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Links between stress, sleep, and inflammation: are there sex differences?

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Abstract

Purpose of this review: Inflammation has emerged as an important biological process in the development of many age-related diseases that occur at different frequencies in men and women. The aim of this review was to examine the current evidence linking stress and sleep with inflammation with a focus on sex differences.

Recent findings: Psychosocial stress that occurs either acutely or chronically is associated with elevated levels of systemic inflammation. While not as robust, insufficient sleep, particularly sleep disturbances, appears to be associated with higher levels of inflammatory activity as well. In several contexts, associations of stress and insufficient sleep with inflammation appear stronger in women than in men. However, this should be interpreted with caution as few studies test for sex differences.

Summary: Stress and poor sleep often predict elevations in systemic inflammation. While there is some evidence that these associations are stronger in women, findings are largely mixed and more systematic investigations of sex differences in future studies are warranted.

Keywords

Stress; sleep; sex; inflammation; immune system

Introduction

Chronic systemic inflammation has emerged as a central biological pathway in the development and progression of a host of age-related conditions, including cardiovascular, metabolic, and autoimmune diseases as well as neurodegenerative conditions and cancers [1] Many of these inflammatory medical conditions occur at different rates among men and women. For example, the prevalence of rheumatoid arthritis, an autoimmune condition, is three times higher in adult women than in men [2]. Furthermore, in major depression, a

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Conflict of Interest

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psychiatric condition where increasing evidence is implicating inflammation as playing a causal role [3], is nearly two times more likely to occur in women than men [4]. Conversely, cardiovascular diseases tend to emerge earlier in the life course for men than women [5].

Because of the important role that inflammation plays in many diseases, there has been growing interest in understanding sex differences in inflammatory biology as well as the psychosocial and behavioral processes known to lead to elevated levels of inflammation. Indeed, there are numerous psychological, environmental, and behavioral factors that contribute to variation in levels of systemic inflammation in adults. Psychological stress and insufficient sleep stand out as two processes intimately tied to one another, which are also known to affect the immune system and are associated with many of the chronic medical conditions where inflammation plays a key role. Moreover, there are data to suggest that men and women can differ not only in their sleep behaviors but also their responses to stress, which in turn may yield differences in measures of inflammation.

In this selective review, we discuss the current evidence linking psychosocial stress and insufficient sleep with inflammatory functioning, focusing on differences between men and women. We then provide a brief discussion of potential future directions. However, we first provide an overview of inflammation to orient the reader.

Overview of inflammation

Inflammation is an adaptive, evolutionarily conserved process orchestrated by the immune system often in response to an infection or injury (e.g., a wound). Clinical signs of inflammation include redness, swelling, heat, and pain at the site of the insult, which occurs because of increased blood flow, the release of inflammatory mediators, and the migration of immune cells to the area of injury. Inflammation is typically well-regulated both locally and systemically, such as via glucocorticoids released by the hypothalamic pituitary adrenal (HPA)-axis, to ensure that the inflammatory processes do not result in harm. However, in instances where there is ongoing stimulus or ineffective regulation, chronic systemic inflammation can lead to damage to the body and promote the development of disease states.

There are a host of key proinflammatory mediators that serve as biomarkers of chronic inflammation. Of particular relevance to this review are interleukin (IL)-6, IL-1 β , and tumor necrosis factor-(TNF)- α , which are the most common proinflammatory cytokines measured in studies that include behavioral and psychosocial components. Proinflammatory cytokines are produced and released by multiple sources within the body, most prominently activated white blood cells, but also adipocytes, and myocytes, and there is increasing interest in the role of these mediators within the central nervous system. In addition to these cytokines, many researchers focus on C-reactive protein (CRP), which is an acute-phase protein released from the liver in response to increasing IL-6. The most common way of measuring these biomarkers of inflammation is to quantify them in peripheral blood. Researchers also often isolate immune cells and stimulate them with known quantities of antigen (e.g., lipopolysaccharide (LPS)) as a way of activating an inflammatory response. Proinflammatory cytokines are then quantified and this metric can provide insight into the capacity for the inflammatory system to respond when challenged. Finally, researchers may

assess the activity of molecular pathways that underlie an inflammatory response, such as NF- κ B activation, by quantifying mRNA gene expression of these processes.

Inflammatory functioning differs between men and women [6]. For example, adult women tend to mount stronger inflammatory responses than men, though this trend reverses in both childhood and old age (for review see [6]). The sexual dimorphism observed in inflammatory activity is thought to be driven, at least in part, by differences in reproductive hormones with testosterone at play for men while estrogen modulates inflammatory activity for women [7]. Estrogen appears to have a dose dependent effect on the inflammatory system, with low doses leading to increased levels of IL-6, IL-1 β , and TNF- α while high levels can suppress inflammatory activity [8, 6]. In addition, evidence from animal studies suggest that glucocorticoids may not work as well in regulating inflammatory activity in response to an inflammatory challenge in women compared to men [9]. While this remains an area of active inquiry, data suggests that estrogen receptors can have antagonistic effects on anti-inflammatory capacity of glucocorticoid receptors [10].

Stress and Inflammation

The term “stress” often serves as an umbrella term that captures stress exposures (e.g., loss of a job, interpersonal conflict, or traumatic events), and stress responses, which include both affective responses (e.g., feelings of distress) and physiological responses to the stressor (e.g., activation of the autonomic nervous system and HPA axis) [11]. Overall, there is consistent evidence that stressful experiences are associated with elevated rates of several medical conditions where inflammation plays an important role [12]. However, heterogeneity in how stress is measured and over what time scale (e.g., past year, month, day, this moment) may obscure important links [11, 12]. Nevertheless, several recent reports highlight a robust association between psychosocial stress and elevated levels of systemic inflammation.

Early childhood stressful experiences can lead to elevated levels of inflammation and subsequent disease later in adulthood (see review [13]). Indeed, a recent meta-analysis demonstrated that exposure to childhood trauma, including physical, sexual, and emotional abuse, was associated with increased circulating levels of IL-6, TNF- α , and CRP in adulthood [14]. Interestingly, moderation analyses using these data did not reveal any age or sex effects, though a recent study suggested that sex differences may still be an important area of exploration. In a prospective study of more than 2,000 participants followed from birth to 18 years of age, exposure to childhood victimization, such as abuse by an adult and bullying by peers, was associated with elevated levels of circulating CRP in later adulthood, and stratified analyses revealed that this association was driven by women [15].

A recent meta-analysis of the human laboratory stress literature also provides strong evidence that acute psychological stress results in alterations in circulating levels of inflammation and production of proinflammatory cytokines in response to in vitro stimulation [16]. In an analysis of 34 studies, acute laboratory stress produced reliable increases in circulating levels of IL-6, TNF- α , IL-1 β , but not CRP. Similarly, analyses revealed that acute stress produced significant increases in the production of IL-6, TNF-

α , and IL-1 β when stimulated in vitro by an antigen (most commonly LPS) [16]. As expected, there was substantial heterogeneity across studies both in terms of stressors used, populations examined, and, perhaps most critically, timing of blood sampling. Because many of the existing studies were small or focused only on one sex, an empirical assessment of sex differences was not possible in the meta-analysis. However, a couple of studies provide evidence of possible sex differences. For example, Prather and colleagues reported that acute laboratory stress resulted in a significant increase in the production of IL-6 and TNF- α , but not IL-1 β following LPS stimulation; when stratified by sex, it was clear that this inflammatory response was stronger in women [17]. Notably, when women were further stratified by menopausal status, it appeared that postmenopausal women showed the largest stress related increase in IL-6 and TNF- α compared to men. In a more recent study of 57 healthy midlife adults, Lockwood and colleagues reported stress-related increases in circulating IL-6 following an acute laboratory stressor that were significantly higher among women than men [18]. This finding is consistent with several prior studies (e.g., [19, 20]). Interestingly, among men in this study, greater stress-related increases in IL-6 was associated with higher concentrations of CRP at baseline though this association was not observed in women. The authors speculated that such an association in men may contribute to the sex differences observed in CVD risk; however, longitudinal studies are needed to test this hypothesis.

While there is no disputing that major life stressors, particularly those that are chronic in nature (e.g., caregiving), can affect health, there is also mounting evidence that the wear and tear of daily stressors can influence long-term health trajectories [21]. Using data from the National Study of Daily Experiences, which is a sub-study of the Midlife in the United States II (MIDUS-II), cohort, Sin and colleagues demonstrated that participants who reported greater decreases in positive affect in response to a daily stressor also showed higher levels of circulating IL-6, a relationship that was independent of sociodemographic factors, health behaviors, and medical comorbidities [22]. Greater reports of negative affect in response to a daily stressor was also associated with higher levels of CRP but only among women, with health behaviors, such as reports of physical activity, sleep quality, and smoking status, largely accounting for this relationship.

Overall, the contemporary literature continues to support links between stress and inflammation, particularly when it comes to early life trauma and acute laboratory stressors. While there appears to be some emerging evidence for sex differences, with several studies finding associations specific to women, as a whole there are too few studies to make clear distinctions.

Sleep and inflammation

There is a mixed literature linking sleep and markers of systemic inflammation. This appears to be in part attributable to the fact that sleep parameters are measured in various ways (e.g., objectively using polysomnography and wrist actigraphy, and subjectively via self-report), and different sleep measures may be more strongly related to markers of inflammation than others. In this regard, a recent meta-analysis of 72 studies [23] revealed that greater sleep disturbances, assessed by questionnaires, were associated with higher levels of circulating

IL-6 and CRP but not TNF- α . Shorter sleep duration, when measured subjectively by self-report, was unrelated to IL-6 or CRP levels, though when measured objectively, shorter sleep duration was significantly related to higher IL-6. In addition, longer sleep duration was associated with higher CRP and IL-6 but not TNF- α , highlighting the curvilinear risk conferred by both long and short sleep. In a recent study not included in that meta-analysis, poorer sleep efficiency measured via wrist actigraphy was associated with higher levels of IL-6 but not CRP in a sample of nearly 300 women [24]. Sleep duration, however, was unrelated to both IL-6 and CRP in this sample. More theoretical and empirical work is needed to better these distinct sleep associations. Furthermore, given the literature supporting stress as a predictor of inflammation and the fact that psychological stress is a common cause of sleep disturbance [25, 26], research exploring the independent and synergistic links with inflammation are needed [27]. Indeed, only 9 (12.5%) of the 72 studies included in a recent meta-analysis of sleep and inflammation considered stress in the research design or statistical analyses [23]. Among the few studies that did measure psychological stress, however, there was still consistent support for an association between sleep and inflammation.

Other studies have examined relationships between sleep variables and inflammation in lab-based studies. A meta-analysis of human experimental studies that employed sleep restriction found little evidence of reliable changes in circulating levels of IL-6, TNF- α , or CRP after sleep restriction, which included restricting sleep across the entire night, partial restriction (e.g., reducing a participant's 8 hours of sleep down to 4 hours), and restriction over consecutive days [23]. This is in contrast to the small handful of studies that have demonstrated that experimental sleep loss produces an increase in the spontaneous production of IL-6 and TNF- α in monocytes [28] as well as increased production of these cytokines following antigenic challenge [29, 30]. Furthermore, acute sleep loss has been shown to lead to alterations in inflammatory gene expression [29] and the upregulation in transcriptional pathways (e.g., NF- κ B) responsible for the inflammatory response [31]. In regard to the latter, following a night of sleep loss women showed a greater upregulation in NF- κ B compared to men [31]. These data suggest that molecular approaches to interrogating inflammatory processes may be more fruitful in demonstrating links to insufficient sleep than traditional measure of inflammation in peripheral circulation

To date, very few studies examining links between sleep and inflammation test for differences between men and women. This is unfortunate given that several sleep parameters have been shown to differ by sex. For example, women often display better sleep when it is measured objectively, including longer sleep duration, shorter sleep onset latency, and a higher percentage of slow-wave sleep compared to men [32–34]. Conversely, women also tend to report more subjective complaints and sleep-related problems [35, 36]. Meta-analytic findings indicate that women are 41% more likely than men to experience insomnia [37].

Are there sex differences in the associations between sleep and inflammation? The previously mentioned meta-analysis [23] suggests that there may be differences for sleep disturbances, which appear to be more strongly linked to higher levels of circulating IL-6 in women than men. However, a recent study in adolescents suggested a more complex relationship. Data from the National Longitudinal Study of Adolescent to Adult Health (Add

Health), supported an association between short sleep duration and higher levels of CRP in men but not women [38]. In contrast, longer sleep duration was associated with higher CRP in women but not men [38]. These findings are in contrast with another recent analysis using data from MIDUS-II cohort that found that longer actigraphy derived sleep onset latency predicted higher levels of circulating IL-6 and CRP in women but not men. Sleep duration was unrelated to markers of inflammation [39]. Prior studies examining adult samples have more commonly noted stronger links between sleep and inflammation in women than men. For example, in a prospective study of 626 men and women with frank coronary heart disease, poorer subjective sleep quality was associated with increases in systemic levels of IL-6 and CRP followed over 5-years for women but not men [40]. This was consistent with sex differences observed in a smaller cross-sectional study [41]. Finally, data from the Whitehall II study demonstrated that sleep duration was associated with CRP levels in men, but women who sleep 5 hours or less had significantly higher levels of CRP compared to women who slept 7 hours [42].

One potential explanation for these sex differences, as well as some of the inconsistent findings for women, may be related the menopausal transition, where sleep disturbance are often associated with hormonal fluctuations [43]. As noted above, estrogen (e.g., estradiol) reduces inflammatory processes and the decreasing estradiol levels observed during the transition to menopause may enhance link between sleep and inflammation in women. However, additional research regarding menopause, sleep, and inflammation is warranted given evidence that estradiol levels and the presence of hot flashes did not account for the association between lower sleep efficiency and higher IL-6 in a study of peri- and postmenopausal women [24].

Future Directions and Conclusions

Overall, the existing literature suggests there may be sex differences in the links between stress and sleep with inflammation, with several studies showing that such effects are stronger in women than men. However, studies reporting these findings are limited and may reflect a bias towards reporting significant results. As such, one solution could be to make the reporting of sex differences standard practice. However, this may be complicated as the underlying processes that likely drive sex differences in stress, sleep, and inflammation may be poorly measured. Fluctuations of reproductive hormones across the day and the month can have significant influences on inflammatory activity and there is evidence that sex hormones can impact the brain, and thus affect stress responses and potentially sleep [44, 45]. Researchers interested in uncovering these associations must carefully assess hormonal status and medications known to impact reproductive hormone levels.

In the basic and translational sciences, sex differences have largely gone unexplored, often due to the exclusion of women (or female animals) from research populations [46, 47]. Contemporary policies that require inclusion of women or thorough justification for exclusion will certainly help address this problem [46]; however, it is likely that many studies will remain underpowered to test for sex differences. That said, there is tremendous opportunity for improving our understanding of the potential biological pathways through which sex differences, including fluctuation in reproductive hormones, alter inflammatory

activity. For example, studies focused on stress-related changes in glucocorticoid activation key to regulating inflammation would be enriched by accounting for estrogen receptor interactions [10]. Future mechanistic work will need to carefully interrogate these complex and dynamic relationships.

There is also a need to more comprehensively account for the bidirectional links between psychological stress and insufficient sleep. It is plausible that the stress-sleep connection reflects a recursive process that confers downstream effects on biological processes, including inflammation, though this possibility has not been well-examined. A first step in this work will be to better measure and model links between stress and sleep in an effort to recognize that these processes may contribute independent and synergistic influences on inflammatory functioning.

In sum, research supports some evidence linking stress and sleep with elevated levels of systemic inflammation. However, sex differences, if not accounted for, may obscure important associations and mechanistic pathways. Here, we provided a brief review of recent findings demonstrating sex differences with respect to associations of stress and sleep with inflammation; there is much more work to be done in this area. We urge researchers, when possible, to test theory driven hypotheses about sex difference, and report on these findings even when null, as a way of improving our understanding of the complex associations between stress, sleep, and inflammatory processes.

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