ISSN: 2689-422X
DOI: 10.33552/GJPNC.2024.05.000603
Global Journal of Pediatrics & Neonatal Care
Iris Publishers

Short Communication

Sleep Disorder Provoked Immune Dysregulation: Too Little or Too Much Sleep That Is the Question?

Thyyar M Ravindranath*

Department of Pediatrics, Division of Pediatric Critical Care Medicine, Columbia University, USA

***Corresponding author:** Thyyar M Ravindranath, Department of Pediatrics, Division of Pediatric Critical Care Medicine, Columbia University, USA

Received Date: July 08, 2024

Published Date: July 19, 2024

Abstract

The activity of sleep is a complex process which is essential for appropriate bodily homeostasis. The lack of sleep leads to maladaptive bodily functions. Hence, a set amount of sleep is essential for healthy living. In this brief review, the topic of sleep disorder provoked immune dysregulation via neuronal, cytokine, hormonal, and gut associated influence will be discussed with suggestions on therapeutic options such as napping and the use of medications to overcome such an unfortunate malady.

Keywords: Sleep disorder; Hypothalamus-pituitary-axis; Autonomic nervous system; Cytokines; Hormones; Immunity

Introduction

Pediatric sleep disorders affect 25% to 40% of children and adolescents [1]. Sleep disorders in children include insomnia (10%-30%), obstructive sleep apnea [OSA] (1%-5%), restless legs syndrome (2%-4%), parasomnia (50%), and delayed sleep phase syndrome (7%-16%). OSA peaks between 2 and 8 years of age and restless legs syndrome is more common in adolescents [2]. The Center for Disease Control (CDC) and Prevention and the American Heart Association suggest a sleep duration of seven hours per night for maintenance of normal health [3]. Sleep deprivation affects about fifty million individuals in the United States [4]. Although much is known about the health effects of disordered sleep, the immune effects have garnered little attention. This chapter will discuss the effect of disordered sleep on immune function. It is meaningful to remember that sleep influences inflammation and inflammation in turn impacts sleep. This article will focus on the former rather than on the latter.

Sleep can be defined as an altered consciousness level wherein there is decreased responsiveness to external stimuli with lack of voluntary movements [5], rapid spontaneous reversibility, adoption of specific postures, homeostatic regulation, and partial control by circadian rhythm [6]. Sleep is essential to maintain the brain's communication system. Sleep helps to preserve perception, mood, flexibility, stable physiological state, the clearance of metabolic waste resulting from metabolic endeavors during the wakeful period [7], boosts learning, controls behavior [8], maintains endocrine rhythm, and improves the function of the immune system [9]. The desired sleep length varies with the age group, as shown in table 1 [10].

Table 1: Sleep length in different age groups.

Age	Hours of sleep (hours)	Mean number of naps in 24 hours
Infants: 4-12 months	12-16	2 at 12 months of age
Infants: 6-9 months	10-12	As above
Toddlers: 1-3 years	11-14	1 at 18 months of age
Preschool children: 3-5 years	10-13	No naps in 50%
School age: 6-12 years	9-12	None
Adolescents: 12-18 years	8-10	none

Sleep loss can clinically be divided into acute and chronic conditions. Acute sleep loss is defined as the absence of or the reduction in the customary sleep time enduring 1-2 days with the rousing period encompassing 16-18 hours in a given 24-hour period. Chronic sleep loss is termed as sleeping less than the amount required for optimal function and health maintenance every day for three months with undue day time sleep [11].

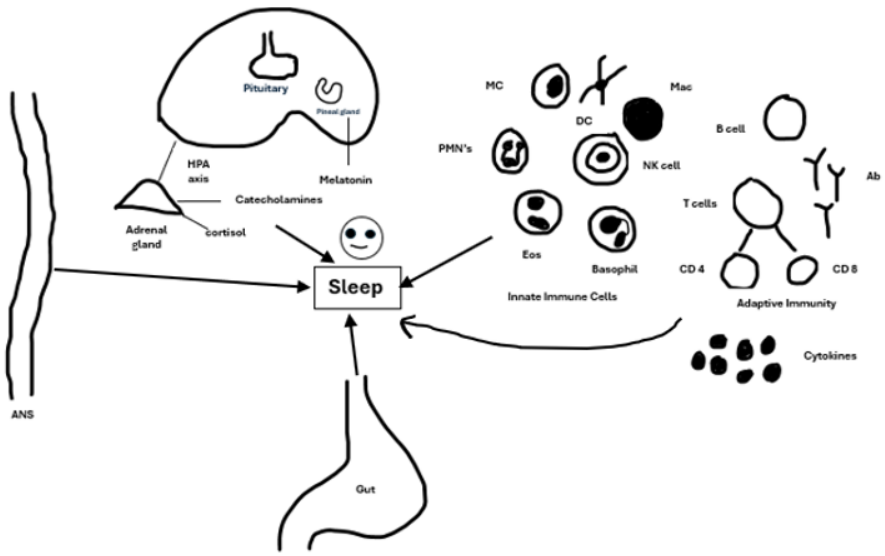
Mature sleep pattern is observed beyond infancy and into adolescents. Mature sleep pattern is divided using EEG criteria into Non-Rapid Eye Movement (NREM) and Rapid Eye Movement (REM) sleep with NREM sleep being further divided into N1 which is characterized by an awake to a sleep state with slow rolling eye movements; N2, which is characterized by a sleep state and which makes up 50% of the sleep time; and N3, also termed as Slow Wave Sleep (SWS), and which makes up 20% of the sleep time. Normally sleep proceeds from NREM to REM lasting 80 to 110 minutes followed by a brief wake state with episodes of 4-6 cycles during the sleep state and consisting of SWS early and REM later [12,13]. SWS predominates during the 1st half of the sleep state and REM during the 2nd half of the sleep state. REM occurs only during the sleep state and the dream state is part of the sleep state wherein muscle activity is suppressed. REM is under circadian control whereas NREM is under homeostatic control.

Infant sleep starts in REM and continues into NREM. Individually the REM-NREM cycle of 45 to 60 minutes consists of 30 minutes of REM and 30 minutes of NREM, and the sequence is repeated one to two times prior to an awakening state [14].

Pathophysiology (Figure 1):

General:

Metabolism is conserved during sleep with an uptick of inflammatory activity that helps to enhance host defense against microbes which is further boosted by infection induced increase in sleep duration. Sleep deprivation shifts inflammation from a nighttime event to a daytime event thus, enhancing inflammatory response via cytokines [15].



ANS: autonomic nervous system, HPA-axis: hypothalamic-pituitary-adrenal-axis, PMN's: polymorph nuclear leukocytes, MC: macrophage, DC: dendritic cell, mac: macrophage, NK cell: natural killer cell, Eos.: eosinophil, Ab: antibody, B-cell: Bursa of Fabricius, T-cell: Thymus derived cell, CD-4: helper T -cell, CD-8: cytotoxic T-cell.

Figure 1: shows various factors affecting sleep.

Regulators of inflammatory response:

The brain-immune signaling:

The CNS and the immune system are connected closely by nerve fibers, soluble mediators, and leukocytes that travel between the brain and the spinal cord. Lymphoid organs are supplied by sympathetic, sensory, and peptidergic (neurotransmitters of short peptide chain) nerve fibers. Immune cells are endowed with receptors that recognize neurotransmitters and efferent nerve generated neuropeptides such as catecholamines. Leukocytes are capable of manufacturing and releasing neuronal messengers [16]. Leukocytes and macrophages are capable of sensing local nerve ending released neurotransmitters and neuropeptides [17]. Leukocytes, in addition, produce neurotransmitters, neuropeptides, and hormones that communicate with the brain via blood and afferent nerve fibers. Furthermore, cytokines and chemokines produced by the immune cells act on neurons, astrocytes, microglia of the CNS, and the peripheral nervous system (PNS) via their receptors.

The CNS-inflammatory axis:

The central nervous system (CNS) regulates inflammatory response via hypothalamic-pituitary-adrenal axis (HPA) through cortisol which exhibits anti-inflammatory property. The mechanism of action of cortisol includes inhibition of expression of proinflammatory genes and induction of anti-inflammatory genes which inhibit pro-inflammatory transcription factors such as nuclear factor kapa beta (NF-κβ) and activator protein-1 (AP-1) [18]. The neuro-endocrine axis control of the immune system is a slow process. Neuronal, glial cells, and nerve fibers can synthesize cytokines and chemokines [19]. All these connections induce microglial activation and neuro inflammation in response to peripheral inflammation inducing fever and ill health.

Patients with insomnia as opposed to healthy controls exhibited suppressed serum levels of neurotrophins including brain-derived neurotrophic factor (BDNF), proteins necessary for neuroplasticity, memory, and sleep [20].

The autonomic nervous system control of immune response:

The sympathetic nervous system (SNS) promotes inflammation by upregulation of interleukin-1 beta (IL-1β), tumor necrosis factor alfa (TNF-α), interleukin-6 (IL-6), and downregulating anti-viral immune response via suppression of type-1 interferon [21]. Adaptive immune response is influenced via β-adrenergic system by upregulation of interleukins 4 and 5 (IL-4 & IL-5), T helper cells-2 (TH-2 response), and suppression of interferon gamma (IFN-ɤ) and interleukin-12B (IL-12B) (TH-1 response). The SNS alters innate immune cells such as neutrophils, monocytes, natural killer cells (NK), and hemopoietic stem cell trafficking [12].

Vagal (parasympathetic) afferents influence the brain signaling mechanism as evidenced by weakening of intraperitoneal TNF-α effect on NREM sleep [22].

The mechanism of enhanced immune defense mechanism following adequate sleep:

Enhanced immune defense mechanism is controlled via the HPA axis, autonomic nervous system (ANS), immune cells, and the gut.

The HPA axis:

Inflammatory activity that follows sleep is associated with a low cortisol level and/or an increase in SWS encouraging anti-viral immunity [23]. Constant activation of the HPA axis leads to immune cells' resistance to glucocorticoids [24]. The method of resistance is via inflammatory cytokines directed accumulation of leading negative isoform of the glucocorticoid receptor [25]. Another mechanism is stress triggered release of damage-associated molecular patterns (DAMPS), triggering nucleotide oligomerization domain (NOD), leucine-rich repeats (LRR), and pyrin domain-containing protein 3 (NLRP3) inflammasome which causes caspase induced cleaving of the glucocorticoid receptor and results in glucocorticoid resistance [26].

The ANS:

The onset of sleep (NREM and SWS) is characterized by decreased sympathetic activity, accompanied by an increase in parasympathetic outflow [27]. Sleep deprivation leads to an increase in sympathetic activity [28]. Increase in sympathetic activity prompts an increase in noradrenaline which, via β-adrenergic receptor, activates NF-κβ and the production of inflammatory cytokines resulting in systemic inflammation [29] and a decrease in NK cell activity [30].

Immune cells:

During adequate sleep of 6-8 hours, antigen presenting cells (APC) and thymus derived cells (T cells) move from circulation into the lymphoid tissue. Sleep encourages the activation of T cells by enhanced production of IL-2 and IFN-ɣ by T cells and IL-12 by dendritic cells (DC's) as well as monocytes thus inducing TH-1 response [31]. Nighttime sleep favors TH-1 immune response characterized by elevated IFN-ɤ by T cells and decreased anti-inflammatory cytokine IL-10 expression by monocytes (TH-2 response) thus enhancing immunity [32]. Sleep maintains lymphocyte proliferative response. Sleep favors both memory and effector phases of immune response to vaccination. Sleep of 6-7 hours enhances antibody response to vaccination compared to short sleep duration. Adequate sleep has no effect on viral replication [33]. Adequate sleep is important to fight invading pathogenic organisms and protect symbiotic organisms that reside in the human body.

The gut:

The gut microbiota predominated by bacteria lives in synergy with the host. Gut health is influenced by brain-gut-microbiome axis. Sleep loss and intermittent hypoxemia lead to alteration in gut microbiome composition and loss of gut barrier function (leaky gut) which results in local and systemic inflammatory responses

from production of proinflammatory cytokines such as IL-6 and translocation of lipopolysaccharide (LPS) [34].

The mechanism of loss of immune defense following sleep deprivation:

The ability of recruitment of APC and T cells into the lymphoid tissue and TH-1 cytokine signaling is disturbed leading to changed interaction between APC and T cells prior to effector T cell formation. Sleep duration of less than 5 hours each night influences pneumonia risk and less than 6 hours of sleep each night predisposes the body to the common cold [35]. Individuals with sleep loss displayed a 1.2-fold elevated risk of herpes zoster infection versus the adequate sleep group [36]. In addition to decreased T cell proliferation and a decreased expression of HLA-DR (a major histocompatibility complex {MHC} II cell surface receptor) which alters antigen presentation to T cells. The explanation for increased risk of infection following sleep deprivation includes increase in CD14+ cells (lipopolysaccharide binding protein [LPSBP]), and alterations in CD4+ (helper) and CD8+ (suppressor) T lymphocytes [37]. TH-2 overactivity is implicated in the increase of some form of allergic response and contributes to some types of tumor generation by the inhibition of cytotoxic T cell proliferation [38].

Sleep and SARS-COV-2:

Sleep deprivation and sleep disorder are possible risk factors for SARS-COV-2 infection particularly among health care workers [39]. Poor sleep related to disturbed circadian rhythm results in decreased prolactin levels, leading to increased susceptibility to SARS-COV-2 infection [40]. OSA results in poor outcome in COVID-19 patients in terms of the disease severity, the intensive care unit admission, the need for mechanical ventilation, and the mortality [41]. Individuals with OSA have eight times more risk of developing SARS-COV-2 infection than those who don't have OSA. The combination of SARS-COV-2 and OSA led to two times the risk of developing respiratory failure and increased risk of hospitalization [42]. The mechanism of OSA induced morbidity associated with SARS-COV-2 may be due to, 1. OSA induced poor sleep quality, leading to intermittent hypoxemia thereby encouraging lung inflammation [43] and exacerbating a cytokine storm related to acute respiratory distress syndrome (ARDS), 2. OSA induced dysregulation of the renin-angiotensin system facilitates the entry of SARS-COV-2 into the host cells [44].

The effects of sleep loss:

Sleep deprivation induces the upregulation of genes involved in Bursa of Fabricius (B-cell) activation, IL-8 production, and LPS binding by LPSBP as described above. In addition, there was an expansion of T lymphocytes, plasma cells, markers of autoimmunity, and alteration in myeloid cell subsets indicating dysregulated immunity [45].

Sleep loss is accompanied by decreased serum levels of melatonin which is an antioxidant involved in overcoming oxidative stress [46]. Melatonin interacts with Brain-Derived Neurotrophic Factor (BDNF) to halt apoptosis and to encourage neurogenesis.

Sleep loss leads to enhanced oxidative stress and a loss of antioxidant defense resulting in cell senescence, systemic inflammation, dysmetabolism, and immune dysregulation [47].

Circulating cell response to adequate sleep and sleep deprivation:

Adequate sleep reduces the leukocyte number transiently. Monocyte, lymphocyte, and lymphocyte subclasses such as B-cells, CD4, and CD8 T cells, as well as NK cells either are unchanged [48] or decreased [49] by adequate sleep versus sleep loss. Most studies point to a decrease in leukocyte subclasses due to the relocation of cells from blood to various tissues and organs.

Sleep loss results in increased circulating total leukocytes, such as neutrophils, monocytes, B cells, CD4 T cells, and a reduced number as well as cytotoxic activity of NK cells [50]. There is also a decrease in the circadian rhythm of circulating leukocytes which are normally at higher levels during night and early morning, as well as suppressed neutrophil phagocytic activity, and altered lymphocyte adhesion molecule appearance [51].

Circulating cytokine levels following inadequate sleep:

Sleep deprivation results in an elevation in the levels of plasma IL-6 and C-reactive protein (CRP). The IL-1 receptor antagonist (IL-I ra) was increased which may reflect a response to elevated proinflammatory cytokine IL-1 [52].

The effect of sleep recovery following sleep loss on immunity:

The cell counts of leukocytes, granulocytes, and NK cells recovered in one night subsequent to the recovery of sleep loss after sleep deprivation [53]. Restoration of the diurnal rhythm of immune cells required longer periods of sleep recovery (5-7 days). The effect of multiple days of sleep recovery on sleep deprived elevations on inflammatory cytokines such as TNF, IL-6, Il-17, and IL-1 was restored to pre-sleep deprived levels [54].

Clinical consequences of sleep deprivation:

Ageing process:

Sleep deprivation has other consequences that include cellular ageing as evidenced by the inhibition of cell progression and the shortening of leukocyte telomere length [55].

Cognition:

Sleep deprivation (<7 hours) or even sleep excess (>7 hours) leads to an impairment in intellectual function due to the activation of inflammatory pathways [56].

Anxiety and depression:

Lack of sleep promotes depressive symptoms especially for at-risk individuals such as those that are exposed to stress and experience underlying inflammatory disorders [57]. Chronic sleep deprivation induced a decrease in testosterone levels which intensifies the gamma-aminobutyric acid (GABA) and serotonin induced prevention of neuro transmission. This can lead to

depression and anxiety.

Autoimmune disorders:

There is an approximately 1.5 times odd ratio of developing autoimmune disorders such as rheumatoid arthritis, ankylosing spondylitis, systemic lupus erythematosus, and systemic sclerosis in those who have sleep related disorders. [58] This is due to the generation of multiple proinflammatory cytokines such as IL-6, IL-17, and Th-17 cell response as well as impaired suppressive activity of CD4 regulatory T cells (Tregs).

Other health effects sleep deprivation:

Immune dysregulation from sleep disorders leads to cardiovascular, metabolic, neuropsychiatric, and some forms of cancers [59].

Therapeutic options to sleep loss:

The inflammatory system does acclimatize, in terms of response to the repeated exposure to sleep restriction-recovery models, over a 3-week period.

Napping appears to restore immune changes generated by acute sleep loss.

Child insomnia is treated by behavior intervention.

OSA treatment involves adenotonsillectomy and the appropriate use of nasal continuous positive airway pressure in selected cases.

Treatment of Parasomnia involves education and support, addressing stressors if detected, and the treatment of comorbid conditions such as OSA, restless legs syndrome, and gastroesophageal reflex.

Restless legs syndrome is treated with iron if there is evidence of iron deficiency.

Delayed sleep phase syndrome therapy includes avoiding exposure to blue and bright light such as what is found in electronic devices prior to bedtime. Melatonin is used before bedtime. Bright light therapy is used within 1-2 hours after awakening [60].

Melatonin treatment may overcome brain oxidative stress and help to prevent sleep loss related to neuronal damage [61]. Probiotics, by restoring gut dysbiosis, may restore disordered sleep.

Conclusion

The immune effects of sleep loss are complex. The CNS, ANS, and the gut play a vital role in immune regulation associated with sleep. There is a switch in immune phenotype from TH-1 to TH-2 following sleep loss resulting in immunosuppression and consequent ill health. The changes to sleep deprivation are modified by restoring adequate sleep duration by treating the underlying causes of sleep disturbance.

Acknowledgement

The author wishes to acknowledge Malini Ravindranath, PhD, for her contribution in reading and editing the manuscript.

Conflict of Interest

None.

References

1. Broman JE, Lundh LG, Hetta J (1996) Insufficient sleep in the general population. Neurophysiol Clinique/Clin Neurophysiol 26(1): 30-39.
2. Carter KA, Hathaway NE, Lettieri CF (2014) Common sleep disorders in children. Am Fam Physician 89(5): 368-377.
3. Liu Y, Wheaton AG, Chapman DP, Cunningham TJ, Lu H, et al. (2016) Prevalence of Healthy Sleep Duration among Adults—United States, 2014. MMWR. Morb Mortal Wkly Rep 65(6): 137-141.
4. Roth T (2007) Insomnia: Definition, prevalence, etiology, and consequences. J Clin Sleep Med 3 (5 suppl): S7-S10.
5. Krueger JM, Frank MG, Wisor JP, Roy S (2016) Sleep function: toward elucidating an enigma. Sleep Med Rev 28: 46-54.
6. Siegel J. Principles and practice of sleep medicine. In: Kryger MH, Roth T, Goldstein CA, et al. (2022) editors. [Kryger, 2022 #181]. Seventh edition. Philadelphia, PA: Elsevier pp. 52-53.
7. Irwin MR (2015) Why sleep is important for health: a psychoneuroimmunology perspective. Annu Rev Psychol 66: 143-172.
8. Beebe DW (2011) Cognitive, behavioral, and functional consequences of inadequate sleep in children and adolescents. Pediatr Clin North Am 58(3): 649-665.
9. Poluektov MG (2021) Sleep and immunity. Neurosci Behav Physiol 51(5): 609-615.
10. Zandieh SO, Johnson S, Katz SE (2023) Sleep from infancy through adolescence. Sleep Med Clin 18(2): 123-134.
11. American Academy of Sleep Medicine (2014). International Classification of Sleep Disorders. 3rd edition.
12. Irwin MR (2019) Sleep and inflammation: partners in sickness and in health. Rev Immunol 19(11): 702-715.
13. Besedovsky L, Lange T, Haack M (2019) The Sleep-Immune Crosstalk in Health and Disease. Physiol Rev 99(3): 1325-1380.
14. Blumberg MS, Gall AJ, Todd WD (2014) The Development of Sleep-Wake Rhythms and the Search for Elemental Circuits in the Infant Brain. Behavioral neuroscience 128(3): 250-63.
15. Vgontzas AN, Papanicolaou DA, Bixler EO, Lotsikas A, Zachman K, et al. (1999) Circadian interleukin-6 secretion and quantity and depth of sleep. J Clin Endocrinol Metab 84(8): 2603-2607.
16. Pert CB, Ruff MR, Weber RJ, Herkenham M (1985) Neuropeptides and their receptors: a psychosomatic network. J Immunol 135 (2 suppl): 820s-826s.
17. Ordovas-Montanes J, Rakoff-Nahoum S, Huang S, Riol-Blanco L, Barreiro O, et al. (2015) The Regulation of Immunological Processes by Peripheral Neurons in Homeostasis and Disease. Trends Immunol 36(10): 578-604.
18. Irwin MR, Cole SW (2011) Reciprocal regulation of the neural and innate immune systems. Nat. Rev Immunol 11(9): 625-632.
19. Boulanger LM (2009) Immune proteins in brain development and synaptic plasticity. Neuron 64(1): 93-109.
20. Giese M, Unternährer E, Hüttig H, Beck J, Brand S, et al. (2014) BDNF: an indicator of insomnia? Mol Psychiatry 19(2): 151-152.
21. Cole SW, Arevalo JM, Takahashi R, Sloan EK, Lutgendorf SK, et al. (2010) Computational identification of gene- social environment interaction at the human IL6 locus. Proc Natl Acad Sci USA 107(12): 5681-5686.
22. Kubota T, Fang J, Guan Z, Brown R A, Krueger J M, et al. (2001) Vagotomy attenuates tumor necrosis factor-alpha-induced sleep and EEG delta

activity in rats. Am J Physiol Regul Integr Comp Physiol 280(4): R1213-1220.

23. Lange T, Dimitrov S, Born J (2010) Effects of sleep and circadian rhythm on the human immune system. Ann NY Acad Sci 1193: 48-59.

24. Miller A, Raison CL (2016) The role of inflammation in depression: from evolutionary imperative to modern treatment target. Nat Rev Immunol 16(1): 22-34.

25. Webster JC, Oakley RH, Jewell CM, Cidlowski JA (2001) Proinflammatory cytokines regulate human glucocorticoid receptor gene expression and lead to the accumulation of the dominant negative beta isoform: a mechanism for the generation of glucocorticoid resistance. Proc Natl Acad Sci USA 98(12): 6865-6870.

26. Paugh SW, Bonten EJ, Evans WE (2016) Inflammasome- mediated glucocorticoid resistance: the receptor rheostat. Mol Cell Oncol 3(1): e1065947.

27. Boudreau P, Yeh WH, Dumont GA, Boivin DB (2013) Circadian variation of heart rate variability across sleep stages. Sleep 36(12): 1919-1928.

28. Irwin M, Thompson J, Miller C, Gillin J, Ziegler M (1999) Effects of sleep and sleep deprivation on catecholamine and interleukin-2 levels in humans: clinical implications. J Clin Endocrinol Metab 84(6): 1979-1985.

29. Irwin MR, Cole SW (2011) Reciprocal regulation of the neural and innate immune systems. Nat Rev Immunol 11(9): 625-632.

30. Irwin MR, Opp MR (2017) Sleep health: reciprocal regulation of sleep and innate immunity. Neuropsychopharmacology 42(1): 129-155.

31. Lange T, Dimitrov S, Born J (2010) Effects of sleep and circadian rhythm on the human immune system. Ann NY Acad Sci 1193: 48-59.

32. Besedovsky L, Lange T, Haack M (2019) Sleep-immune crosstalk in health and disease. Physiol Rev 99(3): 1325-1380.

33. Renegar KB, Floyd RA, Krueger JM (1998) Effects of short-term sleep deprivation on murine immunity to influenza virus in young adults and senescent mice. Sleep 21(3): 241-248.

34. Neroni B, Evangelisti M, Radocchia G, Di Nardo G, Pantanella F, et al. (2021) Relationship between sleep disorders and gut dysbiosis: what affects what? Sleep Med 87: 1-7.

35. Prather AA, Janicki-Deverts D, Hall MH, Cohen S (2015) Behaviorally assessed sleep and susceptibility to the common cold. Sleep 38(9): 1353-1359.

36. Chung W S, Lin H H, Cheng N C (2016) The incidence and risk of herpes zoster in patients with sleep disorders: a population-based cohort study. Medicine (Baltimore) 95(11): e2195.

37. Brown R, Pang G, Husband AJ, King MG (1989) Suppression of immunity to influenza virus infection in the respiratory tract following sleep disturbance. Reg Immunol 2(5): 321-325.

38. Disis ML (2010) Immune regulation of cancer. J Clin Oncol 28(29): 4531-4538.

39. Kim H, Hegde S, LaFiura C, Raghavan M, Luong E, et al. (2021) COVID-19 illness in relation to sleep and burnout. BMJ Nutr Prev Health 4(1): 132-139.

40. Ramos E, López-Muñoz F, Gil-Martín E, Egea J, Álvarez-Merz I, et al. (2021) The Coronavirus Disease 2019 (COVID-19): Key Emphasis on Melatonin Safety and Therapeutic Efficacy. Antioxidants 10(7): 1152.

41. Hariyanto TI, Kurniawan A (2021) Obstructive sleep apnea (OSA) and outcomes from coronavirus disease 2019 (COVID-19) pneumonia: A systematic review and meta-analysis. Sleep Med 82: 47-53.

42. Maas MB, Kim M, Malkani RG, Abbott SM, Zee PC, et al. (2021) Obstructive Sleep Apnea and Risk of COVID-19 Infection, Hospitalization and Respiratory Failure. Sleep Breath 25(2): 1155-1157.

43. Memtsoudis SG, Ivascu NS, Pryor KO, Goldstein PA (2020) Obesity as a risk factor for poor outcome in COVID-19-induced lung injury: The potential role of undiagnosed obstructive sleep apnoea. Br J Anaesth 125(2): e262-e263.

44. Leisman DE, Ronner L, Pinotti R, Taylor MD, Sinha P, et al. (2020) Cytokine elevation in severe and critical COVID-19: A rapid systematic review, meta-analysis, and comparison with other inflammatory syndromes. Lancet Respir Med 8(12): 1233-1244.

45. Liu X, Chen B, Huang Z, Duan R, Li H, et al. (2021) Effects of poor sleep on the immune cell landscape as assessed by single-cell analysis. Commun Biol 4(1): 1-15.

46. Tan DX, Manchester LC, Terron MP, Flores L J, Reiter RJ, et al. (2007) One molecule, many derivatives: a never-ending interaction of melatonin with reactive oxygen and nitrogen species? J Pineal Res 42(1): 28-42.

47. Liguori I, Russo G, Curcio F, Bulli G, Aran L, et al. (2018) Oxidative stress, aging, and diseases. Clin Inter Aging 13: 757-772.

48. Ackermann K, Revell VL, Lao, O, Rombouts EJ, Skene DJ, et al. (2012) Diurnal rhythms in blood cell populations and the effect of acute sleep deprivation in healthy young men. Sleep 35(7): 933-940.

49. Besedovsky L, Dimitrov S, Born J, Lange T (2016) Nocturnal sleep uniformly reduces numbers of different T-cell subsets in the blood of healthy men. Am J Physiol Regul Integr Comp Physiol 311(4): R637-R642.

50. Born J, Lange T, Hansen K, Molle M, Fehm HL, et al. (1997) Effects of sleep and circadian rhythm on human circulating immune cells. J Immunol 158(9): 4454-4464.

51. Redwine L, Dang J, Irwin M (2004) Cellular adhesion molecule expression, nocturnal sleep, and partial night sleep deprivation. Brain Behav Immun 18(4): 333-340.

52. Frey DJ, Fleshner M, Wright KP Jr (2007) The effects of 40 hours of total sleep deprivation on inflammatory markers in healthy young adults. Brain Behav Immun 21(8): 1050-1057.

53. Ruiz FS, Andersen ML, Martins RC, Zager A, Lopes JD, et al. (2012) Immune alterations after selective rapid eye movement or total sleep deprivation in healthy male volunteers. Innate Immun 18(1): 44-54.

54. Pejovic S, Basta M, Vgontzas AN, Kritikou I, Shaffer ML, et al. (2013) Effects of recovery sleep after one work week of mild sleep restriction on interleukin-6 and cortisol secretion and daytime sleepiness and performance. Am J Physiol Endocrinol Metab 305(7): E890-E896.

55. Prather AA, Hecht FM, Epel ES (2016) Factors related to telomere length. Brain Behav Immun 5: 279.

56. Shi L, Chen SJ, Ma MY, Bao YP, Han Y, et al. (2018) Sleep disturbances increase the risk of dementia: a systematic review and meta- analysis. Sleep Med Rev 40: 4-16.

57. Cho HJ, Eisenberger NI, Olmstead R, Breen EC, Irwin MR, et al. (2016) Preexisting mild sleep disturbance as a vulnerability factor for inflammation-induced depressed mood: a human experimental study. Transl Psychiatry 6(3): e750.

58. Hsiao YH, Chen YT, Tseng CM, Wu LA, Lin WC, et al. (2015) Sleep disorders and increased risk of autoimmune diseases in individuals without sleep apnea. Sleep 38(4): 581-586.

59. Irwin MR (2015) Why sleep is important for health: a psychoneuroimmunology perspective. Annu Rev Psychol 66: 143-172.

60. Deshpande P, Salcedo B, Haq C (2022) Common Sleep Disorders in Children. Am Fam Physician 105(2): 68-176.

61. Alghamdi B S (2018) The neuroprotective role of melatonin in neurological disorders. J Neurosci Res 96(7): 1136-1149.