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Inflammatory hypotheses of sleep disturbance - depression link: Update and research agenda

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ABSTRACT

Studies in human and experimental animal models support a role of inflammation in the aetiology of depression, yet the precise role played by sleep disturbance (i.e., difficulties falling or maintaining sleep) is poorly understood. Consistent evidence from prospective epidemiological studies suggests sleep disturbance as a predictor of major depression episodes and depression recurrence. In parallel, up to 20% of individuals with sleep disturbance have low-grade peripheral inflammation (i.e., CRP>3 mg/l), and preliminary longitudinal evidence showed that sleep disturbance may even predict the levels of inflammation. Therefore, it is possible that sleep disturbance may increase inflammation, which in turn may contribute (i.e., mediate) to the onset - or worsening - of depression. Alternatively, sleep disturbance may serve as a vulnerability factor and increase the risk of developing depressive symptoms when facing an immune challenge. The aim of this review was to summarise the state of the science on the role of sleep disturbance in contributing to depression-related inflammation. A research agenda is also proposed to advance the study of sleep disturbance in the psychoneuroimmunology of depression.

1. Introduction

The study of innate immune system responses in depression is a major research topic in psychoneuroimmunology. Over the last decades, evidence in this field highlighted an intimate, intriguing, yet complex association between inflammation and depression. Levels of peripheral (e.g., serum) pro-inflammatory markers such as C-reactive protein (CRP), interleukin-6 (IL-6), tumour necrosis factor (TNF) are on average higher in individuals with depression than in healthy controls (e.g., Osimo et al., 2020). Up to 27% of those with depression show a CRP>3 mg/l (Osimo et al., 2019) which is usually thought to reflect a state of low-grade inflammation (Pearson et al. 2003), although there is still no consensus on canonical standard markers for systemic chronic inflammation (Furman et al., 2019). These differences may not only be restricted to periphery, as a recent meta-analysis detected higher cerebrospinal fluid IL-6 and TNF in individuals with depression compared to controls (Enache et al., 2019), elucidating the presence of central nervous system inflammation in depression, a process often referred to as "neuroinflammation" (e.g., Nettis and Pariante 2020), despite this term is under debate as it may overlook the contribution of individual cells and disease-specific neural circuits involved (Masgrau et al., 2017).

Crucially, longitudinal literature showed that CRP and IL-6 may be not only correlate with depression, but rather be a precursor and/or a consequence of depression (Mac Giollabhui et al., 2021). For instance, Huang et al. (2019) found that IL-6 predicted future depression, and depression predicted future higher CRP, suggesting reciprocal influences between depression and inflammation where IL-6 and CRP may signal different causal pathways. CRP is released by the liver in response to IL-6, therefore one might expect that both biomarkers should be associated with a similar risk of depression. Huang et al. (2019) argued that IL-6 may signal acute inflammatory effects with a direct impact on the brain, while depression-related changes in behavioural and physiological patterns (e.g., physical activity, diet, sleep) may be associated with a slower inflammatory response as measured using CRP (Huang et al., 2019). Additionally, Perry et al. (2021) suggested that the different risk associated with IL-6 and CRP may be explained by collinearity by the two biomarkers and consequent statistical suppression effects as well as the potential differential role of IL-6 classic and trans-signalling with regards to mental health risk (for a review see Hunter and Jones 2015).

According to the inflammatory hypothesis of depression, the effects of peripheral inflammation on mood is thought to be mediated by central inflammation. Specifically, peripheral inflammation may subsequently lead to microglia activation through humoral (i.e., cytokines diffusion through intact or leaky regions of blood-brain-barrier, i.e.,

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circumventricular organs), or neuronal (e.g., binding of cytokines to afferent vagus nerve fibres) paths, determining changes in neurotransmitters, neurotrophic activity, and oxidative stress processes with the following onset of depressive symptoms (e.g., Bakunina et al., 2015; Dantzer, 2018; Nettis and Pariante, 2020; Turkheimer et al., 2023).

To make the picture even more complex, accumulating studies suggested that the association between inflammation and depression may be influenced by individual characteristics, such as sex differences. For instance, higher IL-6 was associated with depression chronicity only in women (Lamers et al., 2019); moreover, women, but not men, showed increased depressed mood and social disconnectedness following experimentally induced inflammatory challenge (Moieni et al., 2015).

In support of a causal role of inflammation in depression, genetic findings applying Mendelian randomisation showed that genetic upregulation of IL-6 signalling may predict depressive symptoms such as suicidality (Kappelmann et al., 2021). Also, emerging experimental meta-analytic evidence suggested that anti-cytokine drugs, as compared to placebo, may alleviate depressive symptoms with moderate effect sizes (standardised mean differences = 0.40, Kappelmann et al., 2018). For instance, anti-TNF and anti-IL-6 therapies were associated with improvements in depressive symptoms, including subjective sleep disturbance in autoimmune diseases (e.g., Fonseka et al., 2015; Karatas et al., 2018; Siebenhüner et al., 2021). Specularly, some experimental studies showed that psychotherapy interventions targeting depression symptoms such as cognitive behavioural therapy (CBT) and mindfulness may indirectly and moderately reduce pro-inflammatory markers such as CRP, IL-6 and IL-8 in individuals with major depression (e.g., Euteneuer et al., 2017; Memon et al., 2017; Ballesio et al. 2023).

Although current knowledge clearly suggests a role of inflammation in individuals with depression (or at least in a subgroup of patients with a state of low-grade chronic inflammation, Osimo et al., 2019), the specific sources of depression-related inflammation are yet to be uniquely established. Previous authors suggested that psychological stress and lifestyle factors may play a role (e.g., Berk et al., 2013; Mac Giollabhui 2021). In this context, sleep disturbance may be a key variable (e.g., Berk et al., 2013; Irwin and Piber 2018; Fang et al., 2019; Ballesio et al., 2022; Mac Giollabhui 2021). In fact, it is well-known that sleep and circadian system exert a substantial regulatory influence on immune system (e.g., Besedovsky et al., 2012) including regulation of immune cell distribution and production of inflammatory cytokines (Irwin et al., 2016). Moreover, sleep disturbance is highly affected by stressors exposure (Zagaria et al., 2022a) and highly prevalent in women (Ohayon 2002), who may be more susceptible than men to the experimentally induced inflammation-related depression (Moieni et al., 2015).

In this scenario, the aim of this review was to summarise the state of the science on the role of sleep disturbance, defined here as persistent difficulties falling asleep and/or maintaining sleep, in contributing to depression-related inflammation. A specific focus was dedicated discussing current theoretical and empirical evidence supporting the inflammatory mediation hypothesis of sleep-depression link (e.g., Fang et al., 2019; Ballesio et al., 2022) and the alterative moderation hypothesis according to which sleep disturbance may serve as a vulnerability factor increasing the risk of inflammation in presence of an inflammatory status (Irwin and Piber, 2018). Finally, a research agenda was proposed to advance the knowledge in this field.

2. Sleep disturbance and depression

Sleep is a complex physiological state predominantly regulated by homeostatic and circadian processes interacting with one another (Borbély 1982). Briefly, levels of homeostatic sleep pressure, as indexed by spectral analysis of slow wave sleep, show an exponential decline during sleep and an increase during wake; thus, the depth of sleep increases proportionally with the amount of previous wake. Circadian process is centrally influenced by the hypothalamic suprachiasmatic nucleus and determines nearly 24h oscillations in biological functions. Sleep is a fundamental restoring process of brain functioning and it is considered a basic dimension of physical and mental health (Baglioni et al., 2016). In contrast, sleep disturbance has been associated with several negative health consequences. For instance, the presence of sleep disturbance was associated with increased risk of dementia (Shi et al., 2018), increased risk of developing or dying from cardiovascular disease (Sofi et al., 2014), and increased risk of developing mental disorders (Hertenstein et al., 2019). Particularly, the association between sleep disturbance and depression has long been recognised. A first set of evidence suggesting a role of sleep in depression derived from sleep manipulation studies in human. Healthy individuals experimentally exposed to sleep deprivation were subject to a variety of consequences resembling depressive symptoms, such as high negative emotion, low positive emotion, emotion dysregulation (Tomaso et al., 2021), poor neurocognitive functioning (Lim and Dinges, 2010), fatigue, interpersonal difficulties (Kahn-Greene et al., 2006), changes in dietary patterns (e.g., Lombardo et al., 2020), and social withdrawal (Simon and Walker 2018). While early studies suggested positive effects of sleep deprivation on mood in depression (e.g., Landsness et al., 2011), likely due to strengthen sleep pressure and continuity (Maurer et al., 2018; Ballesio et al., 2018), recent meta-analytic data concluded that there is no consistent evidence for sleep deprivation interventions in improving depression (Mitter et al., 2022).

On a functional brain level, experimentally healthy sleep deprived individuals show amygdala hyperactivation and a reduction of functional connectivity between medial prefrontal cortex and amygdala in response to emotional stimuli in fMRI when compared to sleep rested subjects (Yoo et al., 2017), suggesting a causal role of sleep loss in emotional dysregulation.

Moreover, naturally occurring persistent sleep disturbance is complained by up to 90% of individuals with major depression (Franzen and Buysse 2008) against the 10–20% prevalence estimated in the general population (Ohayon, 2002). Main hallmarks of sleep in depression include reduced sleep efficiency (the ratio between the time spent asleep, and the total time spent in bed), impaired slow wave sleep, and increased REM pressure which are associated with neuroendocrine stress response (Sculthorpe and Douglass 2010). Objectively, meta-analytic data showed that individuals with major depression have longer polysomnographycally recorded sleep onset latency (i.e., time needed to fall asleep) and nocturnal wake compared to healthy controls with large effect sizes (Baglioni et al., 2016). Interestingly, evidence from cohort studies highlighted that baseline sleep disturbance may prospectively increase the risk of depression at follow-up in both adulthood (Li et al., 2016) and in older age (Cho et al., 2015; Lee et al., 2013). On this matter, a recent meta-analysis (Hertenstein et al., 2019) showed that individuals with persistent sleep disturbance and without depression at baseline had more than doubled risk of meeting diagnostic criteria for depression in the follow-up compared to healthy sleepers (OR: 2.80, 95%CI: 1.55–5.17). While epidemiological research often showed that sleep disturbance and depressive symptoms may be bidirectionally associated and likely reinforcing one another (e.g., Sivertsen et al., 2012), a comparative meta-analysis showed that the influence of sleep disturbance on depression may be significantly stronger than the other way round (Bao et al., 2017). As a note of clinical relevance, the presence of sleep disturbance was prospectively associated not only to the risk of developing depression, but also to recurrence and symptoms worsening (Bao et al., 2017). Additionally, the risk of depression in those with sleep disturbance may not be alleviated following antidepressant treatment (Cho et al., 2008). Conversely, interventions for sleep disturbance such as CBT for insomnia may lead to a reduction of depressive symptoms such as negative mood, fatigue, and repetitive negative thinking in adults (e.g., Benz et al., 2020; Ballesio et al., 2021a, b) and prevent incidence and recurrence of major depression (Irwin et al., 2022). Taken together, previous evidence suggested that sleep disturbance may serve as a vulnerability factor for depression. Notwithstanding, the potential variables underlying the association

between sleep disturbance and depression remain poorly understood whilst the immune system may play a key role.

3. Sleep disturbance and inflammation

Sleep and circadian systems are key modulators of immune system function. While evidence also suggested an association between sleep and adaptive immune responses such as antibody response to vaccination (Irwin et al., 2016), this review was focused on innate responses and inflammation as mostly studied in depression. Reviews on adaptive immune responses in depression can be found elsewhere (e.g., Harris 1999; Pearlman and Najjar 2014; Beurel et al., 2022). Early studies on sleep and innate immune responses showed that experimental sleep deprivation was responsible for a shift in IL-6 peaks expression from night-time to daytime (Vgontzas et al., 1999) and the same profile was later detected in individuals with naturally occurring chronic sleep disturbance for both IL-6 and TNF (Vgontzas et al., 2002). A distinct circadian rhythm of IL-6 (with peak of activity observed during the night) was also detected by other authors (e.g., Dimitrov et al., 2006), who also reported a decrease of IL-6 soluble receptors during continuous wake compared to normal sleep. More recently, a meta-analysis combining subjective and objective sleep measures suggested that shorter sleep duration may be associated with higher IL-6, CRP, and TNF (Irwin et al., 2016). Interestingly, experimental data showed that sleep loss may increase IL-6 and TNF by activating nuclear factor-kappaB, which is a key transcriptional control pathway in the inflammatory response (Irwin et al., 2008) involved in the secretion of peripheral (e.g., TNF, IL-1 and IL-6, Neurath et al., 1996; Atreya et al., 2008), and central (e.g., chemokine interferon-γ inducible protein 10 kDa (CXCL10) and chemokine C–C ligand 2 (CCL2), Brambilla et al., 2005) proinflammatory markers. Interestingly, the effects of sleep loss on inflammation may be shaped by sex differences. For instance, Irwin et al. (2010) showed that lipopolysaccharide-stimulated production of IL-6 and TNF were more markedly increased in sleep deprived women compared to men. Also, sleep disturbance is comorbid with many autoimmune diseases with an abnormal inflammatory response such as inflammatory bowel disease (Ballesio et al., 2021), rheumatoid arthritis (Kwiatkowska et al., 2019), and psoriasis (Gupta et al., 2016), and with inflammation-related conditions such as obesity (Bacaro et al., 2020). Examining the direction of the associations between sleep disturbance and inflammation, research provided contrasting results which may be likely due to the differences between physiological sleep-immune interactions and their chronic, pathological dysregulation. For instance, cytokines such as IL-1 and TNF are involved in promoting nonrapid eye movement sleep by altering hypothalamic and brainstem circuits involved in sleep regulation (e.g., Opp 2005; Krueger 2008), and increased sleepiness is traditionally a common feature of (neuro) inflammation-mediated sickness behaviour (e.g., Irwin et al., 2016). Instead, chronic sleep disturbance was a significant predictor of higher IL-6 and CRP at five years follow-up after full adjustment for baseline inflammation as well as health and psychosocial confounders in young adults of the Coronary Artery Risk Development in Young Adults (CARDIA) study (Cho et al., 2015). Consistently, we recently showed that sleep disturbance was associated with higher levels of high-sensitivity CRP at four-year follow-ups in older adults of the English Longitudinal Study of Aging (ELSA), even after controlling for baseline inflammation, health status, and socio-economic factors (Ballesio et al., 2022; Zagaria et al., 2022b) and this effect was stronger in women (Ballesio et al., 2022). Interventional studies indirectly supported an association between sleep disturbance and inflammation. For instance, randomised controlled trials of CBT for insomnia have been associated with a reduction of inflammatory markers (Irwin et al., 2014; Carroll et al., 2015). Taken together, evidence summarised in this paragraph indicated that sleep disturbance may be associated with, or even cause, inflammation, partially due to hypothalamic–pituitary–adrenal (HPA) axis activation and glucocorticoid resistance (Irwin 2019). However, the precise role of sleep disturbance in influencing depression-associated inflammation is yet to be clearly understood and remain largely hypothetical.

4. Inflammatory hypotheses of sleep disturbance - depression link

I stated already that inflammation may be particularly relevant for at least a subgroup of individuals with depression, which was estimated at 27% by Osimo et al. (2019). Therefore, it appeared upmost important to characterise this subgroup of patients at higher risk. Pursuing this aim, a recent cross-sectional network analysis (Fried et al., 2020) showed that somatic symptoms of depression, including sleep disturbance, but not cognitive and affective symptoms (e.g., anhedonia), were directly associated with inflammation (CRP) in the Netherlands Study of Depression and Anxiety (NESDA). Consistent results were also found in a recent pooled analysis of 15 population-based studies including 56351 adults which showed that CRP and IL-6 were more strongly associated with somatic symptoms of depression, including sleep disturbance, both cross-sectionally and longitudinally compared to cognitive and affective symptoms (Frank et al., 2021).

Also, different research groups argued that sleep disturbance may play a role in enhancing inflammation in depression. For instance, Berk et al. (2013) stated that "sleep deficiency" may be a source of inflammation in major depression, and other researchers argued that sleep disturbance may even contribute to depression by increasing the levels of inflammation (e.g., Lopresti et al., 2013; Fang et al., 2019; Palagini et al., 2022; Ballesio et al., 2022; Piber et al., 2022). More specifically, it is possible that sleep disturbance may trigger the inflammatory sequelae starting from increased peripheral inflammation activating, via humoral or neuronal paths, central nervous system inflammation and microglia cells with the subsequent depressive symptoms (Fig. 1).

Empirical research testing this mediation hypothesis is still lacking. Using data from three waves of the English Longitudinal Study of Aging, we recently reported that higher sleep disturbance at baseline was associated with mid-assessment serum CRP, which in turn significantly mediated the association between self-reported sleep disturbance and severity of depressive symptoms at follow-up in women even after controlling for baseline depression and relevant socioeconomic and health confounders (Ballesio et al., 2022). This study provided first longitudinal evidence supporting the mediation of peripheral inflammation on the sleep-depression link considering long intervals (2 years between each wave). Looking at closer time intervals, Piber et al. (2022) examined the associations between polysomnographic sleep, next morning serum cytokine levels, and daily depressive symptoms in non-depressed older adults. Findings of mediation analysis showed that the association between sleep disturbance and daily depression was attenuated by 28% when accounting for morning IFN-γ, although the mediation test was not significant likely due to lack of statistical power for IFN-γ and other cytokines under study including TNF, IL-6, IL-8. IFN-γ is a cytokine which is primarily produced by activated $CD4^+$ or $CD8^+$ T cells and natural killer cells and is considered a mediator of both innate and adaptive immunity (Muhl and Pfeilschifter 2003), by upregulating other cytokines such as IL-6 and TNF (e.g., Hayes et al., 1995; Yoshida et al., 2021), although anti-inflammatory actions of IFN-γ on IL-8 were also reported (Muhl and Pfeilschifter 2003). Beyond sleep disturbance, longitudinal data also preliminarily suggested that long sleep (7–9h) may be associated with suicide ideation through the mediation of increased IL-6 in individuals with comorbid depression and anxiety (Dolsen et al., 2021). To the best of my knowledge, no studies to date examined the presence of central nervous system inflammation in individuals with sleep disturbance.

An alternative hypothesis in this field conceives inflammation and sleep disturbance as potential moderators of depression. According to the two-hit model of depression, sleep disturbance and inflammation may reciprocally interact with one another in influencing the onset and

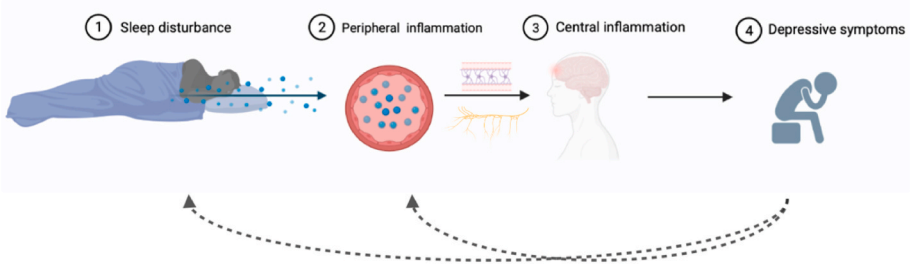

Fig. 1. Inflammatory mediation hypothesis of sleep disturbance - depression link. Sleep disturbance may lead to increased peripheral inflammation as detected in bloodstream. Peripheral inflammation may activate central inflammation through humoral (i.e., cytokines diffusion through intact or leaky regions of blood-brain-barrier, i.e., circumventricular organs), or neuronal (e.g., binding of cytokines to afferent vagus nerve fibres) paths, which are thought to work in parallel. Cytokines diffused into the parenchyma may also induce prostaglandins by blood-brain-barrier endothelial cells with consequent activation of glial cells (i.e., microglia, astrocytes, oligodendrocytes). In turn, these may decrease catecholamines concentrations, neurotrophic activity (i.e., brain-derived neurotrophic factor-related signalling pathways), and increase oxidative stress (i.e., reactive oxygen species production), with the following onset of depressive symptoms. Notably, depressive symptoms may be bidirectionally be associated with sleep disturbance and inflammation as represented by the dashed arrow.

worsening of depression (Irwin and Piber, 2018). Specifically, sleep disturbance may serve as a vulnerability factor and increase the severity of depression following exposure to an inflammatory challenge such as infectious disease or stressful live events; reciprocally, inflammation itself may act as a vulnerability factor and increase the risk of depression when individuals experience sleep disturbance. This moderation hypothesis was partially empirically tested in the aforementioned study of Piber et al. (2022), which showed that IFN-γ moderated the association between sleep disturbance and depression severity. In other words, the association between sleep disturbance and daily depressive symptoms was stronger in individuals with higher morning IFN-γ. Despite the growing interest in the role of inflammation on the sleep-depression link, available knowledge in this field remains mostly theoretical. Very few empirical studies supported the role of inflammation as mediator or moderator of the association between sleep disturbance and depression.

5. Research agenda and model testing

The study of the role of sleep disturbance on inflammation in depression requires methodological considerations. By guidelines (e.g., Riemann et al., 2017), the assessment of sleep disturbance should be based on the sole use of self-reported information provided by patients through sleep diaries, questionnaires, and clinical interviews. However, the gold standard to physiologically assess sleep is polysomnography, which is based on electroencephalography, electrooculography, and electromyography and allows a more precise estimate of sleep architecture. While subjective sleep measures are highly used in population-based studies exploring the role of inflammation on sleep-depression link in large samples (e.g., Ballesio et al., 2022), the implementation of polysomnography is more feasible in laboratory studies with smaller samples (e.g., Piber et al., 2022) which are instead at risk of statistical underpower. Future studies assessing the associations between objective sleep and cytokines levels may benefit from considering the use of actigraphy, based on accelerometer, which could combine a precise estimate of sleep parameters such as sleep onset latency and night-time wake with a non-invasive, non-expensive, and ecological methodology of data collection (e.g., Friedman 2011).

Crucially, only the assessment of sleep disturbance, inflammation, and depression at three different time-points would allow to rigorously test the mediation hypothesis of inflammation on sleep-depression link (Zagaria et al., 2022a). This would allow to properly control for baseline levels of depression and inflammation and permit a sufficient time for inflammation and depression to occur and be detected. As demonstrated by Piber et al. (2022), momentary assessments of sleep disturbance, serum inflammation, and depression in rapid succession (e.g., during the course of one or more nights and days) may elegantly serve this scope. While the collection of subjective and objective (actigraphic) sleep measures and depressive symptoms (e.g., questionnaires or mood diaries such as the Profile of Mood States (Shacham, 1983) may be particularly useful in momentary assessments in daily life (ecological settings), the repeated collection of blood samples to assess peripheral inflammation may be challenging. Also, it has been previously shown that intravenous catheters used for repetitive blood sampling may be associated with increase IL-6 due to local cytokine production rather than by physiological changes in circulating IL-6 levels (Haack et al., 2002). Salivary assay for the assessment of cytokines such as IL-6, IL-10, and TNF appear to be robust and unaffected by outlier and could be considered in future ecological studies (Szabo and Slavish, 2021). To the best of my knowledge, however, little is known about the associations between sleep disturbance and salivary measures of inflammation (LaVoy et al., 2020). Additionally, saliva sampling requires specific actions (see Szabo and Slavish, 2021 for best practices in ecological studies with saliva sampling). Urine sampling of neopterin, a marker of cell-mediated immunity synthetised by macrophages in response to IFN-γ signalling, has been employed to assess immune activation in depression and other mental disorders (Dunbar et al., 1992). In sleep medicine, it has been rarely used to assess immune activation in patients with sleep disordered breathing with controversial results (e.g., Ursavaş et al., 2008). Therefore, evidence appears too scarce to recommend the employment of urine neopterin as a marker of inflammation in sleep-depression link studies.

The assessment of central nervous system inflammation using cerebrospinal fluid or imaging techniques is remarkably invasive and not routinary implemented in individuals with sleep disturbance. A recent study provided evidence for the assessment of depression-related central inflammation using serum astrocyte-derived extracellular vesicles (Xie et al., 2022). Such technique may be a valid tool to properly assess the role of neuroinflammation on the association between sleep disturbance and depression.

6. Conclusions

Evidence summarised in this review consistently demonstrated an influence of sleep disturbance on the onset, severity, and remission of depression. While accumulating evidence suggest that inflammation may similarly be involved in aetiology of depression, the role of sleep disturbance on depression-associated inflammation remain poorly explored. I argued in this review that sufficient evidence was produced to hypothesise that sleep disturbance may causally be involved in increased inflammation in individuals with depression. However, this hypothesis still needs to be properly tested. The specific mechanisms by which sleep disturbance may lead to inflammation remain to be clarified. HPA activation may be a main one (Irwin 2019). Impairment in glymphatic system and astrocyte function may also play a role, despite evidence in human is limited (Yan et al., 2021). Another possibility is that sleep may induce inflammation via reducing anti-inflammatory mechanisms. Cross-sectional data suggested that individuals with sleep disturbance showed lower levels of anti-inflammatory serum IL-10 compared to controls (e.g., He et al., 2021). Also, experimentally

disturbed sleep has been recently associated with a decrease in resolvins, mediators of inflammatory resolution mainly derived from omega-3 fatty acids (Engert et al., 2020). It would be informative to further evaluate longitudinal associations between sleep disturbance and anti-inflammatory cytokines.

Whether sleep disturbance and inflammation may reciprocally interact in influencing the onset and worsening of depression also requires empirical testing which was neglected to date. Similarly, literature on the mediation of inflammation on the association between sleep disturbance and the onset and severity of depressive symptoms is still in its youth and may hopefully flourish in light of promising results of recent pilot studies (Ballesio et al., 2022; Piber et al., 2022). This review was theory-driven, and sleep disturbance was mainly conceptualised as a potential predictor of inflammation and depression. While it was beyond the aim of this work to provide a comprehensive review of the bidirectional associations of the variables under study, it is worth mentioning that sleep disturbance has also been conceived as an outcome of immune challenge (e.g., Bauer et al., 1995). This should be considered when planning future research in this field.

Author declaration template

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

We understand that the Corresponding Author is the sole contact for the Editorial process (including Editorial Manager and direct communications with the office). He/she is responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs. We confirm that we have provided a current, correct email address which is accessible by the Corresponding Author and which has been configured to accept email from (andrea.ballesio@uniroma1.it)

Declaration of competing interest

In relation to the manuscript BBIH-D-23-00026 entitled **"Inflammatory hypotheses of sleep disturbance-depression link: update and research agenda**", I state that I have no conflict of interest to disclose and that there are no data associated with the manuscript.

Data availability

No data was used for the research described in the article.

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