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Association of Inflammatory Markers with Cardiovascular Risk and Sleepiness

Michelle A. Miller, Ph.D.
University of Warwick, Warwick Medical School, Division of Metabolic and Vascular Health, Coventry, UK

SUPPLEMENT

There is emerging evidence suggesting that disturbances in sleep and sleep disorders play a role in the morbidity of chronic conditions including obesity and hypertension as well as in the development of type-2 diabetes. This brief review examines the role of inflammation in the development of atherosclerosis. Furthermore, it outlines the utility of inflammatory markers and, in particular, adhesion molecules as biomarkers for cardiovascular risk and the factors that affect their level in the circulation. It then discusses the relationship between sleep and markers of inflammation and the role of sleep in immune function.

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Sleep is a fundamental and natural process and yet the exact purpose of sleep and its effects on health and disease remain to be elucidated fully. In order to consider if inflammatory markers might be considered as a biomarker of sleepiness we need to consider first if they can be objectively measured and evaluated under normal biological conditions and to see if the level of these markers change in response to sleep. While a biomarker may not need to be causally related to the desired endpoint, the measurements do need to be analytically valid and non-dependent upon confounding factors such as food intake. Inflammatory markers are subject to activation by a number of different factors and it is therefore imperative that these factors are controlled for when considering the effect of sleep *per se* on inflammation. To illustrate this, the utility of markers of inflammation as a biomarker for cardiovascular disease is first examined. Second, the evidence to suggest that poor sleep may lead to the development of cardiovascular disease potentially through the elevation of inflammatory markers is presented and, finally, the utility of inflammatory markers as a biomarker of sleepiness is considered.

In the development of atherosclerosis and subsequent cardiovascular disease (CVD), activation of the adhesion molecule pathway leads to the expression of adhesion molecules which attract leukocytes to the endothelium. These cells "roll" along the endothelium before becoming firmly attached. Subsequently, they move in to the interstitial space where they take up lipids to form foam cells and ultimately atherosclerotic plaques. Our studies have indicated that the level of these factors may also be affected by confounding factors including age, ethnicity, gender, obesity, and smoking, which would need adjustment.[1] An approximate 2% increase in soluble E-selectin level, for example, is associated with a 1 unit higher BMI and a 0.01 unit greater waist-hip ratio.[2]

Short sleep arising either as a result of a known sleep disorder such as obstructive sleep apnea or from behavioral sleep restructure, for example arising from adverse working hours, can lead to a sleep deficit. This may lead to endothelial dysfunction and activation of the adhesion molecule pathway. Short sleep acting through these pathways might therefore be associated with increased CVD risk. The innate immune system, which allows the body to respond to and rapidly isolate foreign particles, including tumors, transplanted material, or invading pathogens, has been previously associated with CVD risk. Double-stranded (ds) viral RNA produced following infection, for example, induces inflammatory cytokines. It is also associated with increased NREM sleep. Toll-like receptors (TLRs), which are key components of this innate immune system, are activated by a diverse array of microbial factors. In turn these receptors activate the nuclear-factor-Kappa B (NF-κB) pathway, leading to the expression of cellular adhesion molecules and cytokines. Activation of the host defense mechanisms and immune system not only results in an increase in inflammatory cytokines but also promotes an increase in body temperature and longer periods of SWS and reduced wakefulness. However, in advanced stages of inflammation, the sleep promoting effects are diminished and reduced NREM and increased wakefulness may result. The effect of viral and bacterial antigens and this reciprocal relationship between sleep and the immune system are important when evaluating the potential for inflammatory markers to be used as markers of sleepiness.

Chronic conditions, such as hypertension, can also activate the innate immune system, some components of which, such as TNF-α, are known to exhibit diurnal rhythms. Other factors, including vaccination, ethnicity, gender, obesity and smoking can affect the level of these inflammatory components. This system also exhibits two different types of response, the defense-mediated pro-inflammatory response mediated by type 1 leukocytes and the anti-inflammatory type 2 response. The balance between these two systems is tightly regulated but is shifted toward type 1 in women and type 2 in men. Moreover, sleep deprivation shifts the balance in favor of type 2 activity.

In the last century the duration of sleep in the United States has been declining and evidence suggests that short sleep duration is associated with obesity, all-cause mortality, diabetes, and cardiovascular disease.[3-5] A recent systematic review and meta-analysis of cross-sectional studies in children and adults provides the global evidence in support of the presence of a relationship between short duration of sleep and obesity, providing a quantitative estimate of the risk.[3] The meta-analysis included a total of 36 population samples with 30,002 children and 604,509 adult participants from around the world. Age ranged from 2 to 102 yr and included boys, girls, men and women. The observed association was seen to be consistent across different populations and was observed in both children and adults. In children the pooled odds ratio (OR) for short duration of sleep (< 10h per night) and obesity was 1.89 (1.46 to 2.43; $p < 0.0001$) and in adults (short sleep defined as < 5h per night) the pooled OR was 1.55 (1.43 to 1.68; $p < 0.0001$). Subsequent meta-analyses now have shown that there is an increased risk of dying from all causes,[4] and cardiovascular disease in both in short and long sleeping individuals.[5] Likewise, we have demonstrated an increased risk of developing diabetes in short and long sleep individuals.[6]

There are a number of potential mechanisms that might be responsible for these associations and include effects of sleep on appetite and satiety, on insulin resistance, on endothelial function, on inflammation, or on thrombotic or hemostatic factors. It is, however, still possible that obesity may lead to short sleep. Indeed, obese individuals are at increased risk of obstructive sleep apnea (OSA), a condition that is associated with disturbed and short sleep. It is therefore conceivable that a bi-directional pathway may exist between sleep and obesity and obesity and sleep and it is important to consider this when the mechanisms underlying these associations are considered.

Short term sleep deprivation is associated with an increase in hs-CRP[7], but to date the potential impact of chronic sleep deprivation on the inflammatory system and immune responses has not been fully investigated. A lack of sleep may lead to increased fat accumulation, increased secretion of pro-inflammatory cytokines and increased CVD risk.

We have examined the relationship between markers of inflammation and sleep duration in over 4,000 individuals from the Whitehall II Study. Following multiple adjustments there were no overall linear or non-linear trends between sleep duration and IL-6. However, in women but not men (interaction $p < 0.05$), levels of IL-6 tended to be lower in individuals who slept 8 h (11% [95%CI 4 to 17]) as compared to 7 h.[8] This is in contrast to the Cleveland Family study in which increasing sleep was associated with an increase in IL-6.[9]

Significant gender differences in the association with hs-CRP and sleep were also observed. In men there was no significant association between hs-CRP and sleep. In women, however, there was a significant non-linear association with higher levels in short sleepers.[8] These results are in contrast to Taheri et al. who failed to demonstrate any significant association between hs-CRP levels and sleep duration.[10] The observed gender interactions in the relationship between sleep and inflammation may account for the observed differences in outcomes. Taheri et al. may have failed to find an association between sleep and markers of inflammation as the number of females in their study was much smaller, and a gender adjusted analysis, as opposed to a sex-stratified analysis, was used.[10] Longitudinal studies are required to investigate fully the possible temporal relationships between short sleep and markers of inflammation in both male and female individuals. Circadian rhythms and diural variability may affect the level of inflammatory markers. Investigation of the effect of sampling time on the inflammatory markers measures however indicated that there was no major effect of time on these levels over this time period. The proportion of the variability due to "time of sampling" for hs-CRP was 0.03% and for IL-6 was 0.3%. Sleep disorders such as OSA are associated with increased CVD risk and are associated with increased inflammation.[11]

Damage to the endothelium can lead to activation of haemostatic, coagulation and thrombotic pathways, which may lead to the formation of a thrombus, impaired blood flow, and possibly a stroke. We examined the relationship between self-reported sleep duration and 3 important factors in these pathways (von Willebrand factor (vWF), fibrinogen, and factor VII) in approximately 6400 individuals from the Whitehall II Study.[12] There was a significant gender interaction. After multiple adjustments, vWF levels were significantly higher in men with both short sleep duration (≤ 6 h per night; 1.05 [95% CI, 1.01 to 1.08] [data given as geometric mean]) and long sleep duration (≥ 8 h per night; 1.05 [95% CI, 1.02 to 1.08]) compared with those who slept 7 h ($p < 0.05$ for both). In women, levels of vWF were significantly higher in individuals who slept 8 h or longer (1.11 [95% CI, 1.06 to 1.16]) compared with 7 h ($p < 0.05$). This effect was observed in premenopausal and postmenopausal women. But, in premenopausal women the levels were also increaseed in short sleepers. In women, the association was nonlinear ($p = 0.02$), but not in men ($p = 0.09$). The highest levels were observed in long sleepers, irrespective of menopausal status. No major associations between sleep and factor VII or fibrinogen were observed. Longitudinal studies are required to investigate causality but it is of interest that, in a recent study, we have demonstrated that the risk of developing or dying of stroke among short sleepers and long sleepers is increased.[5]

In summary, important bi-directional effects between inflammation and sleep exist and short and long term sleep deprivation may have different effects on markers of inflammation. Chronic short sleep appears to be associated with markers of inflammation and thrombotic factors but important gender differences exist.

For an inflammatory marker to be considered as a biomarker of sleepiness, there are a number of factors that need to be considered. These include specificity, feedback mechanisms, sampling time/diurnal rhythm, the accessibility of marker for measurement along with its precision, and accuracy of measurement. Other factors that are important include the stability of marker with storage and the possible confounding factors (e.g., age, sex, ethnicity, alcohol, smoking, exercise, socio-economic status, marital status, pre-existing disease, etc.). The acute effect of possible invading pathogens must also be considered and ultimately the cost of the measurement will also determine its utility.

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CORRESPONDENCE

Address correspondence to: Michelle A. Miller, Ph.D., Macad.M.Ed., F.F.P.H., Associate Professor (Reader) of Biochemical Medicine, University of Warwick, Warwick Medical School, Division of Metabolic and Vascular Health, Clinical Sciences Research Laboratory, CSB, UHCW Campus, Clifford Bridge Road, Coventry, CV2 2DX UK; Tel: 024 7696 8666; Fax: 024 7696 8660; E-mail: Michelle.Miller@warwick.ac.uk

DISCLOSURE STATEMENT

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