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# Sleep and inflammation: a bidirectional relationship

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## Abstract

Sleep and inflammation are bidirectionally linked, and this relationship is assumed to be important for the health and wellbeing of patients and the general population. Inflammatory activation affects sleep through pro-inflammatory mediators, such as cytokines and prostaglandins, which act on the central nervous system. These molecules can enhance but also disturb sleep, depending mainly on the magnitude of the inflammatory processes. Sleep, in turn, has far-reaching but complex effects on inflammation. Sleep deficiency has been shown to increase inflammatory molecules and activate pro-inflammatory signaling cascades, which may lead to immunopathology when chronically activated. In addition, sleep was shown to affect counter-inflammatory mechanisms, including anti-inflammatory glucocorticoid and pro-resolving resolution pathways. Here, we summarize established concepts and the most recent research in the field of sleep and inflammation. We further highlight the relevance of sleep–immune interactions in the clinical context, with examples related to insomnia, long COVID, and critical care. Finally, practical guidance is given for sleep and immune health in healthcare settings, and a research agenda is provided.

**Keywords**
Sleep deficiency · Insomnia · Immune system · Cytokines · Psychoneuroimmunology

## Introduction

Sleep and inflammation are bidirectionally linked [3, 20]. It is an ordinary experience that the need for sleep is enhanced during acute (infectious) illness, and it seems intuitive that a good night's sleep supports recovery. This common belief is backed by scientific evidence demonstrating an intimate relationship between the two systems involved in the regulation of sleep and inflammation, i.e., the central nervous system and the immune system. The cellular components of these systems, including neurons and leukocytes, communicate with and influence each other via neuronal innervation, cell–cell interactions, and endocrine signaling [26, 36]. In the following, we first review the bidirectional relationship between sleep and inflammation. Thereafter, we set focus on the relevance of these interactions in the clinical context, with examples related to insomnia, long coronavirus disease (long COVID), and critical care. Finally, we provide practical guidance for the healthcare setting and highlight areas for future research.

## The influence of inflammation on sleep

Inflammation is a pivotal biological process with various manifestations ranging from the well-known acute inflammatory response to infection or injury, up to regulation of homeostatic processes in the absence of any noxious challenges [29]. The difference between these manifestations is related to the magnitude or quality of the inflammatory process [29]. Chronic but still mild increases in inflammatory factors in the circulation, known as low-grade systemic inflammation, are associated with

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almost every human disease, where they lead to a loss of structure in tissues, a loss of function in various physiological processes, and a loss of homeostatic control in general [13, 29]. Therefore, uncontrolled inflammation can have far-reaching effects on health and disease.

Activation of a pro-inflammatory response triggers the release of cytokines such as interleukin (IL)-1β and tumor necrosis factor (TNF) from immune cells as well as the synthesis of prostaglandins (PG) in surrounding cells and tissues to coordinate the acute inflammatory response [3, 39]. However, these peripheral mediators, in particular IL-1β, TNF, and $PGD_2$, also act on the central nervous system to induce a behavioral sickness response (so-called sickness behavior) that includes, among other things, an increase in sleep and specifically in non-rapid eye movement (NREM) sleep [8, 43, 51]. The induction of sickness behavior, including sleepiness, in response to acute infection is thought to conserve metabolic energy, allowing maximization of the immune response to combat pathogens and support recovery [43]. However, inflammatory signals do not only affect sleep during acute sickness but are also relevant for the regulation of sleep under physiological conditions, as demonstrated by a reduction in physiological NREM sleep following blockade of the biological actions of certain pro-inflammatory cytokines in animals [20]. In contrast, increased signaling of certain anti-inflammatory cytokines, including IL-4 and IL-10, was shown to reduce the amount of NREM sleep and/or sickness behavior in rodents [20]. Of note, these physiological regulations of NREM sleep and sickness behavior seem to be related to the early-onset phase of infectious disease or mild inflammatory response activation, whereas stronger immune responses characterized by fever and high levels of circulating cytokines were shown to induce sleep disturbances [3, 14, 32]. The latter phenomenon might mark the shift to an elevated, and metabolically more costly [49], inflammatory response in an all-in approach of the body to combat more severe disease. Finally, inflammatory signals do not only affect sleep during acute sickness and physiological sleep but can also have a maladaptive component in the context of chronic infectious or inflammatory diseases, which are often associated with sleep disturbances and daytime sleepiness [3].

In summary, inflammatory factors affect sleep under physiological conditions as well as during acute infectious or other inflammatory challenges, which has been studied most for the pro-inflammatory cytokines IL-1β and TNF in animal experiments and likely serves a beneficial recovery function. On the other hand, inflammatory upregulation can lead to sleep disturbances and excessive daytime sleepiness in chronic infectious or inflammatory diseases, revealing its potentially maladaptive component.

## The influence of sleep on inflammation

Several experimental studies have shown that sleep deprivation affects a broad spectrum of classical inflammatory markers, including blood counts of total leukocytes and various subsets, C-reactive protein (CRP) levels, inflammatory cytokine production, complement activation, and expression of cell adhesion molecules [3, 20]. While not all experimental studies have found effects of sleep deprivation on inflammatory markers and some studies even found opposite effects, the most consistent findings are increases in circulating leukocytes and leukocyte subsets as well as in certain pro-inflammatory cytokines, especially after more prolonged sleep-deprivation protocols [3]. In addition to sleep deprivation, a few studies have induced experimental sleep disruption (by induction of repeated forced awakenings) and also found effects on inflammatory markers [4, 24]. Of note, effects of sleep loss or disruption on inflammation can persist after one or even several nights of recovery sleep [15, 23, 47, 52]. Moreover, at least some effects seem to be sex dependent (e.g., [4, 22]). In addition to sleep deprivation or disruption, night-to-night variability in sleep parameters has also been found to be associated with inflammation. Specifically, one study reported that actigraphy-assessed sleep inconsistency, operationalized by the standard deviation of various sleep parameters (such as sleep onset latency, wake after sleep onset, and number of awakenings) measured over 1 week in humans, was associated with an increase in inflammatory markers, including levels of IL-6, CRP, and fibrinogen [9]. Another study found that a higher irregularity of sleep, defined in this study by the standard deviation of sleep duration and of sleep onset time measured over 14 days with actigraphy, was associated with increased counts of circulating leukocytes and some leukocyte subsets in healthy young adults [19]. However, experimental studies are needed to show whether such night-to-night variability in sleep parameters is indeed causally responsible for the increase in inflammatory markers.

Experimental studies have also investigated effects of sleep on counter-regulatory mechanisms to inflammation, including classical anti-inflammatory mediators such as glucocorticoids and anti-inflammatory cytokines, e.g., IL-10, as well as pro-resolving mediators, i.e., the so-called specialized pro-resolving lipid mediators (SPMs) [3, 4, 11, 47]. The effects of sleep deprivation on the glucocorticoid cortisol are rather complex, with studies reporting mostly short-term and mild elevations, no changes, or even decreases in cortisol levels [30, 47]. Such discrepancies might be explained at least in part by sex differences [4], and effects also depend on the measurement timepoint [30]. With regard to inflammatory resolution pathways, a recent study found that prolonged experimental sleep disturbance induced a pronounced downregulation of a specific class of SPMs, namely the D-series resolvins and their precursor 17-HDHA, compared to undisturbed sleep [11]. Taken together, the evidence suggests that sleep is important to regulate anti-inflammatory pathways and that these can become dysregulated when sleep is deficient; however, further studies are needed in this understudied research field.

The influence of sleep on inflammation has not only been shown in experimental settings using objective measures of sleep but is also supported by studies investigating subjective sleep variables. For instance, a recent study showed that poor subjective sleep quality is associated with increased expression of IL-6 and TNF in lipopolysaccharide (LPS)-stimulated

monocytes in healthy older adults [35]. Moreover, several epidemiological studies have investigated the relationship between (mostly subjective) sleep measures and inflammation. While many of these studies found significant associations between a short habitual sleep duration or sleep disruption and increased inflammatory markers, such as plasma levels of CRP and IL-6, other studies failed to find such associations (reviewed in [3]). This is in line with more recent research. For example, two recent studies found associations between self-reported sleep disturbance symptoms and inflammatory markers, including CRP levels and the neutrophil-to-lymphocyte ratio [18, 58], while another recent study did not find associations between various self-reported sleep variables, including sleep duration and insomnia symptoms, and cell counts of various immune cell subsets [34]. Of note, in studies assessing only subjective sleep parameters, it remains unclear whether these are accompanied by objective changes in sleep, which may at least in part explain discrepancies in findings. Objective changes in sleep might be important for affecting inflammatory variables [53]; however, more research is needed to evaluate how purely subjective sleep changes without objective changes may influence inflammation. Discrepancies between study findings might also be explained by the fact that different sleep and inflammatory parameters were investigated in the different studies [3]. In addition, the time of day at which blood sampling was performed is not standardized, which can be problematic given the large circadian variation in most immune parameters [26, 55]. This can obscure the effects of sleep on inflammation and might explain why some studies failed to find significant associations. Based on the several experimental and epidemiological studies that did find associations between insufficient or disturbed sleep and inflammatory upregulation, the overall picture clearly indicates a relevant role of sleep in regulating inflammation.

The mechanisms underlying the effects of sleep deficiency on inflammation are not well known so far. However, it seems that various signaling pathways play a role. For example, intracellular expression of the inflammatory transcription factor nuclear factor κB (NF-κB) was shown to be increased in the morning after partial sleep deprivation [21]. The same experimental model of partial sleep deprivation found increases in the expression of activated signal transducer and activator of transcription (STAT) family proteins [23]. A recent study employing a prolonged sleep disturbance protocol found increases in the stimulated intracellular production of cyclooxygenase-2 (COX-2), which is responsible for the formation of inflammatory PGs, compared to undisturbed sleep [15]. The relevance of PGs in sleep deprivation-induced inflammation was also shown in a recent study in mice, in which total sleep deprivation of 4 days was induced by housing mice in cages with a shallow layer of water, preventing the animals to assume their typical sleep posture [44]. This intervention induced an enhanced efflux of $PGD_2$ from the brain across the blood–brain barrier, thus triggering a systemic cytokine-storm-like pro-inflamma-

tory response with increased immune cell infiltration into organs, resulting in lethal multiple organ dysfunction syndrome [44]. While animal studies are important to decipher underlying pathways, such extreme, readily lethal techniques to prevent sleep are not directly comparable to sleep deprivation studies in humans and translation of the findings to humans therefore has to be done with caution. Overall, further studies are necessary to understand whether and how different molecular pathways interact to induce the complex effects of sleep deficiency on inflammatory markers.

The impact of sleep deficiency on inflammation is likely to have detrimental effects on health. Several epidemiological studies have shown that a short habitual sleep duration is associated with higher mortality and prospectively with an increased disease risk, such as for cancer, chronic pain, and cardiovascular, neurodegenerative, and metabolic diseases [3, 6, 7, 17, 46]. Importantly, the association between a short sleep duration and an increased mortality risk has been found to be mediated by markers of inflammation [16]. This demonstrates the relevance of the effects of sleep loss on inflammation for health overall. It was also shown recently that short sleep duration or poor sleep quality are associated with increased odds for acquiring COVID-19 or presenting more severe disease, including a higher mortality risk (e.g., [27, 38]). Chronic inflammation is suspected to be a factor relevant for this connection by dampening immunity against infection [13, 38]. While it is beyond the scope of the current review, it is worth mentioning that sleep also affects other components of the immune system besides classical inflammatory markers, such as T cell function and migration, antigen-specific responses to vaccination, and NK cell activity, as reviewed in detail elsewhere [3, 48].

In summary, the influence of sleep on inflammation has been shown in several experimental studies and is overall also reflected in epidemiological and smaller-scale correlational studies. There is a growing number of studies showing that sleep also affects counter-regulatory mechanisms to inflammation, suggesting that the effects of deficient sleep on inflammation can be mediated either by a direct upregulation of pro-inflammatory mechanisms, by a dysregulation of counter-inflammatory mechanisms, or both. Future studies will be necessary to disentangle such complex effects of sleep deficiency, also at the molecular level. Regardless of the underlying mechanisms, the effects of sleep deficiency on inflammation seem to have far-reaching effects on health, given that inflammation has been found to mediate the association between a short sleep duration and all-cause mortality risk [6].

## The relevance of sleep and inflammation in the clinical context

In the following, we discuss the relevance of the relationship between inflammation and sleep in the clinical context, with a focus on specific examples related to insomnia disorder, long COVID, and critical care.

### Insomnia disorder

Chronic insomnia disorder is one of the most frequent sleep disorders (up to 10% of adults are affected), with a higher prevalence in females than in males (60% vs. 40%), and is characterized by prolonged sleep latency, difficulties in maintaining sleep, and/or early morning awakenings combined with impaired daytime functioning [40]. Epidemiological studies have shown that insomnia disorder or insomnia symptoms are prospectively associated with an increased risk for developing various disease conditions, including cancer, chronic pain, and cardiovascular, metabolic, and autoimmune diseases [10]. Insomnia is associated with changes in several physiologic systems, including the immune system, which are thought to mechanistically link insomnia with this increased disease risk [3, 10]. These physiological consequences seem to be most pronounced in individuals with insomnia in combination with objectively assessed short sleep duration [12, 53]. It was shown recently that insomnia disorder in older adults is associated with higher gene expression (measured in the form of specific transcription factor activity) related to the pro-inflammatory NF-κB pathway but reduced gene expression related to the anti-inflammatory glucocorticoid pathway [35]. These results are in line with previous findings of inflammatory upregulation in insomnia disorder (e.g., [5, 56]) and further indicate a dysregulation of the balance between pro- and anti-inflammatory pathways, which might contribute to an increased morbidity risk in this population [35]. Of note, the diagnosis of insomnia is based solely on subjective symptoms and no objective measurements are required for the diagnostic process [40]. Future studies are necessary to investigate whether different forms of insomnia disorder, such as with or without objective short sleep duration, present with different inflammatory outcomes and also examine which role potential comorbidities might play in the associations found so far.

### Long COVID

Long COVID is a debilitating condition, in which individuals who had an infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; i.e., the virus inducing COVID-19)—whether asymptomatic, mild, or severe—suffer from persistent symptoms [1]. According to the World Health Organization (2022), long COVID is defined as "the continuation or development of new symptoms 3 months after the initial SARS-CoV-2 infection, with these symptoms lasting for at least 2 months with no other explanation." Common symptoms include fatigue, sleep disturbances, shortness of breath, and cognitive dysfunction [31]. About 10% of patients present with long COVID 6 months after acute SARS-CoV-2 infection [50]. Thus, long COVID is an unprecedented global health problem. Sleep disturbances are among the most frequently reported symptoms in long COVID [28, 31, 50]. Moreover, a recent study suggested a prospective association of pre-infection sleep quality, quantity, and severity of insomnia symptoms with the manifestation of long-term symptoms 3 months after acute COVID-19 [42]. Whether this finding also translates to the persistence of long COVID symptoms more than 3 months after acute COVID-19 illness is not known so far. Inflammatory dysregulation, in particular persistent immune activation, is assumed to be associated with

the manifestation of long COVID [1]. In turn, sleep disturbances can increase systemic inflammation, as described above. Therefore, a better understanding of the role of sleep deficiency and inflammation in long COVID might help to decipher the complex etiology and pathogenesis of this condition.

### Critical care

The sleep of patients is frequently interrupted in the hospital environment, especially in the intensive care unit (ICU) [37, 54]. Thus, it was suggested that disturbed and deficient sleep in the ICU might affect immune function and make patients more vulnerable to infection and sepsis, potentially via an increase in inflammation [54]. Multiple strategies have been investigated to improve sleep and support recovery in the ICU. These include melatonergic drug administration in the evening and blue light therapy during the day to stabilize diurnal rhythmicity as well as the use of earplugs and eye masks to reduce environmental noise and light at night [33, 54]. There are first indications that these countermeasures could be beneficial for promoting sleep and reducing delirium and inflammation in the ICU [2, 54, 57]. However, further research in this area is needed to support the implementation of such strategies into daily clinical practice.

## Practical conclusions

In conclusion, sleep and inflammation share a bidirectional relationship, which is likely relevant for the acute and long-term health of patients and the general population. Therefore, recognition of the importance of sleep health in in- and outpatient healthcare settings is crucial. While good sleep health can help maintain inflammatory homeostasis, poor sleep health appears to promote disease progression and affect recovery. Furthermore, the effects of inflammation on sleep may lead to sleep problems in chronic infectious and inflammatory diseases. Thus, the following aspects should be considered:

- Good sleep health supports good immune health. In the long term, good sleep health could presumably reduce the risk of development of chronic diseases with an inflammatory component, including cancer, chronic pain, and cardiovascular, metabolic, autoimmune, and neurodegenerative diseases, and also reduce all-cause mortality risk.
- Sufficient and undisturbed sleep appears to be especially important for inpatient settings, as it may reduce the risk of infection or sepsis and improve infection outcome. Simple measures to improve sleep, such as providing earplugs and eye masks and exposure to morning light, might help to promote sleep and its potential beneficial effects on recovery in the hospital and especially the ICU.
- Chronic infectious and inflammatory diseases may induce sleep disturbances and excessive daytime sleepiness. While these are perturbing symptoms that justify treatment *per se*, targeting these sleep-related symptoms might also help to reduce the progression and severity of the underlying disease, given the bidirectional interaction between sleep and inflammation. Therefore, educating patients about good sleep habits seems even more important in this context.
- Many medications can affect sleep, which should always be considered in treatment decisions (for comprehensive reviews see [41, 45]). This is especially true for immune modulatory drugs that can directly affect the regulation of sleep, e.g., antihistamines [41].
- As distinct sex differences in inflammatory diseases [25] and sleep-deficiency-related inflammation become ever-more apparent, sex-conscious research, care, and treatment are crucial in sleep-health-related settings.

## Research agenda

Despite substantial knowledge gained in the field, many aspects of the complex bidirectional relationship between sleep and inflammation are still unknown. Thus, future studies should address knowledge gaps and disentangle the complex effects of sleep deficiency on inflammation and *vice versa*. We propose the following tasks to address some of the most relevant open questions:

- Scrutinization of the effects of inflammatory signaling on sleep under physiological and pathophysiological conditions in humans.
- Investigation of interactions and imbalances between pro-inflammatory, anti-inflammatory, and pro-resolving effects of sleep deficiency or inconsistency.
- Unravelment of the molecular mechanisms underlying the interaction between sleep and inflammation.
- Further exploration of the role of the connection between sleep and inflammation and potential interventions in the clinical context, such as for long COVID and critical care.
- Investigation of sex differences in the relationship between sleep and inflammation.

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## Declarations

**Conflict of interest.** L.C. Engert and L. Besedovsky declare that they have no competing interests.

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Zusammenfassung

## Schlaf und Entzündung: eine wechselseitige Beziehung

Schlaf und Entzündung beeinflussen sich gegenseitig, und diese Beziehung wird als wichtig für Gesundheit und Wohlbefinden von Patientinnen und Patienten sowie der allgemeinen Bevölkerung angesehen. Entzündungsreaktionen beeinflussen den Schlaf über entzündungsfördernde Botenstoffe, wie Zytokine und Prostaglandine, welche auf das zentrale Nervensystem wirken. Diese Moleküle können den Schlaf fördern, aber auch stören, was insbesondere von der Stärke der entzündlichen Prozesse abhängt. Schlaf wiederum hat weitreichende, aber komplexe Auswirkungen auf Entzündungsparameter. Es wurde gezeigt, dass Schlafmangel entzündliche Botenstoffe und entzündungsfördernde Signalkaskaden aktiviert, was sich bei chronischem Bestehen vermutlich immunpathologisch auswirken kann. Des Weiteren wurde gezeigt, dass Schlaf entzündungshemmende Mechanismen beeinflussen kann, einschließlich der Glukokortikoid- und Resolutions-Signalwege. Im Folgenden werden allgemein anerkannte Prinzipien und neueste Forschungsergebnisse aus dem Gebiet der Schlaf- und Entzündungsforschung zusammengefasst. Des Weiteren wird die Bedeutung von Schlaf-Immun-Interaktionen im klinischen Kontext mit Beispielen zu den Krankheitsbildern Insomnie und Long-COVID sowie aus der Intensivmedizin verdeutlicht. Abschließend werden einige praktische Orientierungshilfen bzgl. der Schlaf-Immun-Interaktionen für die Gesundheitsversorgung gegeben und Bereiche mit weiterem Forschungsbedarf genannt.

**Schlüsselwörter**
Schlafmangel · Insomnie · Immunsystem · Zytokine · Psychoneuroimmunologie