[Frontiers in Bioscience E4, 2490-2501, June 1, 2012]

Sleep, inflammation and cardiovascular disease

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1. ABSTRACT

In data from prospective cohort studies, self report of insufficient or disturbed sleep is related to increased overall and cardiovascular morbidity. Inflammation is established as a key mechanism in the development of arteriosclerotic heart and vascular disease. Inflammation has been considered a possible link between short sleep and cardiovascular disease and morbidity. Measures of inflammation are increased by experimental sleep deprivation, but in cohort studies a relationship of sleep duration to inflammatory markers is less clear. In these studies the association of self reported short sleep to cardiac morbidity is confounded by many psychological and socioeconomic variables. More studies are needed to explain the link between short sleep duration and cardiac morbidity. Experimental studies of sleep deprivation mimicking habitual shortened sleep over long time intervals, and studies employing sleep extension in habitual short sleepers will allow better characterization of the health benefits of adequate sleep duration. Prospective cohort studies should include objective measures of sleep duration and should to control for the known confounding variables.

2. INTRODUCTION

In the United States and other developed countries the rate of death from cardiovascular disease has declined over the past 3 decades. This is attributed to the evolution of treatments for acute cardiac disease and positive trends in the control of cardiac risk factors (1). The prevalence of cigarette smoking in the United States has decreased by about half since 1965, and average cholesterol level and systolic blood pressure are decreasing, largely due to more widespread pharmacologic treatment of hyperlipidemia and hypertension. However, the prevalence of hypertension, diabetes mellitus, and inadequate levels of physical activity are rising, in part related to a dramatic rise in the prevalence of obesity (2). In contrast, the prevalence of cardiac risk factors (including smoking) and the death rate from cardiovascular disease are increasing in many developing countries.

Short sleep duration has been associated with increased rates of cardiovascular morbidity and mortality. While a significant reduction of average sleep duration has not been shown in the limited data that is available from population surveys (3, 4), there is a widespread perception

that contemporary work- and leisure-schedules encroach on time previously reserved for sleep (5). Inflammation has been considered a plausible mechanism linking cardiac disease to short sleep. The present review will summarize findings of research in human subjects relating sleep duration to measures of inflammation and cardiovascular morbidity and will integrate these with the concept of inflammation as a key mediator of cardiovascular disease.

3. CARDIOVASCULAR DISEASE AND INFLAMMATION

Cardiovascular disease remains the leading cause of death in many developed nations. Research over the past three decades has shown that inflammation plays a key role in the initiation and progression of cardiovascular disease (6). The vascular atherosclerotic plaque is now understood as a complex inflammatory reaction of the vascular wall to noxious stimuli from within the blood stream. These stimuli alter the normal properties of endothelial cells to increase adhesion and recruitment of inflammatory cells, predominantly monocytes and T-cells, to the vascular wall. The production of cytokines leads to activation and translocation of those cells across the endothelial vessel lining to produce a lesion in the vascular wall comprised of immunologically active cells and proliferating smooth muscle cells and fibroblasts, collectively called the atherosclerotic plaque. This plaque represents the key lesion of atherosclerosis and serves as a nidus for thrombotic vascular obstruction and resulting in end organ damage such as myocardial, cerebral, or peripheral limb infarction (7). Inflammatory mediators not only regulate and drive interaction of the cells inside the atherosclerotic plaque. Sources of systemic inflammation, such as those found in connective tissue diseases, accelerate the development of atherosclerosis presumably through the effect of circulating inflammatory cytokines on the vessel wall and atherosclerotic plaques (8, 9). Cardiovascular disease is now recognized as a major cause of excess mortality in patients with rheumatoid arthritis and lupus erythematosus (10, 11). Many recognized risk factors for cardiovascular disease, including tobacco smoke (12), hypertension (13, 14), obesity (15), the metabolic syndrome (16), and diabetes (17) are associated with increased inflammation. Biomarkers of inflammation predict long-term cardiovascular morbidity in diverse populations and do so independently of previously defined risk factors, adding to the overall risk assessment in healthy or low risk subjects (18, 19), but also predict short term morbidity in patients with acute myocardial infarction (20). Pharmacologic agents proven to decrease mortality in cardiovascular patients such as beta blockers (21) and angiotensin converting enzyme inhibitors (22) are associated with decreased levels of inflammatory markers. Correction of cardiovascular risk factors including weight loss (23, 24), smoking cessation (25), and also cholesterol-lowering therapy (26), reduce inflammation and the long-term risk of cardiovascular events.

4. SLEEP DURATION AND CARDIOVASCULAR MORBIDITY

The suggestion that sleep duration is related to morbidity and mortality stems from several large cohort studies. In these studies, information on sleep duration was obtained as part of a larger data collection. The reader is directed to four recent publications (27-30) that have summarized the available data on sleep duration and overall mortality. This review will focus on studies of sleep duration and cardiovascular morbidity.

The relationship of short sleep to many established cardiac risk factors such as hypertension (31), insulin resistance (32), or diabetes (33) has been reviewed. Recent studies have highlighted a direct short term effect of sleep deprivation on endothelial function (34, 35), an important marker of vascular health (36). Because short sleep is associated with an increased likelihood of established cardiac risk factors, some of the cohorts showing a relationship between self-reported sleep duration and overall mortality have subsequently been analyzed with regard to cause-specific mortality. Most cohorts have included middle-aged or older adults, and sleep complaints and sleep duration data are usually collected by questionnaire. Cardiovascular endpoints include unequivocal events such as cardiovascular death, myocardial infarction, or stroke, but frequently also include less objective endpoints such as angina, congestive heart failure, or cardiac surgery. Studies report the associated risk before and after adjustment for other factors, and there are large differences between the number and quality of covariates included in the adjusted analyses among published studies. Authors rarely explain why some covariates are included in multivariate adjustments, when others are not. Sleep complaints reported to be associated with cardiac events include difficulty falling asleep (37-40), daytime sleepiness (41), and restless sleep (39). One study reported that insufficient sleep was an important mediator in the development of cardiovascular disease in depressed individuals (42).

Studies assessing sleep duration report an increase in cardiovascular endpoints with self-reported short sleep (33, 43-52), self-reported long sleep (33, 45, 48, 50, 53), or no relationship (40), respectively. Qureshi reported an increased risk of stroke but not coronary heart disease in subjects reporting long sleep and daytime somnolence (54). Ikehara found a U-shaped relationship between sleep duration and all cause mortality, but cardiovascular mortality was associated only with short sleep in women, whereas stroke was associated only with longer sleep (49). Cappuccio detected an increased risk of hypertension with short sleep duration only in women (51).

Sleep duration was assessed at two time points during follow up in two studies (44, 45), and the association between morbidity and self-reported sleep duration appeared consistent over time in both studies. Two studies also analyzed the association between sleep duration and morbidity when excluding events during the first five years after baseline assessment (45, 49), and both found that excluding events occurring early after study enrollment did not weaken the overall association, suggesting that the relationship between sleep duration and morbidity is not driven by associated short term mortality.

A recent study found that self-reported sleep disturbance rather than sleep duration was related to morbidity (55). Subjects with short sleep and sleep disturbance had the highest risk of morbidity, whereas subjects with short sleep but no sleep disturbance had little increase in the risk of cardiovascular morbidity.

The different cardiac endpoints evaluated in these studies were cardiovascular death (40, 44, 45, 48, 49), fatal and non-fatal myocardial infarction (33, 46, 55), non-fatal myocardial infarction only (43), angina (55), any incident cardiovascular disease (47), hypertension (50-52), fatal stroke (49), and fatal and non-fatal stroke (47, 54).

One limitation of these cohort studies is that subjects were usually not evaluated for the presence of sleep disorders or sleep apnea, a condition that is widely prevalent and may lead to sleep complaints, and clearly predisposes to inflammation and cardiovascular disease (56, 57).

Studies of self-reported sleep duration consistently show that long sleep duration (usually defined as 9 or more hours) is also associated with increased mortality (58) including cardiovascular mortality (30, 33, 48). The reason for this relationship remains unclear. Studies of factors associated with sleep duration have identified illness, low socioeconomic status or living alone to be associated with longer sleep duration (59-61). Two studies showed that self-reported long sleep maintained its association with morbidity even when only events occurring more than five years after the baseline assessment were considered for analysis (45, 49), suggesting that acute illness related short term mortality is unlikely to account for the observed increase in mortality with longer sleep duration. Experimental studies are lacking as there is no known non-pharmacological method to extend natural sleep. Even a scheduled recovery sleep period of 10 hours following an accumulated sleep deficit generally results in less than 9.5 hours of obtained sleep (62).

5. SLEEP AND INFLAMMATION

Inflammatory cytokines best studied in sleep deprivation include Interleukin-6 and tumor necrosis factor-alpha. Both are secreted by white blood cell populations, endothelial cells, and adipocytes and other cells. C-reactive protein (CRP) is an acute phase protein synthesized by the liver in response to stimulation predominantly by Interleukin-6. CRP is a well established marker of systemic inflammation in clinical medicine for many decades. CRP has a long half-life and in the absence of acute illness has little diurnal (63) or long-term variability (64). CRP is also an attractive marker because it is now well documented that basal levels in human subjects predict the development of many other medical conditions that are of great importance for public health. CRP is named after its property to bind and precipitate the C-polysaccharide moiety on the surface of *Streptococcus pneumoniae*. Its role in the non-specific, early immune response is believed to be in facilitating the opsonization of foreign organisms by phagocytic cells. CRP itself appears not to have a causal role in the development of atherosclerosis (65-67) but is understood as an indicator of the systemic concentration of inflammatory cytokines and may reflect the extent of atherosclerotic plaque in addition to other inflammatory processes in the body.

5.1. Experimental studies

Controlled experimental studies of sleep deprivation have focused on inflammatory systems after early animal data suggested that animals succumb to an inflammatory illness after prolonged total sleep deprivation (68-71). Table 1 provides a comprehensive summary of experimental studies using acute total (column TSD) or chronic partial (column PSD) sleep deprivation in human subjects that measured markers of inflammation. For the sake of completeness, the table includes some references not specifically discussed in the text.

Studies of human sleep deprivation began with a focus on immunocompetent and phagocytic cell numbers and activity (72-77). Early studies tended to use within-subjects designs and most lacked independent control groups. These early studies were furthermore characterized by infrequent sampling. The largest of these studies (78) followed army recruits during a training course involving strenuous physical challenges, restricted food intake and restricted sleep. While such studies have been criticized for generalizability, since severe sleep deprivation is seldom encountered in normal life, and some experimental settings may be considered an unnaturally stressful environment, subsequent studies of one or more nights of partial sleep restriction in a well controlled experimental setting have similarly shown increased white blood cells (93, 94). The first study to report plasma cytokine measurements after sleep deprivation was by Dinges in 1995 (77). Since that report, the focus of experimental sleep deprivation studies in humans has increasingly shifted from assessment of cell counts and cell activity to mediators of the inflammatory process. Most studies used assays to measure cytokines in plasma, but some authors have measured cytokines in stimulated monocytes ex-vivo by flow-cytometry (86, 87, 89).

Table 1 emphasizes study findings for TNF-alpha, IL-6, and CRP as reported by the study authors, and we selected these specific markers because of their accepted association with cardiovascular disease. It is important to realize that studies differ in what constitutes a significant 'increase' of markers, varying from a significant difference between sleep conditions at one (86) or a subset of multiple time-points (85), to a mean daily value integrated from multiple measurements (82, 84, 90). As the table demonstrates, all but three experimental studies since 2001 demonstrated increases in either TNF-alpha, IL-6, or CRP in sleep-deprived subjects. Differences in findings may be due to study differences including the nature of the control group, insufficient statistical power, differences between sampling timing and frequency (due to factors including diurnal rhythms and half-life of the analyte), subtle differences in handling of subjects or blood probes, methods of collection or processing, or differences in assay performance between studies and over time. Interestingly

Table 1. Studies of experimental sleep deprivation and inflammatory markers

Reference	**Subjects**			**Sleep Condition**			**Control group**	**Sample Frequency**	**Findings**			
				TSD	PSD							
	N	N = female	Age (range or mean)	Vigil (hrs)	sleep/24h (hrs)	For # of days		(#/24 hr in each condition)	WBC	TNFα	IL-6	CRP
Kuhn et. al., 1969 (72)	28	?	20-30	72-126			no	1	▲			
Palmblad 1976 (73)	8	8	23-44	77			no	1	—			
Palmblad 1979 (74)	12	0	19-30	64			no	1				
Moldowsky 1989 (75)	10	0	19-27	40			no	23				
Dinges 1994 (76)	20	7	21-30	64			no	2	▲			
Dinges 1995 (77)	12	?	21-30	64			no	1		—	—	
Boyum 1996 (78)	87	0	21-27		2-3	5-7	no	1	▲		▼	
Born 1997 (79)	10	0	21-29	51			Within-subjects	8	▲	—	—	
Vgontzas 1999 (80)	8	0	20-29	40			Within-subjects	48			▲	
Heiser *et al* 2000 (81)	10	0	27	40			Within-subjects	2	▲			
Shearer 2001 (82)	42	0	21-47	88	4	4	TSD compared to PSD	4		—	▲	
Haack 2002 (83)	12	0	18-35	24			Within-subjects	48			—	
Meier-Ewert 2004 (84)	10	0	22-37	88			no	8				▲
	10	4	26-38		4.2	10	yes	24				▲
Vgontzas 2004 (85)	25	13	19-34		6	8	no	48		▲	▲	
Irwin 2006 (86)	30	13	25-59		4	1	no	5		▲	▲	
Dimitrov 2006 (87)	15	0	21-30	24			Within-subjects cross-over	10			—	—
Zheng 2006 (88)	22	7	29	~30			Within subjects	1		—	▲	▲
Lange 2006 (89)	11	0	25	24			Within subjects	14				
Haack 2007 (90)	18	6	21-40		4	10	yes	≥24			▲	—
Frey 2007 (91)	19	9	28	40			no	48			▼	▼
Kerkhofs 2007 (93)	10	10	55-65		4	3	no	1	▲			
Boudjeltia 2008 (94)	8	0	22-29		4	3	yes	1	▲			—
Van Leeuwen 2009 (95)	13	0	19-29		4	5	yes	1		▼	▲	▲
Sauvet 2010 (96)	12	0	29	40			no	1		—	▲	—
Irwin 2010 (97)	26	11			4	1	no	5		▲	▲	

TSD – total sleep deprivation; PSD – partial sleep deprivation; WBC – white blood cells; TNFα – Tumor necrosis factor alpha; IL – Interleukin; CRP – C-reactive protein; IFN – Interferon; GCSF – Granulocyte colony stimulating factor; LPS – lipopolysaccharide; PGE2 – prostaglandin E2; PGI2 – prostaglandin I2; ICU – intensive care unit; VCAM – vascular cell adhesion molecule; ICAM – inter-cellular adhesion molecule; FMD – flow mediated vascular dilatation; ▲ – increase; ▼ – decrease; — - no change

two of the experimental studies that showed no increase in IL-6 (83, 91) and CRP (91) used the constant routine protocol (92) in sleep-deprived subjects. This restriction of physical activity during enforced wakefulness may be considered unnatural but its significance in this context has not been further elucidated.

It is important to note that small basal shifts detected in these studies are consistent with the degree of changes seen in studies associating inflammatory markers

to cardiovascular risk, so that while the changes are indeed small, they may nonetheless be meaningful.

5.2. Cohort studies

Because experimental studies showed increased inflammatory biomarkers with sleep deprivation and cohort studies suggest an association of sleep complaints and cardiovascular morbidity, several more recent studies have assessed C-reactive protein levels in cohorts and correlated these to self-reported or measured sleep data. Increased C-reactive protein levels were associated with self-reported sleep latency greater than 5 minutes, but were not related to self-reported sleep duration or sleep disturbance in a cohort of older adults (98). C-reactive protein was also increased with self-reported sleep disturbance in a cohort of young adults (99), but sleep duration was not recorded. Elevated C-reactive protein was related to poor sleep quality in a cohort of young women (100) and both C-reactive protein and Interleukin-6 were increased with shorter self-reported sleep duration in women, but not men, in a large cohort of middle-aged government employees (101).

Studies that measured sleep duration in addition to self report have reported conflicting results. In one study of adolescents, the association of increased C-reactive protein and sleep disordered breathing was in part explained by sleep duration assessed by polysomnography (102). In another study of adults, C-reactive protein was not associated with sleep duration by polysomnography or self report (103). In a third study, longer self reported sleep but not measured sleep was associated with increased C-reactive protein and Interleukin-6. Conversely, in that same study, tumor necrosis factor-alpha was increased with shorter measured sleep but was not related to self-reported sleep duration (104). Vgontzas (105) found increased levels of Interleukin-6 but not tumor necrosis factor-alpha was associated with short and inefficient sleep in 13 healthy older adults (mean age 71 yrs) when compared to 15 healthy young adults (mean age 25 yrs), each studied for four consecutive nights in the sleep laboratory. Similarly, in two other studies (106, 107), increased Interleukin-6 levels were positively correlated with light or disrupted sleep, and negatively correlated to sleep efficiency and percent slow wave sleep, but there was no relationship of Interleukin-6 levels to total sleep time.

6. MECHANISMS LINKING SLEEP LOSS TO INFLAMMATION

The mechanisms by which sleep loss leads to increased inflammatory markers in humans have not been defined. An attractive explanation is that sleep deprivation leads to altered autonomic nervous system output which in turn may influence the activity of inflammatory processes. Sleep restriction appears to shift the sympatho-vagal balance towards more sympathetic output (vagal withdrawal). Along with this change several studies have observed increased blood pressure as a consequence of sleep deprivation (reviewed in (108)). Sympathetic nervous system activity is related to increased production of inflammatory markers from different cell populations (109, 110), and it is likely that similar mechanisms apply to the stress of sleep deprivation. A second mechanism by which sleep restriction induces inflammation may be via insulin resistance. Several small studies have shown that sleep restriction in humans increases glucose levels and reduces insulin sensitivity (111, 112), and in some studies this occurs without or before definite changes in inflammatory markers occur (113). Metabolic disturbance and inflammation are Interconnected at multiple levels (114). It is of Interest that increased sympathetic output also causes insulin resistance, and increased insulin concentrations further augment sympathetic tone (115). For example, ablation of sympathetic renal innervation in humans results in improved insulin sensitivity (116).

7. FACTORS MODULATING THE RELATIONSHIP BETWEEN SLEEP LOSS AND INFLAMMATION

7.1. Psychological factors

Subjects that are sleep deprived would be expected to have a short sleep latency and high sleep efficiency. Paradoxically, in cohort studies inflammatory markers appear more strongly related to poor sleep efficiency or increased sleep latency than to sleep duration. This highlights the present difficulty of reconciling findings from studies of self-reported sleep duration and morbidity with studies that find objectively measured shortened sleep duration related to increased markers of inflammation. The few studies that have analyzed both measured and self-reported sleep duration have reported divergent findings with regard to morbidity (117) or inflammatory markers (104). Studies comparing subjectively and objectively assessed sleep duration in the same subjects have reported a correlation of these measures, but with significant imprecision of the subjective data. Self-reported duration may differ from the measured duration by 1 to 2 hours (118, 119), suggesting that significant misclassification is possible when only self-reported sleep is considered. Self-reported sleep duration is thought to better reflect time in bed than time asleep. Supporting this concept is that most studies show that self-reported duration overestimates actual sleep duration, if measured by actigraphy or by polysomnography (120). Additionally sleep quality or efficiency is overestimated by both self-report or actigraphy, when compared to polysomnography (120). One study further suggests that psychosocial factors influence the relationship of self-reported to measured sleep duration, perhaps in a systematic fashion. Subjects with depression or distress appear to overestimate sleep latency and underestimate actual sleep time (121), a bias that could shape the findings from cohort studies of self-reported sleep duration and morbidity. An Interaction of measures of stress and mood with self-reported sleep quality and duration is also supported by some of the sleep studies summarized above. Frequently data collected in these studies includes questions about stress, mood, and socioeconomic factors, and in multivariable adjustments these items frequently interacted with self-reported measures of sleep in their relation to mortality or inflammatory markers (37, 39, 40, 107). Suarez found that self-reported poor sleep quality, frequent difficulty falling asleep and increased sleep latency was associated with greater psychosocial distress, higher fasting insulin,

fibrinogen and inflammatory biomarkers in women, suggesting that self-report of sleep complaints identifies subjects with a cluster of other co-morbidities, that are associated with inflammation and greater risk for morbidity (122). Support for this concept also comes from survey data from the National Sleep Foundation. In these surveys, adult individuals who report inadequate sleep also report a higher frequency of other behaviors associated with cardiovascular disease including not participating in exercise (28% vs. 7%), eating unhealthy foods including foods high in carbohydrates (18% vs. 5%), consuming fried foods (34% vs. 23%) and/or have meals from fast food restaurants or eat take-out (28% vs. 19%), cigarette smoking at least once a day (26% vs. 16%), use of an alerting medication prescription or over-the-counter drugs to help them get through the day (13% vs. 5%), and are more likely to be obese (35% vs. 26%), when compared to subjects reporting adequate sleep duration (123)

7.2. Sex

The observation that many inflammatory illnesses are more common in females than males has led some authors to ask if the inflammatory reaction to sleep deprivation differs in men and women. Why the distribution of inflammatory illnesses favors females is not well understood. To date neither genetic nor hormonal differences sufficiently explain the observed distribution of incidence rates (124). Of the studies evaluating inflammatory markers that were reviewed above some reported higher markers in men only, including tumor necrosis factor-alpha (85), interleukin-6 (106) and C-reactive protein (100). In contrast, others reported an association of increased inflammatory markers interleukin-6 and C-reactive protein with sleep duration (101) or sleep complaints (122) only in women. Of the remaining investigators who included women among their subjects, authors adjusted their analyses for sex (104) or did not report separate results by sex in their unadjusted analyses (103). A small experimental study intended to assess sex differences in the inflammatory response to partial sleep deprivation found a different pattern of increase in interleukin-6 and tumor necrosis factor-alpha between males and females. When comparing *ex vivo* production of cytokines by stimulated monocytes after partial sleep deprivation to baseline measurements, both markers were significantly elevated in either sex on the morning after sleep deprivation, but remained elevated over baseline over the next 16 hours only in females, whereas levels decreased below the baseline levels for similar time-points in males (97). Among investigations associating sleep complaints or sleep duration to morbidity or mortality evidence supporting an increased risk of morbidity in females compared to males appears stronger. Newman first noted that daytime sleepiness predicted overall mortality only in women even after adjustment for other confounders (41). Both Meisinger and Ikehara reported in large cohorts that the signal for risk of coronary heart disease associated with sleep duration was stronger for females than males (46, 49). In contrast, Amagai found a significantly increased risk of total mortality (125) and cardiovascular mortality (126) associated with shorter sleep only in males. Similarly, Mallon reported that difficulty initiating sleep, but not sleep duration, was associated with the risk of subsequent cardiovascular death only in men (40). Heslop found a similar relationship of sleep duration to mortality risk in both men and women, but analyses in women were limited by the smaller sample size (44). Other cohort studies adjusted their analysis for gender (39, 47, 53, 102) or included only women (33, 38) or only men (37), and one study excluded female cases and controls from their analysis (43). At this time, a sex difference in the inflammatory response to short sleep or the resultant morbidity of self-reported sleep disturbance remains speculative, in part because few of the studies available at this time set out to investigate this question.

8. SUMMARY AND CONCLUSIONS

After more than 4 decades of research, the role of sleep as a cause of cardiovascular disease remains hypothetical. A role for shortened sleep and sleep-related inflammation in morbidity and mortality is suggested by the available data, but studies to date cannot prove this relationship (127). Few studies have attempted to model the long-term partial sleep deprivation that may best reflect the daily reduction of sleep time related to work and leisure related time constraints. Well controlled prospective cohort studies with serial objective and subjective assessment of all aspects of sleep, inflammation, and the many known covariates of sleep and associated risks are needed to achieve this goal. However, the multitude of confounding factors (behavioral, socioeconomic, cardiac risk factors) that are illustrated by the complex models put forward in recent summaries of the data (29, 128) will make such studies difficult to design and analyze. We believe that intervention studies will more easily test whether adequate sleep duration has an important role in health. Such studies can include subjects reporting habitual short sleep and may also begin to include not just healthy adults, but individuals with preexisting conditions who may be much more vulnerable to the effects of sleep restriction. It is interesting to note that one prospective randomized trial of sleep restriction in elderly subjects, with the aim to consolidate and improve sleep efficiency, unexpectedly found increased morbidity in the sleep restriction group (129). Studies employing behavioral extension of sleep duration in habitual short sleepers are being conducted (130, 131) and preliminary results from the latter study suggest that sleep extension can improve blood pressure in pre-hypertensive adults (131).

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Key Words: Sleep, Inflammation, Cardiovascular disease, Hypertension, C-reactive protein, Interleukin-6, Tumor necrosis factor-alpha, Leukocyte, Sleep deprivation, Sleep complaint, Review

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