Published in final edited form as:
Obes Rev. 2009 November ; 10(0 2): 37–45. doi:10.1111/j.1467-789X.2009.00663.x.

Epidemiological evidence for the links between sleep, circadian rhythms and metabolism

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Summary

Epidemiological data reveal parallel trends of decreasing sleep duration and increases in metabolic disorders such as obesity, diabetes and hypertension. There is growing evidence that these trends are mechanistically related. The seasonal expression of the thrifty genotype provides a conceptual framework to connect circadian and circannual rhythms, sleep and metabolism. Experimental studies have shown sleep deprivation to decrease leptin, increase ghrelin, increase appetite, compromise insulin sensitivity and raise blood pressure. Habitually short sleep durations could lead to insulin resistance by increasing sympathetic nervous system activity, raising evening cortisol levels and decreasing cerebral glucose utilization that over time could compromise β-cell function and lead to diabetes. Prolonged short sleep durations could lead to hypertension through raised 24-h blood pressure and increased salt retention resulting in structural adaptations and the entrainment of the cardiovascular system to operate at an elevated pressure equilibrium. Cross-sectional and longitudinal epidemiological studies have shown associations between short sleep duration and obesity, diabetes and hypertension. If metabolic changes resulting from sleep restriction function to increase body weight, insulin resistance and blood pressure then interventions designed to increase the amount and improve the quality of sleep could serve as treatments and as primary preventative measures for metabolic disorders.

Keywords

Circadian rhythms; epidemiology; metabolism; sleep

Introduction

The Pennington Biomedical Research Center convened the symposium ‘Circadian Biology and Sleep: Missing Links in Obesity and Metabolism’ to develop a bridge linking the field of metabolism and obesity research to that of circadian biology and sleep. At first glance these fields seem unrelated, but the relationships between them come into clearer focus when viewed from an evolutionary perspective. Circadian and metabolic regulatory systems

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Conflict of Interest Statement
None.

evolved to be functional and adaptive during a time when the lifestyles and the environmental exposures of our hunter-gatherer ancestors were quite different from today. The circadian rhythms of our early ancestors were more closely synchronized to the rising and setting of the sun, so they were likely to have obtained more sleep. Today we have artificial lights to extend our active phases and distractions, such as longer work days and commuting times, increases in shift work and an increase in the use of television, personal computers and the internet, which curtail our sleep. Hunter-gatherers ate foods that were available seasonally whereas today we can eat virtually any food year-round. The thrifty genotype is hypothesized to have evolved through natural selection over millions of years so as to be expressed during seasons of high food availability when induction of high blood insulin, insulin resistance and glucose intolerance would facilitate increased fat deposition, to adaptively prepare for subsequent seasons of relative food scarcity (1). The central biological clock or suprachiasmatic nucleus (SCN) evolved to synchronize activity, consumption, and rest to the circadian and circannual cycles using hormones and the autonomic nervous system. To generate and organize autonomic rhythms, the SCN requires repeated metabolic cues from light exposure, sleep, activity and nutrient intake. Reliable environmental cues of the impending seasons for our nomadic ancestors would have been the length of the daily photoperiod that changed in a precise and predictable fashion throughout the year and the intake of seasonally available nutrients. Longer photoperiods in summer would have corresponded to shorter sleep durations and higher availability of food and simple sugars. Short sleep durations could therefore help trigger the expression of the thrifty genotype to induce metabolic changes to increase caloric intake and fat deposition. Today we can have year-round short sleep durations with electric lights and year-round availability of highly palatable foods and simple sugars, which together facilitate year-round fat accumulation. We are also experiencing parallel trends of increasing body mass index, increasing prevalence of hypertension and diabetes and decreasing average sleep duration. The idea of the seasonal expression of the thrifty genotype is consistent with metabolic changes resulting from chronically short sleep durations leading to diseases associated with the metabolic syndrome such as obesity, diabetes and hypertension. What evolved to be adaptive for the environments faced by our ancestors can be maladaptive for the strikingly different environment that humans face today.

The SCN responds to external and internal zeitgebers such as light exposure, sleep, activity and feeding to entrain autonomic rhythms to the external environment. It is hypothesized that dramatic alterations in the timing and duration of these zeitgebers over the last century in modern industrialized society have caused SCN-mediated rhythms to become metabolically flattened in susceptible individuals, disrupting ‘normal’ autonomic balance. A disturbed SCN could cause or exacerbate diseases associated with the metabolic syndrome through the paradoxical concurrent dominance of the parasympathetic and sympathetic systems in different metabolic organs (2). The SCN has been shown to connect directly via the autonomic nervous system to each of the metabolic organs that malfunction in diabetes: pancreas, liver and adipose tissue (3–5). Hypertension is characterized by a disturbance in the circadian rhythmicity of many physiological variables, such as a shifting of the daily blood pressure profile to higher values, an increased prevalence of the non-dipping pattern, increased blood pressure variability (6) and disturbances in the diurnal rhythm of cardiac

output (7). The chronic exposure to sleep parameters such as timing and duration that are different from, and inconsistent with, the environmental parameters in which the SCN evolved over millions of years to be adaptive, could therefore, function as risk factors for diseases associated with the metabolic syndrome. Risk factors increase the risk for disease by working in unison with the presence or absence of other risk and protective factors through multiple possible causal pathways to the development of disease.

There is debate about what sleep durations should be considered ‘natural’ or ‘normal’ in humans. One way to address this issue is to consider the circadian rhythms of early humans, which varied by season and by their distance from the equator. The length of the daily photoperiod at the equator is 12 h. As the distance from the equator increases, the length of the longest light exposure increases in summer to an extreme of 24 h at the poles and decreases in winter to an extreme of continuous darkness. Early humans who lived away from the equator would have been exposed to both shortened and lengthened daily photoperiods on a circannual basis, inducing shorter sleep durations in summer and longer sleep durations in winter. Periodic exposure to photoperiods of longer or shorter than 12 h would have been the norm, but prolonged or year-round exposure to either of these extremes would have been anomalous. The circannual rhythms of humans were likely to have evolved to accommodate these seasonal perturbations in light exposure and resultant changing requirements for activity, feeding and sleep. Ethnic groups that evolved at varying distances from the equator have been found to have dissimilar genetic polymorphisms that mediate the circadian pacemaker, potentially affecting adaptability to varying durations of daylight (8). Because the circadian rhythms of early humans were more closely synchronized to the rising and setting of the sun, their sleep durations were likely to have been greater than 8 h during a majority of the year. In a study with healthy subjects, exposure to a cycle of 10 h of light and 14 h of darkness with ample time in bed without distractions resulted in a natural tendency to sleep longer than 8 h (9).

Obesity

Results from experimental studies suggest a mechanistic link between inadequate sleep and increasing body weight. Experimental sleep deprivation studies conducted at the University of Chicago with normal, healthy, young adults found sleep deprivation to decrease leptin levels, increase ghrelin levels and elevate hunger and appetite (10). Subjects were found to particularly crave sweets, starch and salty snacks. A recent study has shown that sleep curtailment is accompanied by increased intake of calories from snacks with higher carbohydrate content (11). Two population-based studies with adults have also shown associations between inadequate sleep and alterations in leptin and/or ghrelin indicative of increased appetite (12,13). Short sleep duration has also been theorized to decrease energy expenditure (14) by impacting non-exercise activity thermogenesis (15) and by dropping core body temperature (16). Sleep deprivation has been shown to decrease glucose tolerance and compromise insulin sensitivity (17).

Short sleep duration could also lead to weight gain and obesity by increasing the time available to eat and by making maintenance of a healthy lifestyle more difficult. Inadequate

sleep has been shown to be associated with feeling tired, stressed and pessimistic (18), emotional states that could lessen one's resolve to follow dietary or exercise regimens.

Numerous cross-sectional and longitudinal epidemiological studies have revealed associations between chronic sleep restriction and increased body mass index in children, adolescents and adults (19–21). The associations between short sleep duration and body weight are strongest in children. With increasing age the associations become weaker, possibly because of higher sleep requirements in children, a lower likelihood of survival into later years for those suffering from obesity and age-related sleep changes with increased difficulties initiating and maintaining sleep. Individuals who engage in shift work have been shown to be at increased risk for the metabolic syndrome, implicating both the timing of sleep and sleep duration in the association (22). One of the primary effects of circadian desynchrony from shift work is a reduction in total sleep time, so the most parsimonious explanation for the apparent impact of shift work on metabolism-related outcomes is the effect of circadian desynchrony on sleep duration rather than direct effects from perturbations in the circadian system.

Diabetes

Experimental studies have shown sleep restriction to decrease glucose tolerance and compromise insulin sensitivity. The restriction of sleep in normal subjects resulted in insulin responses to hyperglycaemia characteristic of insulin resistance and a prediabetic metabolic state (23). Healthy men whose sleep was restricted to 4 h per night for six nights experienced a 30% reduction in insulin response to glucose (17). Short sleepers have been shown to have lower glucose concentrations after an oral glucose tolerance test (24). Lower glycaemia after an oral glucose challenge has been shown to be correlated with weight gain over time (25) and to act as a partial mediator in the relationship between sleep duration and type 2 diabetes (26). The relationship between diabetes and sleep disorders is increasingly being recognized as bidirectional with reduced sleep duration or quality favouring the development of type 2 diabetes and obesity and diabetes contributing towards sleep disorders (27).

Although the mechanisms by which sleep duration and diabetes risk are related are not fully understood, a number of pathways have been theorized by which habitually short sleep durations could adversely impact glucose tolerance (28). First, sleep deprivation has been shown to increase sympathetic nervous system activity, as evidenced by increased urinary and plasma catecholamine levels (29,30). Second, sleep deprivation has been shown to decrease cerebral glucose utilization in positron emission tomography scans (17). Because the brain is a major source of non-insulin-dependent glucose utilization, decreased brain glucose uptake may result in higher circulating glucose concentrations that over time could facilitate the development of insulin resistance (28). Third, acute sleep deprivation has been shown to raise evening levels of cortisol, an insulin antagonist, which under conditions of chronic sleep restriction could, compromise insulin sensitivity in peripheral sites (31). The increased burden on the pancreas from insulin resistance can compromise β-cell function over time and lead to type 2 diabetes.

Table 1 shows longitudinal and cross-sectional studies on the relationships between sleep duration and diabetes incidence and prevalence (24,26,32–39). The majority of these studies have shown *U*-shaped relationships, with both short and long sleep durations being associated with diabetes incidence and prevalence. Beihl *et al*. found both short and long sleep durations to be associated with diabetes incidence in unadjusted analyses, but the relationship between long sleep duration and diabetes incidence was no longer significant after controlling for covariates (33). The study by Bjorkelund *et al*. showed no relationship between sleep duration and diabetes incidence, but this study had a follow-up period of 32 years, and initial baseline sleep duration was unlikely to have been representative of the subjects' cumulative sleep loss over that many years (34). The study by Mallon *et al*. found short sleep durations to be associated with diabetes incidence only in men, and long sleep durations to be associated with diabetes incidence only in women, although the association in women was not statistically significant, possibly because of a lack of statistical power from having few female subjects who reported sleeping for long durations (36). Shift work that affects both the timing and duration of sleep has also been found to be associated with the incidence of diabetes (40).

The association between long sleep duration and diabetes constitutes a conundrum as no published laboratory or epidemiologic studies have demonstrated a possible mechanism by which long sleep duration might exacerbate morbidity (41). The sleep inducing and metabolic effects of pro-inflammatory cytokines represents one plausible explanation for the association (38). Pro-inflammatory cytokines have been shown to negatively impact both glucose homeostasis and β-cell function (42) and have been found to be elevated in obesity and in conditions in which the primary pathogenic mechanism is insulin resistance (43). Pro-inflammatory cytokines impact sleepiness and fatigue and are believed to play key roles in sleep pathologies, such as sleep apnoea (44). The sleep inducing effects of pro-inflammatory cytokines are presumed to be an evolutionary adaptation to promote rest and recovery from illness. Long sleep duration is therefore unlikely to be a cause of diabetes, but rather a consequence of diabetes and other conditions associated with chronic inflammation.

Hypertension

There is growing evidence that prolonged exposure to short sleep durations could contribute to the development and maintenance of hypertension and its vascular and cardiac complications. Experimental studies with both normotensive (30,45) and hypertensive (46) subjects show that sleep restriction significantly increases blood pressure and sympathetic nervous system activity. In two studies, on days following nights of sleep deprivation, significant increases in blood pressure were accompanied by increases in the urinary excretion of noradrenaline, indicative of increased sympathetic nervous system activity (30,46). These findings have led to the hypothesis that the mechanism by which sleep deprivation raises blood pressure is through increased synthesis of catecholamines via the activation of superior centres (46). Blood pressure and heart rate follow a diurnal pattern with the lowest values occurring during sleep. Blood pressure gradually falls with sleep onset and then remains an average of 10–20% below waking level until the moment of awakening, when it promptly rises (47). Shorter sleep durations therefore function to raise average blood pressure and heart rate. Less sleep also results in longer exposure to elevated

sympathetic nervous system activity and to waking physical and psychosocial stressors. Exposure to stress has been shown to promote salt appetite and suppress renal salt-fluid excretion (6). Long-term exposure to increased total 24-h haemodynamic load associated with short sleep durations could lead to the entrainment of the cardiovascular system to operate at an elevated pressure equilibrium through structural adaptations, such as arterial and left ventricular hypertrophic remodelling (48).

Table 2 shows longitudinal and cross-sectional studies on the relationships between sleep duration and hypertension incidence and prevalence (49–58). Short sleep duration has been shown in longitudinal studies to be associated with hypertension incidence in middle-aged subjects (49–51) and significantly higher systolic and diastolic blood pressure in adults (51) and young adults (52). In cross-sectional studies with middle-aged subjects, two studies revealed significant associations between short sleep duration and hypertension prevalence (53,54) while one study found short sleep duration to be associated with higher systolic and diastolic blood pressures (51). One longitudinal study (50) and two cross-sectional studies revealed no relationship between sleep duration and hypertension incidence and prevalence among elderly subjects (56,58).

A number of factors may help explain these differences between younger and older age groups. First, individuals suffering from hypertension and risk factors associated with hypertension such as obesity and diabetes are less likely to survive into their later years. Second, advanced age is associated with changes in sleep architecture characterized by increased difficulties initiating and maintaining sleep (59). Third, sleep-disordered breathing is associated with hypertension in subjects below the age of 60, but not in subjects 60 years of age or older (60). Sympathetic nervous system activation is the mechanism by which sleep-disordered breathing impacts systolic and diastolic hypertension, which is common in middle-aged hypertensive patients. However, no causal link has been identified between sleep-disordered breathing and the isolated systolic hypertension resulting from age-related loss of arterial compliance that accounts for nearly 60% of hypertension in elderly populations (60). Finally, short sleep duration has been shown to be more strongly associated with obesity, a potent risk factor for hypertension, in younger subjects than in older subjects (61,62). The timing of sleep has also been implicated as a risk factor for hypertension, with shift workers being at increased risk for high blood pressure (63,64).

Elevated blood pressure resulting from decreased sleep could also contribute towards the relationship between sleep duration and other cardiovascular diseases. Hypertension is an established risk factor for coronary artery calcification, which is a subclinical predictor of future coronary heart disease events. Longer sleep durations have been found to be significantly associated with reduced calcification incidence (65). In an analysis of data from the Nurses' Health Study, short sleep duration was shown to increase the risk for the incidence of myocardial infarction and fatal cardiovascular disease in women, possibly as a consequence of increased blood pressure (66). In that study, many known risk factors for hypertension were included in the multivariate models, such as body mass index, smoking, exercise level, hypercholesterolemia, alcohol consumption and family history of myocardial infarction. Hypertension and diabetes were then added into multivariate models resulting in

attenuation of the relative risks even after a large proportion of the variability associated with these diseases was likely accounted for by controlling for other risk factors.

Mortality

A *U*-shaped relationship between sleep duration and mortality, with both short and long sleep durations associated with higher mortality, has been called a ubiquitous finding in epidemiologic studies (67). Such results are not surprising for short sleep duration, given the associations between inadequate sleep and diseases associated with the metabolic syndrome, but the association between long sleep duration and mortality is difficult to explain as there is little evidence that sleeping longer than 8 h has adverse health effects (41). The associations found in epidemiological studies between long sleep duration and mortality are likely to be related to the measurement of sleep durations relatively close before death (typically about 10 years) and the fact that the majority of deaths occur in the elderly as the average life expectancy in the developed world is about 75 years. Sleep durations measured closely to the time of death may be influenced by the presence of medical conditions that eventually played a part in the subjects' deaths. The majority of deaths in the developed world are attributable to major cardiovascular diseases, cancers and diabetes. The inflammatory process has been shown to play key roles in the pathogenesis and pathophysiology of cancer (68) and of metabolic disorders such as cardiovascular disease and type 2 diabetes (69,70). The human immune response involves a dynamic and ever-shifting balance between pro-inflammatory and anti-inflammatory cytokines (71). Pro-inflammatory cytokines have been shown to promote sleep, whereas anti-inflammatory cytokines have been shown to inhibit sleep (72,73). The sleep durations of elderly subjects reported at baseline may therefore have been either shortened or lengthened as a result of inflammatory responses to medical conditions – conditions that, over time, ultimately contributed towards their deaths. Long sleep duration is therefore unlikely to contribute towards mortality. It is more likely an epiphenomenal consequence of conditions associated with chronic inflammation and age-related sleep changes (74).

Common limitations in epidemiological studies

Large population-based studies are expensive to conduct and often do not include the most definitive measures of exposures and outcomes. Many of the studies on the relationship between sleep duration and metabolic disorders lack objective and repeated measures of sleep duration, making it difficult to determine the representativeness of baseline sleep measures. Objective measures for sleep duration and sleep quality such as polysomnography, and less expensive methods such as actigraphy, can be cost prohibitive in large studies. Body mass index, which is often used to determine overweight and obesity status in population-based studies, does not necessarily provide accurate estimates of percentage body fat or body composition. Disease outcomes in large studies are often based upon self-reports of physician diagnoses or from hospital admission records. Diabetes and hypertension frequently go undiagnosed, and it is unknown whether individuals with short sleep durations are more or less likely to seek or receive treatment and therefore be diagnosed with these diseases. Diseases associated with the metabolic syndrome are complex with numerous genetic, environmental and behavioural risk and protective factors.

When exploring the relationships between clinical and behavioural exposures and these diseases, it would be ideal to follow subjects over the course of their lives to obtain repeated measures of exposures to gauge their ultimate influence over the life course upon morbidity and mortality. It would also be preferable to have repeated measurements of all potential confounders and mediators of the relationships. Obtaining accurate dietary intake data in large epidemiological studies has been notoriously difficult, and this variable is theorized to be one of the primary mediators between sleep duration and diseases associated with the metabolic syndrome. Sleep restriction has been shown in laboratory studies to increase appetite, with particular cravings for sweet and starchy snacks, but increased appetite does not necessarily result in increased consumption. If consumption does increase, then characteristics of the foods consumed, such as glycaemic index, fibre content and caloric content, can affect the ultimate influence upon weight gain and insulin sensitivity. Future studies on the relationships between sleep duration and metabolic disorders would ideally have long follow-up durations and include repeated and objective measures of sleep-related exposures, disease outcomes and potentially confounding and mediating variables to appropriately assess the influence of sleep length on health over the life course. Epidemiological evidence alone cannot establish the cause–effect relationships between sleep duration and diseases associated with the metabolic syndrome. Previously conducted experimental studies have been brief and have had small sample sizes. Randomized prospective interventional trials could help elucidate the affect of sleep duration on the risks for these diseases. Depriving subjects of sleep for extended periods of time would be unethical, but extending sleep in individuals with short sleep duration and metabolic diseases, although logistically challenging, could help clarify these relationships.

Conclusions

Evidence from epidemiological studies is consistent with hypothesized mechanistic links between circadian biology, sleep and metabolism. The SCN evolved to use cues from light exposure, sleep, activity and nutrient intake to synchronize activity, consumption, and rest to the circadian and circannual cycles. Circadian and metabolic regulatory systems evolved to be functional and adaptive under conditions and environments quite different from those encountered in modern society, and these systems did not evolve to face today’s lifestyle contingencies. Today humans can be exposed to artificial light around the clock and can rely upon modern conveniences to minimize physical activity. Our endogenous opiate systems evolved to reward the consumption of sweet foods that are available only seasonally in nature, but we now have year-round access to highly palatable manufactured foods that combine highly refined sugars with high concentrations of fat. As a result, the endogenous opiate system now paradoxically rewards the consumption of foods that have potentially deleterious health effects. Modern lifestyles are incompatible in many ways with the intrinsic attributes we inherited. The autonomic nervous system up- and down-regulates numerous subsystems in an attempt to meet these contingencies. Imbalances can result from this process to dys-regulate our circadian and metabolic systems, resulting in maladaptive and dysfunctional health outcomes such as obesity, diabetes and hypertension. Given the wide disparities between our current environments and lifestyles and those of our hunter-gatherer ancestors, it is not surprising that a large proportion of us are suffering from these

illnesses. The evidence linking circadian biology and metabolism points to the potential efficacy of interventions that modify our environments and behaviours to be more consistent with those of our ancient ancestors when these systems evolved to be adaptive. Getting adequate sleep is one of these behaviours.

The results from epidemiological studies suggest that chronic sleep restriction could play a significant role in the aetiology of diseases associated with the metabolic syndrome. If metabolic changes resulting from sleep loss function to increase body weight, insulin resistance and blood pressure then interventions designed to increase the amount of, and improve the quality of, sleep could potentially augment the most common behavioural interventions for diseases associated with the metabolic syndrome, i.e. increased physical activity and improved nutrition. These interventions could include educating patients about healthier sleep-hygiene practices and helping them to modify maladaptive sleep habits. Further research is needed to further explicate the biological mechanisms behind these relationships and to determine whether interventions addressing inadequate sleep or poor sleep quality help treat or prevent these disorders.

Acknowledgments

Dr Gangwisch receives funding from the National Institutes of Health/National Heart, Lung, and Blood Institute (1R21HL091443-01A2). Helpful comments for this manuscript from Sanjay R Patel, MD, Assistant Professor, Case Western Reserve University and University Hospital Case Medical Center, Division of Pulmonary, Critical Care and Sleep Medicine are gratefully appreciated.

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Table 1

Longitudinal and cross-sectional studies of the relationship between sleep duration and diabetes

Source	Sample	Follow-up period (years)	Results
Longitudinal studies			
Ayas *et al*. (2003) (32)	70 026 US women, ages 40–65	10	*U*-shaped relationship with symptomatic cases of diabetes incidence
Beihl *et al*. (2009) (33)	900 US women and men, ages 40–69	5	Short sleep associated with diabetes incidence
Bjorkelund *et al*. (2005) (34)	661 Swedish women, ages 38–60	32	No relationship
Chaput *et al*. (2009) (26)	276 Canadian women and men, ages 21–64	14–23	*U*-shaped relationship with diabetes incidence or impaired glucose tolerance
Gangwisch *et al*. (2007) (35)	8 992 US women and men, ages 32–86	8–10	*U*-shaped relationship with diabetes incidence
Mallon *et al*. (2005) (36)	1 187 Swedish women and men, ages 45–65	12	Short sleep with diabetes incidence in men and long sleep in women
Yaggi *et al*. (2006) (37)	1 139 US men, ages 40–70	15–17	*U*-shaped relationship with diabetes incidence
Cross-sectional studies			
Chaput *et al*. (2007) (24)	740 Canadian women and men, ages 21–64	N/A	*U*-shaped relationship with diabetes prevalence
Gottlieb *et al*. (2005) (38)	1 486 US women and men, ages 53–93	N/A	*U*-shaped relationship with diabetes prevalence
Tuomilehto *et al*. (2008) (39)	2 770 Finnish men and women, ages 45–74	N/A	*U*-shaped relationship with diabetes prevalence

N/A, not applicable.

Table 2

Longitudinal and cross-sectional studies of the relationship between sleep duration and hypertension

Source	Sample	Follow-up period (years)	Results
Longitudinal studies			
Cappuccio *et al*. (2007) (49)	3691 English women and men, ages 35–55	7	Short sleep associated with hypertension incidence only in women
Gangwisch *et al*. (2006) (50)	8992 US women and men, ages 32–86	8–10	Short sleep associated with hypertension incidence only in ages 32–59
Knutson *et al*. (2009) (51)	578 US women and men, ages 33–45	5	Short sleep associated with hypertension incidence and adverse changes in systolic and diastolic blood pressure levels
Wells *et al*. (2008) (52)	4452 Brazilian women and men, ages 10–12	11–12	Significantly higher systolic and diastolic blood pressure at follow-up
Cross-sectional studies			
Bjorn *et al*. (2007) (53)	8860 Norwegian women and men, ages 40–45	N/A	Significantly higher systolic blood pressure
Cappuccio *et al*. (2007) (49)	5766 English women and men, ages 35–55	N/A	Short sleep associated with hypertension prevalence only in women
Choi *et al*. (2008) (54)	4222 Korean women and men, ages ≥20	N/A	Short sleep duration associated with hypertension prevalence only in ages <60
Gottlieb *et al*. (2006) (55)	5910 US women and men, ages 40–100	N/A	*U*-shaped relationship with hypertension prevalence
Knutson *et al*. (2009) (51)	578 US women and men, ages 33–45	N/A	Short sleep associated higher systolic and diastolic blood pressure levels
Lima-Costa *et al*. (2008) (56)	1423 Brazilian women and men, mean age 69	N/A	No association between sleep duration and hypertension prevalence
Stang *et al*. (2008) (57)	4766 German women and men, ages 45–74	N/A	Short sleep associated with hypertension prevalence only in women
van den Berg *et al*. (2007) (58)	5058 Netherlander women and men, ages 58–98	N/A	No association between sleep duration and hypertension prevalence

N/A, not applicable.