1993; Gonzalez-Ortiz *et al.* 2000), and also as a result of sustained sleep debt owing to habitually sleeping less than 6 h per day (Shigeta *et al.* 2001). Thus, restricted sleep and glucose intolerance may be causally related.

Taken together, these data suggest that sleep deprivation may be both indirectly (through obesity) and directly implicated as a risk factor for the metabolic syndrome.

Shift work

Insufficient sleep is not only a consequence of voluntary sleep curtailment, but also a common feature of shift work. On average, shift workers get less sleep during the week compared with regular day workers. In contrast to habitual sleep deprivation, however, shift work is also characterized by changes in biological rhythms, cumulative circadian phase delay, variable photoperiod, napping, 'paying back' sleep debt in the daytime, etc.

Shift work increases the risk of hypertension and may exert potentially detrimental effects on circadian blood pressure control, such that the diurnal variation is changed from a dipper to a non-dipper pattern (Yamasaki *et al.* 1998; Kitamura *et al.* 2002). Decreased brachial artery endothelial function was found in shift workers and was independently related to the length of shift work history (Amir *et al.* 2004). Other metabolic effects of shift work include abdominal obesity, dyslipidaemia (lower HDL cholesterol and higher triglycerides) and changes in glucose tolerance (Hampton *et al.* 1996; Karlsson *et al.* 2001, 2003; Nagaya *et al.* 2002; Di Lorenzo *et al.* 2003), all suggestive of the possibility that shift work may contribute to the metabolic syndrome. Reduced fibrinolytic activity has also been reported in men on night shift compared with those on day shift (Meade *et al.* 1979). In addition, shift work may act as an oxidative stressor and decrease plasma antioxidant capacity (Sharifian *et al.* 2005).

Table 2. Putative influences of sleep disturbances on various components of the metabolic syndrome

	OSA	Sleep deprivation	Shift work
Insulin resistance	+ (↑↓)	+	+
Abdominal obesity	+ (↑↓)	+	+
Dyslipidaemia	+		+
Hypertension	+	+	+
Inflammation	+ (↑↓)	+	
Oxidative stress	+/–	+/–	+/–
Endothelial dysfunction	+		+
Hypercoagulability	+		+/–

(↑↓) indicates a reciprocal feedforward relationship between OSA and individual features of the metabolic syndrome.

Summary and conclusions

Considering the prevalence of sleep disorders in the general population and considering the epidemiological and pathophysiological links between the metabolic syndrome and incident diabetes and cardiovascular disease, the association of OSA with the metabolic syndrome and insulin resistance is of critical importance. The weight of evidence clearly suggests that the two conditions coexist, although the exact nature of this association is not entirely clear. While OSA may be just another component of the metabolic syndrome ('Syndrome Z'; Wilcox *et al.* 1998), both human and experimental data suggest that OSA may also be causally related to individual components of the metabolic syndrome, including insulin resistance. The complex interactions between OSA and the metabolic syndrome are summarized in Table 2. Regardless of the exact underlying mechanism/s, the available data suggest that treatment of OSA may attenuate features of the metabolic syndrome.

It also appears that the relationship between sleep and the metabolic syndrome goes beyond OSA and probably also extends to other forms of sleep disturbance, especially sleep deprivation and shift work (Table 2). This paradigm, suggesting that sleep curtailment and shift work have detrimental metabolic consequences, may have important implications for population-based approaches to combat the epidemic of metabolic and cardiovascular disease.

Nevertheless, it has to be emphasized that at this stage the evidence is mainly circumstantial and at times controversial, such that there are only limited data from which definitive conclusions can be drawn. Available data are often observational, uncontrolled and based on small sample sizes. Even controlled studies are often confounded by the presence of comorbidities in the control population. Finally, a publication bias cannot be excluded such that negative data are not published as often as the positive findings. Carefully designed experimental and clinical studies are necessary to better elucidate the link between sleep disorders and the metabolic syndrome, and in particular with insulin resistance.

References

Alberti KG & Zimmet PZ (1998). Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med* **15**, 539–553.

Amir O, Alroy S, Schliamser JE, Asmir I, Shiran A, Flugelman MY, Halon DA & Lewis BS (2004). Brachial artery endothelial function in residents and fellows working night shifts. *Am J Cardiol* **93**, 947–949.

Ayas NT, White DP, Al-Delaimy WK, Manson JE, Stampfer MJ, Speizer FE, Patel S & Hu FB (2003). A prospective study of self-reported sleep duration and incident diabetes in women. *Diabetes Care* **26**, 380–384.

Babu AR, Herdegen J, Fogelfeld L, Shott S & Mazzone T (2005). Type 2 diabetes, glycemic control, and continuous positive airway pressure in obstructive sleep apnea. *Arch Intern Med* **165**, 447–452.

Carlson JT, Hedner J, Elam M, Ejnell H, Sellgren J & Wallin BG (1993). Augmented resting sympathetic activity in awake patients with obstructive sleep apnea. *Chest* **103**, 1763–1768.

Carlson JT, Rangemark C & Hedner JA (1996). Attenuated endothelium-dependent vascular relaxation in patients with sleep apnoea. *J Hypertens* **14**, 577–584.

Chin K, Kita H, Noguchi T, Otsuka N, Tsuboi T, Nakamura T, Shimizu K, Mishima M & Ohi M (1998). Improvement of factor VII clotting activity following long-term NCPAP treatment in obstructive sleep apnoea syndrome. *QJM* **91**, 627–633.

Chin K, Nakamura T, Shimizu K, Mishima M, Nakamura T, Miyasaka M & Ohi M (2000). Effects of nasal continuous positive airway pressure on soluble cell adhesion molecules in patients with obstructive sleep apnea syndrome. *Am J Med* **109**, 562–567.

Chin K, Ohi M, Kita H, Noguchi T, Otsuka N, Tsuboi T, Mishima M & Kuno K (1996). Effects of NCPAP therapy on fibrinogen levels in obstructive sleep apnea syndrome. *Am J Respir Crit Care Med* **153**, 1972–1976.

Chin K, Shimizu K, Nakamura T, Narai N, Masuzaki H, Ogawa Y, Mishima M, Nakamura T, Nakao K & Ohi M (1999). Changes in intra-abdominal visceral fat and serum leptin levels in patients with obstructive sleep apnea syndrome following nasal continuous positive airway pressure therapy. *Circulation* **100**, 706–712.

Ciftci TU, Kokturk O, Bukan N & Bilgihan A (2004). The relationship between serum cytokine levels with obesity and obstructive sleep apnea syndrome. *Cytokine* **28**, 87–91.

Coughlin SR, Mawdsley L, Mugarza JA, Calverley PM & Wilding JP (2004). Obstructive sleep apnoea is independently associated with an increased prevalence of metabolic syndrome. *Eur Heart J* **25**, 735–741.

D'Almeida V, Lobo LL, Hipolide DC, de Oliveira AC, Nobrega JN & Tufik S (1998). Sleep deprivation induces brain region-specific decreases in glutathione levels. *Neuroreport* **9**, 2853–2856.

Di Lorenzo L, De Pergola G, Zocchetti C, L'Abbate N, Basso A, Pannacciulli N, Cignarelli M, Giorgino R & Soleo L (2003). Effect of shift work on body mass index: results of a study performed in 319 glucose-tolerant men working in a Southern Italian industry. *Int J Obes Relat Metab Disord* **27**, 1353–1358.

Dyugovskaya L, Lavie P & Lavie L (2002). Increased adhesion molecules expression and production of reactive oxygen species in leukocytes of sleep apnea patients. *Am J Respir Crit Care Med* **165**, 934–939.

El-Solh AA, Mador MJ, Sikka P, Dhillon RS, Amsterdam D & Grant BJ (2002). Adhesion molecules in patients with coronary artery disease and moderate-to-severe obstructive sleep apnea. *Chest* **121**, 1541–1547.

Everson CA, Laatsch CD & Hogg N (2005). Antioxidant defense responses to sleep loss and sleep recovery. *Am J Physiol Regul Integr Comp Physiol* **288**, R374–R383.

Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol In Adults(2001). Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA* **285**, 2486–2497.

Furukawa S, Fujita T, Shimabukuro M, Iwaki M, Yamada Y, Nakajima Y, Nakayama O, Makishima M, Matsuda M & Shimomura I (2004). Increased oxidative stress in obesity and its impact on metabolic syndrome. *J Clin Invest* **114**, 1752–1761.

Gangwisch JE, Heymsfield SB, Boden-Albala B, Buijs RM, Kreier F, Pickering TG, Rundle AG, Zammit GK & Malaspina D (2006). Short sleep duration as a risk factor for hypertension: analyses of the first National Health and Nutrition Examination Survey. *Hypertension* **47**, 833–839.

Gangwisch JE, Malaspina D, Boden-Albala B & Heymsfield SB (2005). Inadequate sleep as a risk factor for obesity: analyses of the NHANES I. *Sleep* **28**, 1289–1296.

Gonzalez-Ortiz M, Martinez-Abundis E, Balcazar-Munoz BR & Pascoe-Gonzalez S (2000). Effect of sleep deprivation on insulin sensitivity and cortisol concentration in healthy subjects. *Diabetes Nutr Metab* **13**, 80–83.

Gopalakrishnan A, Ji LL & Cirelli C (2004). Sleep deprivation and cellular responses to oxidative stress. *Sleep* **27**, 27–35.

Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, Gordon DJ, Krauss RM, Savage PJ, Smith SC Jr, Spertus JA & Costa F (2006). Diagnosis and management of the metabolic syndrome: an American Heart Association/ National Heart, Lung, and Blood Institute scientific statement. *Curr Opin Cardiol* **21**, 1–6.

Guardiola JJ, Matheson PJ, Clavijo LC, Wilson MA & Fletcher EC (2001). Hypercoagulability in patients with obstructive sleep apnea. *Sleep Med* **2**, 517–523.

Hampton SM, Morgan LM, Lawrence N, Anastasiadou T, Norris F, Deacon S, Ribeiro D & Arendt J (1996). Postprandial hormone and metabolic responses in simulated shift work. *J Endocrinol* **151**, 259–267.

Harsch IA, Koebnick C, Wallaschofski H, Schahin SP, Hahn EG, Ficker JH, Lohmann T & Konturek PC (2004*a*). Resistin levels in patients with obstructive sleep apnoea syndrome – the link to subclinical inflammation? *Med Sci Monit* **10**, CR510–CR515.

Harsch IA, Schahin SP, Bruckner K, Radespiel-Troger M, Fuchs FS, Hahn EG, Konturek PC, Lohmann T & Ficker JH (2004*b*). The effect of continuous positive airway pressure treatment on insulin sensitivity in patients with obstructive sleep apnoea syndrome and type 2 diabetes. *Respiration* **71**, 252–259.

Harsch IA, Schahin SP, Radespiel-Troger M, Weintz O, Jahreiss H, Fuchs FS, Wiest GH, Hahn EG, Lohmann T, Konturek PC & Ficker JH (2004*c*). Continuous positive airway pressure treatment rapidly improves insulin sensitivity in patients with obstructive sleep apnea syndrome. *Am J Respir Crit Care Med* **169**, 156–162.

Harsch IA, Wallaschofski H, Koebnick C, Pour Schahin S, Hahn EG, Ficker JH & Lohmann T (2004*d*). Adiponectin in patients with obstructive sleep apnea syndrome: course and physiological relevance. *Respiration* **71**, 580–586.

Hertz R, Magenheim J, Berman I & Bar-Tana J (1998). Fatty acyl-CoA thioesters are ligands of hepatic nuclear factor-4α. *Nature* **392**, 512–516.

Hotamisligil GS, Shargill NS & Spiegelman BM (1993). Adipose expression of tumor necrosis factor-α: direct role in obesity-linked insulin resistance. *Science* **259**, 87–91.

Ip MS, Lam B, Chan LY, Zheng L, Tsang KW, Fung PC & Lam WK (2000*a*). Circulating nitric oxide is suppressed in obstructive sleep apnea and is reversed by nasal continuous positive airway pressure. *Am J Respir Crit Care Med* **162**, 2166–2171.

Ip MS, Lam KS, Ho C, Tsang KW & Lam W (2000*b*). Serum leptin and vascular risk factors in obstructive sleep apnea. *Chest* **118**, 580–586.

Ip MS, Lam B, Ng MM, Lam WK, Tsang KW & Lam KS (2002). Obstructive sleep apnea is independently associated with insulin resistance. *Am J Respir Crit Care Med* **165**, 670–676.

Karlsson B, Knutsson A & Lindahl B (2001). Is there an association between shift work and having a metabolic syndrome? Results from a population based study of 27485 people. *Occup Environ Med* **58**, 747–752.

Karlsson BH, Knutsson AK, Lindahl BO & Alfredsson LS (2003). Metabolic disturbances in male workers with rotating three-shift work. Results of the WOLF study. *Int Arch Occup Environ Health* **76**, 424–430.

Kato M, Phillips BG, Sigurdsson G, Narkiewicz K, Pesek CA & Somers VK (2000*a*). Effects of sleep deprivation on neural circulatory control. *Hypertension* **35**, 1173–1175.

Kato M, Roberts-Thomson P, Phillips BG, Haynes WG, Winnicki M, Accurso V & Somers VK (2000*b*). Impairment of endothelium-dependent vasodilation of resistance vessels in patients with obstructive sleep apnea. *Circulation* **102**, 2607–2610.

Kitamura T, Onishi K, Dohi K, Okinaka T, Ito M, Isaka N & Nakano T (2002). Circadian rhythm of blood pressure is transformed from a dipper to a non-dipper pattern in shift workers with hypertension. *J Hum Hypertens* **16**, 193–197.

Kjeldsen SE, Rostrup M, Moan A, Mundal HH, Gjesdal K & Eide IK (1992). The sympathetic nervous system may modulate the metabolic cardiovascular syndrome in essential hypertension. *J Cardiovasc Pharmacol* **20** (Suppl. 8), S32–S39.

Kruszynska YT, Worrall DS, Ofrecio J, Frias JP, Macaraeg G & Olefsky JM (2002). Fatty acid-induced insulin resistance: decreased muscle PI3K activation but unchanged Akt phosphorylation. *J Clin Endocrinol Metab* **87**, 226–234.

Li J, Grigoryev DN, Ye SQ, Thorne L, Schwartz AR, Smith PL, O'Donnell CP & Polotsky VY (2005*a*). Chronic intermittent hypoxia upregulates genes of lipid biosynthesis in obese mice. *J Appl Physiol* **99**, 1643–1648.

Li J, Thorne LN, Punjabi NM, Sun CK, Schwartz AR, Smith PL, Marino RL, Rodriguez A, Hubbard WC, O'Donnell CP & Polotsky VY (2005*b*). Intermittent hypoxia induces hyperlipidemia in lean mice. *Circ Res* **97**, 698–706.

Lusardi P, Mugellini A, Preti P, Zoppi A, Derosa G & Fogari R (1996). Effects of a restricted sleep regimen on ambulatory blood pressure monitoring in normotensive subjects. *Am J Hypertens* **9**, 503–505.

Maddux BA, See W, Lawrence JC Jr, Goldfine AL, Goldfine ID & Evans JL (2001). Protection against oxidative stress-induced insulin resistance in rat L6 muscle cells by mircomolar concentrations of α-lipoic acid. *Diabetes* **50**, 404–410.

Makino S, Handa H, Suzukawa K, Fujiwara M, Nakamura M, Muraoka S, Takasago I, Tanaka Y, Hashimoto K & Sugimoto T (2006). Obstructive sleep apnoea syndrome, plasma adiponectin levels, and insulin resistance. *Clin Endocrinol (Oxf)* **64**, 12–19.

Matsuoka T, Kajimoto Y, Watada H, Kaneto H, Kishimoto M, Umayahara Y, Fujitani Y, Kamada T, Kawamori R & Yamasaki Y (1997). Glycation-dependent, reactive oxygen species-mediated suppression of the insulin gene promoter activity in HIT cells. *J Clin Invest* **99**, 144–150.

Meade TW, Chakrabarti R, Haines AP, North WR & Stirling Y (1979). Characteristics affecting fibrinolytic activity and plasma fibrinogen concentrations. *Br Med J* **1**, 153–156.

Meier-Ewert HK, Ridker PM, Rifai N, Regan MM, Price NJ, Dinges DF & Mullington JM (2004). Effect of sleep loss on C-reactive protein, an inflammatory marker of cardiovascular risk. *J Am Coll Cardiol* **43**, 678–683.

Minoguchi K, Tazaki T, Yokoe T, Minoguchi H, Watanabe Y, Yamamoto M & Adachi M (2004). Elevated production of tumor necrosis factor-α by monocytes in patients with obstructive sleep apnea syndrome. *Chest* **126**, 1473–1479.

Nagaya T, Yoshida H, Takahashi H & Kawai M (2002). Markers of insulin resistance in day and shift workers aged 30–59 years. *Int Arch Occup Environ Health* **75**, 562–568.

Narkiewicz K, Pesek CA, Kato M, Phillips BG, Davison DE & Somers VK (1998*a*). Baroreflex control of sympathetic nerve activity and heart rate in obstructive sleep apnea. *Hypertension* **32**, 1039–1043.

Narkiewicz K, van de Borne PJ, Montano N, Dyken ME, Phillips BG & Somers VK (1998*b*). Contribution of tonic chemoreflex activation to sympathetic activity and blood pressure in patients with obstructive sleep apnea. *Circulation* **97**, 943–945.

Narkiewicz K, van de Borne PJ, Pesek CA, Dyken ME, Montano N & Somers VK (1999). Selective potentiation of peripheral chemoreflex sensitivity in obstructive sleep apnea. *Circulation* **99**, 1183–1189.

Newman AB, Nieto FJ, Guidry U, Lind BK, Redline S, Pickering TG & Quan SF (2001). Relation of sleep-disordered breathing to cardiovascular disease risk factors: the Sleep Heart Health Study. *Am J Epidemiol* **154**, 50–59.

Ogawa Y, Kanbayashi T, Saito Y, Takahashi Y, Kitajima T, Takahashi K, Hishikawa Y & Shimizu T (2003). Total sleep deprivation elevates blood pressure through arterial baroreflex resetting: a study with microneurographic technique. *Sleep* **26**, 986–989.

Ohga E, Nagase T, Tomita T, Teramoto S, Matsuse T, Katayama H & Ouchi Y (1999). Increased levels of circulating ICAM-1, VCAM-1, and L-selectin in obstructive sleep apnea syndrome. *J Appl Physiol* **87**, 10–14.

Ohga E, Tomita T, Wada H, Yamamoto H, Nagase T & Ouchi Y (2003). Effects of obstructive sleep apnea on circulating ICAM-1, IL-8, and MCP-1. *J Appl Physiol* **94**, 179–184.

Ohike Y, Kozaki K, Iijima K, Eto M, Kojima T, Ohga E, Santa T, Imai K, Hashimoto M, Yoshizumi M & Ouchi Y (2005). Amelioration of vascular endothelial dysfunction in obstructive sleep apnea syndrome by nasal continuous positive airway pressure – possible involvement of nitric oxide and asymmetric NG, NG-dimethylarginine. *Circ J* **69**, 221–226.

Peppard PE, Young T, Palta M, Dempsey J & Skatrud J (2000*a*). Longitudinal study of moderate weight change and sleep-disordered breathing. *JAMA* **284**, 3015–3021.

Peppard PE, Young T, Palta M & Skatrud J (2000*b*). Prospective study of the association between sleep-disordered breathing and hypertension. *N Engl J Med* **342**, 1378–1384.

Phillips BG, Hisel TM, Kato M, Pesek CA, Dyken ME, Narkiewicz K & Somers VK (1999*a*). Recent weight gain in patients with newly diagnosed obstructive sleep apnea. *J Hypertens* **17**, 1297–1300.

Phillips BG, Kato M, Narkiewicz K, Choe I & Somers VK (2000). Increases in leptin levels, sympathetic drive, and weight gain in obstructive sleep apnea. *Am J Physiol Heart Circ Physiol* **279**, H234–H237.

Phillips BG, Narkiewicz K, Pesek CA, Haynes WG, Dyken ME & Somers VK (1999*b*). Effects of obstructive sleep apnea on endothelin-1 and blood pressure. *J Hypertens* **17**, 61–66.

Piemonti L, Calori G, Mercalli A, Lattuada G, Monti P, Garancini MP, Costantino F, Ruotolo G, Luzi L & Perseghin G (2003). Fasting plasma leptin, tumor necrosis factor-α receptor 2, and monocyte chemoattracting protein 1 concentration in a population of glucose-tolerant and glucose-intolerant women: impact on cardiovascular mortality. *Diabetes Care* **26**, 2883–2889.

Polotsky VY, Li J, Punjabi NM, Rubin AE, Smith PL, Schwartz AR & O'Donnell CP (2003). Intermittent hypoxia increases insulin resistance in genetically obese mice. *J Physiol* **552**, 253–264.

Polotsky VY, Wilson JA, Haines AS, Scharf MT, Soutiere SE, Tankersley CG, Smith PL, Schwartz AR & O'Donnell CP (2001). The impact of insulin-dependent diabetes on ventilatory control in the mouse. *Am J Respir Crit Care Med* **163**, 624–632.

Punjabi NM, Ahmed MM, Polotsky VY, Beamer BA & O'Donnell CP (2003). Sleep-disordered breathing, glucose intolerance, and insulin resistance. *Respir Physiol Neurobiol* **136**, 167–178.

Punjabi NM, Sorkin JD, Katzel LI, Goldberg AP, Schwartz AR & Smith PL (2002). Sleep-disordered breathing and insulin resistance in middle-aged and overweight men. *Am J Respir Crit Care Med* **165**, 677–682.

Rajala MW, Obici S, Scherer PE & Rossetti L (2003). Adipose-derived resistin and gut-derived resistin-like molecule-β selectively impair insulin action on glucose production. *J Clin Invest* **111**, 225–230.

Ramadan W, Petitjean M, Loos N, Geloen A, Vardon G, Delanaud S, Gros F & Dewasmes G (2006). Effect of high-fat diet and metformin treatment on ventilation and sleep apnea in non-obese rats. *Respir Physiol Neurobiol* **150**, 52–65.

Ramanathan L, Gulyani S, Nienhuis R & Siegel JM (2002). Sleep deprivation decreases superoxide dismutase activity in rat hippocampus and brainstem. *Neuroreport* **13**, 1387–1390.

Reaven GM (2006). The metabolic syndrome: is this diagnosis necessary? *Am J Clin Nutr* **83**, 1237–1247.

Rebrin K, Steil GM, Mittelman SD & Bergman RN (1996). Causal linkage between insulin suppression of lipolysis and suppression of liver glucose output in dogs. *J Clin Invest* **98**, 741–749.

Robinson GV, Pepperell JC, Segal HC, Davies RJ & Stradling JR (2004). Circulating cardiovascular risk factors in obstructive sleep apnoea: data from randomised controlled trials. *Thorax* **59**, 777–782.

Rudich A, Tirosh A, Potashnik R, Hemi R, Kanety H & Bashan N (1998). Prolonged oxidative stress impairs insulin-induced GLUT4 translocation in 3T3-L1 adipocytes. *Diabetes* **47**, 1562–1569.

Saarelainen S, Seppala E, Laasonen K & Hasan J (1997). Circulating endothelin-1 in obstructive sleep apnea. *Endothelium* **5**, 115–118.

Sanner BM, Konermann M, Tepel M, Groetz J, Mummenhoff C & Zidek W (2000). Platelet function in patients with obstructive sleep apnoea syndrome. *Eur Respir J* **16**, 648–652.

Sartipy P & Loskutoff DJ (2003). Monocyte chemoattractant protein 1 in obesity and insulin resistance. *Proc Natl Acad Sci U S A* **100**, 7265–7270.

Schafer H, Pauleit D, Sudhop T, Gouni-Berthold I, Ewig S & Berthold HK (2002). Body fat distribution, serum leptin, and cardiovascular risk factors in men with obstructive sleep apnea. *Chest* **122**, 829–839.

Schulz R, Mahmoudi S, Hattar K, Sibelius U, Olschewski H, Mayer K, Seeger W & Grimminger F (2000*a*). Enhanced release of superoxide from polymorphonuclear neutrophils in obstructive sleep apnea. Impact of continuous positive airway pressure therapy. *Am J Respir Crit Care Med* **162**, 566–570.

Schulz R, Schmidt D, Blum A, Lopes-Ribeiro X, Lucke C, Mayer K, Olschewski H, Seeger W & Grimminger F (2000*b*). Decreased plasma levels of nitric oxide derivatives in obstructive sleep apnoea: response to CPAP therapy. *Thorax* **55**, 1046–1051.

Segal KR, Landt M & Klein S (1996). Relationship between insulin sensitivity and plasma leptin concentration in lean and obese men. *Diabetes* **45**, 988–991.

Sekine M, Yamagami T, Handa K, Saito T, Nanri S, Kawaminami K, Tokui N, Yoshida K & Kagamimori S (2002). A dose–response relationship between short sleeping hours and childhood obesity: results of the Toyama Birth Cohort Study. *Child Care Health Dev* **28**, 163–170.

Shamsuzzaman AS, Winnicki M, Lanfranchi P, Wolk R, Kara T, Accurso V & Somers VK (2002). Elevated C-reactive protein in patients with obstructive sleep apnea. *Circulation* **105**, 2462–2464.

Sharifian A, Farahani S, Pasalar P, Gharavi M & Aminian O (2005). Shift work as an oxidative stressor. *J Circadian Rhythms* **3**, 15.

Shearer WT, Reuben JM, Mullington JM, Price NJ, Lee BN, Smith EO, Szuba MP, Van Dongen HP & Dinges DF (2001). Soluble TNF-α receptor 1 and IL-6 plasma levels in humans subjected to the sleep deprivation model of spaceflight. *J Allergy Clin Immunol* **107**, 165–170.

Shigeta H, Shigeta M, Nakazawa A, Nakamura N & Yoshikawa T (2001). Lifestyle, obesity, and insulin resistance. *Diabetes Care* **24**, 608.

Shinohara E, Kihara S, Yamashita S, Yamane M, Nishida M, Arai T, Kotani K, Nakamura T, Takemura K & Matsuzawa Y (1997). Visceral fat accumulation as an important risk factor for obstructive sleep apnoea syndrome in obese subjects. *J Intern Med* **241**, 11–18.

Simeoni E, Hoffmann MM, Winkelmann BR, Ruiz J, Fleury S, Boehm BO, Marz W & Vassalli G (2004). Association between the A-2518G polymorphism in the monocyte chemoattractant protein-1 gene and insulin resistance and Type 2 diabetes mellitus. *Diabetologia* **47**, 1574–1580.

Somers VK, Dyken ME, Clary MP & Abboud FM (1995). Sympathetic neural mechanisms in obstructive sleep apnea. *J Clin Invest* **96**, 1897–1904.

Spicuzza L, Bernardi L, Balsamo R, Ciancio N, Polosa R & Di Maria G (2006). Effect of treatment with nasal continuous positive airway pressure on ventilatory response to hypoxia and hypercapnia in patients with sleep apnea syndrome. *Chest* **130**, 774–779.

Spiegel K, Leproult R, Colecchia EF, L'Hermite-Baleriaux M, Nie Z, Copinschi G & Van Cauter E (2000). Adaptation of the 24-h growth hormone profile to a state of sleep debt. *Am J Physiol Regul Integr Comp Physiol* **279**, R874–R883.

Spiegel K, Leproult R & Van Cauter E (1999). Impact of sleep debt on metabolic and endocrine function. *Lancet* **354**, 1435–1439.

Spiegel K, Tasali E, Penev P & Van Cauter E (2004). Brief communication: Sleep curtailment in healthy young men is associated with decreased leptin levels, elevated ghrelin levels, and increased hunger and appetite. *Ann Intern Med* **141**, 846–850.

Stefan N, Stumvoll M, Vozarova B, Weyer C, Funahashi T, Matsuzawa Y, Bogardus C & Tataranni PA (2003). Plasma adiponectin and endogenous glucose production in humans. *Diabetes Care* **26**, 3315–3319.

Stefan N, Vozarova B, Funahashi T, Matsuzawa Y, Weyer C, Lindsay RS, Youngren JF, Havel PJ, Pratley RE, Bogardus C & Tataranni PA (2002). Plasma adiponectin concentration is associated with skeletal muscle insulin receptor tyrosine phosphorylation, and low plasma concentration precedes a decrease in whole-body insulin sensitivity in humans. *Diabetes* **51**, 1884–1888.

Steppan CM, Bailey ST, Bhat S, Brown EJ, Banerjee RR, Wright CM, Patel HR, Ahima RS & Lazar MA (2001). The hormone resistin links obesity to diabetes. *Nature* **409**, 307–312.

Svatikova A, Wolk R, Lerman LO, Juncos LA, Greene EL, McConnell JP & Somers VK (2005). Oxidative stress in obstructive sleep apnoea. *Eur Heart J* **26**, 2435–2439.

Svatikova A, Wolk R, Shamsuzzaman AS, Kara T, Olson EJ & Somers VK (2003). Serum amyloid A in obstructive sleep apnea. *Circulation* **108**, 1451–1454.

Tan KC, Chow WS, Lam JC, Lam B, Wong WK, Tam S & Ip MS (2006). HDL dysfunction in obstructive sleep apnea. *Atherosclerosis* **184**, 377–382.

Tassone F, Lanfranco F, Gianotti L, Pivetti S, Navone F, Rossetto R, Grottoli S, Gai V, Ghigo E & Maccario M (2003). Obstructive sleep apnoea syndrome impairs insulin sensitivity independently of anthropometric variables. *Clin Endocrinol (Oxf)* **59**, 374–379.

Tochikubo O, Ikeda A, Miyajima E & Ishii M (1996). Effects of insufficient sleep on blood pressure monitored by a new multibiomedical recorder. *Hypertension* **27**, 1318–1324.

Uysal KT, Wiesbrock SM, Marino MW & Hotamisligil GS (1997). Protection from obesity-induced insulin resistance in mice lacking TNF-α function. *Nature* **389**, 610–614.

VanHelder T, Symons JD & Radomski MW (1993). Effects of sleep deprivation and exercise on glucose tolerance. *Aviat Space Environ Med* **64**, 487–492.

Vettor R, De Pergola G, Pagano C, Englaro P, Laudadio E, Giorgino F, Blum WF, Giorgino R & Federspil G (1997). Gender differences in serum leptin in obese people: relationships with testosterone, body fat distribution and insulin sensitivity. *Eur J Clin Invest* **27**, 1016–1024.

Vgontzas AN, Bixler EO & Chrousos GP (2003). Metabolic disturbances in obesity versus sleep apnoea: the importance of visceral obesity and insulin resistance. *J Intern Med* **254**, 32–44.

Vgontzas AN, Bixler EO & Chrousos GP (2005). Sleep apnea is a manifestation of the metabolic syndrome. *Sleep Med Rev* **9**, 211–224.

Vgontzas AN, Papanicolaou DA, Bixler EO, Hopper K, Lotsikas A, Lin HM, Kales A & Chrousos GP (2000). Sleep apnea and daytime sleepiness and fatigue: relation to visceral obesity, insulin resistance, and hypercytokinemia. *J Clin Endocrinol Metab* **85**, 1151–1158.

Vgontzas AN, Papanicolaou DA, Bixler EO, Kales A, Tyson K & Chrousos GP (1997). Elevation of plasma cytokines in disorders of excessive daytime sleepiness: role of sleep disturbance and obesity. *J Clin Endocrinol Metab* **82**, 1313–1316.

Vgontzas AN, Papanicolaou DA, Bixler EO, Lotsikas A, Zachman K, Kales A, Prolo P, Wong ML, Licinio J, Gold PW, Hermida RC, Mastorakos G & Chrousos GP (1999). Circadian interleukin-6 secretion and quantity and depth of sleep. *J Clin Endocrinol Metab* **84**, 2603–2607.

Vgontzas AN, Zoumakis E, Lin HM, Bixler EO, Trakada G & Chrousos GP (2004). Marked decrease in sleepiness in patients with sleep apnea by etanercept, a tumor necrosis factor-α antagonist. *J Clin Endocrinol Metab* **89**, 4409–4413.

Vorona RD, Winn MP, Babineau TW, Eng BP, Feldman HR & Ware JC (2005). Overweight and obese patients in a primary care population report less sleep than patients with a normal body mass index. *Arch Intern Med* **165**, 25–30.

Wessendorf TE, Thilmann AF, Wang YM, Schreiber A, Konietzko N & Teschler H (2000). Fibrinogen levels and obstructive sleep apnea in ischemic stroke. *Am J Respir Crit Care Med* **162**, 2039–2042.

Weyer C, Funahashi T, Tanaka S, Hotta K, Matsuzawa Y, Pratley RE & Tataranni PA (2001). Hypoadiponectinemia in obesity and type 2 diabetes: close association with insulin resistance and hyperinsulinemia. *J Clin Endocrinol Metab* **86**, 1930–1935.

Whitehead JP, Richards AA, Hickman IJ, Macdonald GA & Prins JB (2006). Adiponectin – a key adipokine in the metabolic syndrome. *Diabetes Obes Metab* **8**, 264–280.

Wilcox I, McNamara SG, Collins FL, Grunstein RR & Sullivan CE (1998). 'Syndrome Z': the interaction of sleep apnoea, vascular risk factors and heart disease. *Thorax* **53** (Suppl. 3), S25–S28.

Wolk R, Gami AS, Garcia-Touchard A & Somers VK (2005*a*). Sleep and cardiovascular disease. *Curr Probl Cardiol* **30**, 625–662.

Wolk R, Shamsuzzaman AS & Somers VK (2003). Obesity, sleep apnea, and hypertension. *Hypertension* **42**, 1067–1074.

Wolk R, Svatikova A, Nelson CA, Gami AS, Govender K, Winnicki M & Somers VK (2005*b*). Plasma levels of adiponectin, a novel adipocyte-derived hormone, in sleep apnea. *Obes Res* **13**, 186–190.

Yaggi HK, Araujo AB & McKinlay JB (2006). Sleep duration as a risk factor for the development of type 2 diabetes. *Diabetes Care* **29**, 657–661.

Yamasaki F, Schwartz JE, Gerber LM, Warren K & Pickering TG (1998). Impact of shift work and race/ethnicity on the diurnal rhythm of blood pressure and catecholamines. *Hypertension* **32**, 417–423.

Yokoe T, Minoguchi K, Matsuo H, Oda N, Minoguchi H, Yoshino G, Hirano T & Adachi M (2003). Elevated levels of C-reactive protein and interleukin-6 in patients with obstructive sleep apnea syndrome are decreased by nasal continuous positive airway pressure. *Circulation* **107**, 1129–1134.

Young T, Palta M, Dempsey J, Skatrud J, Weber S & Badr S (1993). The occurrence of sleep-disordered breathing among middle-aged adults. *N Engl J Med* **328**, 1230–1235.

Young T, Shahar E, Nieto FJ, Redline S, Newman AB, Gottlieb DJ, Walsleben JA, Finn L, Enright P & Samet JM (2002). Predictors of sleep-disordered breathing in community-dwelling adults: the Sleep Heart Health Study. *Arch Intern Med* **162**, 893–900.

Zhang XL, Yin KS, Wang H & Su S (2006). Serum adiponectin levels in adult male patients with obstructive sleep apnea hypopnea syndrome. *Respiration* **73**, 73–77.

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