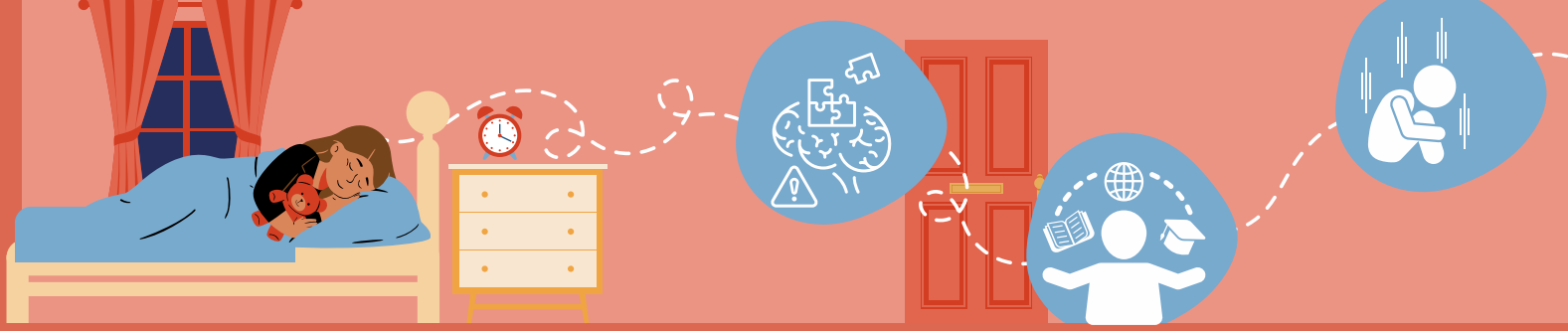

EXPLORING THE SEVERITY OF SLEEP-RELATED COGNITIVE IMPAIRMENTS AMONG CHILDREN WITH FAMILIAL MEDITERRANEAN FEVER: A NARRATIVE REVIEW

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ABSTRACT

Background: Familial Mediterranean Fever (FMF) is the most common autoinflammatory disorder across both Canada and the United States. Children with FMF are thought to experience poorer sleep quality than their healthy counterparts. Sleep is a vital component of overall well-being and a strong predictor of healthy cognitive development. As such, the importance of understanding the cognitive impairments that result from poor sleep quality among this group must not be overlooked.

Objective: This narrative review aims to synthesize relevant research findings to determine the extent to which cognitive development is influenced by poor sleep quality in children with FMF. This information can inform future intervention strategies to improve sleep quality and cognitive developmental outcomes in children ages 8-15.

Results: Attacks of FMF are highly related to negative sleep experiences. Inadequate sleep deprives the childhood brain from undergoing necessary structural and functional developments. Sleep deprivation is thought to inhibit neuroplasticity, hinder academic outcomes, and give rise to a range of comorbidities. Unresolved, this issue can give rise to a myriad of developmental problems via disruptions in cognitive functioning, behaviour, and emotional well-being.

Conclusions: This review suggests that children with FMF experience a wide range of sleep disturbances. To protect the cognitive health of children with this disorder, clinical assessment and support through behaviour or pharmacological therapy is crucial. By recognizing the relevance of sleep quality on cognitive development, healthcare providers and health policy experts can best meet the healthcare needs of children with FMF.

INTRODUCTION

Familial Mediterranean Fever (FMF) is a hereditary autoinflammatory disorder characterized by recurrent episodes of fever and serositis in the chest, abdomen and joints [1]. FMF is a recurrent fever syndrome that primarily affects the paediatric population with approximately 65 and 90 percent of patients experiencing their first attack before the ages of 10 and 20, respectively [2]. It is the most common monogenic autoinflammatory disorder in Canada and the United States, with children of Turkish, Armenian, Middle Eastern, North African Jewish, and Arab descent being the most frequently affected ethnic groups [3].

FMF attacks within the paediatric population present with a range of symptoms, including fever, abdominal pain, chest pain, joint pain, and erysipelas-like skin lesions. These episodes typically last between one and three days and often resolve spontaneously, with patients remaining asymptomatic between attacks [2]. FMF is most frequently attributed to a mutation in the Mediterranean fever (MEFV) gene and is typically inherited in an autosomal recessive fashion [4]. A mutation in this gene leads to a misfolded pyrin protein and dysregulated inflammatory response, resulting in the characteristic episodes of fever and inflammation seen in FMF patients [4]. The triggers of FMF attacks remain elusive; however, research has shown notable positive associations between the likelihood of an FMF attack and various factors such as infection, physical or emotional stress, and menstruation.

Quality sleep is vital to a child's proper functioning and well-being [5]. Greater sleep duration and sleep efficiency are associated with high sleep quality, while a greater number of sleep disturbances, and sleep-onset delay are associated with poorer sleep quality [6]. Sleep quality impacts all domains of a child's health, including socioemotional and cognitive development [7]. Sleep quality is also associated with several behavioural outcomes in children, including temperament, emotional regulation and motivation [8], and impacts several cognitive functions, including memory consolidation, concentration and problem-solving [9]. Healthy sleep habits are essential for promoting optimal cognitive development in children. Consistent bedtimes, a calming bedtime routine, and a comfortable sleep environment are key components of healthy sleep habits [10].

A study conducted by Makay et al. suggests that children with FMF may be at greater risk of experiencing poor sleep quality compared to children without FMF [11]. Pain during FMF episodes, anxiety about future attacks, and disruptions in daily routines due to FMF symptoms could potentially contribute to poorer sleep quality, posing a threat to a child's normal development [11].

Understanding the impact of FMF on children's sleep quality and subsequent cognitive development is crucial for developing targeted interventions to mitigate potential adverse outcomes. This review aims to explore the extent to which sleep quality impacts cognitive development in children with FMF aged 8-15. Adolescence is typically marked by the beginning of puberty, which begins between the ages of 8 and 14 years for girls, and 9 and 15 years for boys. Puberty is characterized by significant biological and social transformations which impact both health and behaviour, including sleep patterns [12]. By understanding the intricate interplay between FMF, sleep quality, and cognitive development in children of this age, this narrative review aims to inform interventions that can optimize sleep health and enhance cognitive functioning in children. Addressing sleep-related issues in children with FMF holds the potential to improve overall quality of life, academic performance, and long-term health outcomes [11].

METHODS

A targeted search of the databases PubMed, Web of Science, and OVID was conducted. Key search terms included "Familial Mediterranean Fever", "FMF", "sleep disturbances", and "cognitive development", among others. Boolean operators were strategically utilised to ensure that all relevant studies were presented. While our primary focus was on literature significant to Canada and the United States, we prioritized studies from all countries to capture a broader understanding of the topic. [LA1] The inclusion of primary studies and articles that focused on a paediatric population (ages 8-15), were emphasized.

RESULTS

Impacts on Sleep

Mechanisms of Impact:

Children with FMF are known to experience more sleep disturbances than their healthy counterparts [11]. While this relationship has been proposed within existing literature, there is a paucity of information about the exact mechanism causing this effect. The leading hypothesis suggests that pain resulting from symptoms caused by this disorder could contribute to sleep disruptions. FMF is in part characterised by the recurrent presentation of serositis, which can induce chest and abdominal pain [11,13]. Other common presentations include myalgia—muscle pain—in response to physical exertion [14]. Recurrent pain has long been associated with sleep impairments among children and adolescents and may help to explain the common sleep disturbances faced within this group [15]. Pain experienced by FMF patients could itself be related to sleep quality, as sleep disturbances have been known to exacerbate the perception of pain [16]. However, more research is warranted to investigate this proposed model.

Sleep Disruptions:

Sleep quality is influenced by an amalgamation of factors within a child's life. Familial lifestyle choices, sociodemographics, environmental factors and significant life events all contribute to sleep quality in important ways [17]. Hence, the irregular presentation of FMF attacks may unexpectedly force changes in sleep habits among those affected [17]. Previous reports have suggested that FMF impacts sleep quality in several important ways [18]. Increased bedtime resistance, sleep-onset delay, sleep anxiety, night wakings, parasomnias, and sleep-disordered breathing have all been noted among children with FMF [11,19]. These effects are worsened in children with FMF who experience a greater number of attacks [11]. Interestingly, sleep is also worsened by the recency of a child's last attack, with patients who experienced an attack in the last month demonstrating greater sleep impairments [19].

Psychological Associations:

Issues with sleep quality can pose a considerable mental burden on children with FMF. Poor sleep-related outcomes are known to contribute to a wide array of behavioural and mood problems among adolescents [20]. Adolescent patients with FMF who experience sleep-related problems scored significantly higher on the Revised Child Anxiety and Depression Scale - Child Version than other children with FMF [19]. Behaviourally, children with sleep deprivation demonstrate increased emotional problems, difficult behaviours, and poorer temperament, among a myriad of cognitive functioning issues [21]. In particular, increased bedtime resistance among children with FMF demonstrates an existing behavioural problem that can adversely affect quality of life [11,19,22]. To prevent or

address these issues, sleep-related fatigue among children with FMF should be closely evaluated and addressed by healthcare professionals [17].

Managing Symptoms:

Unfortunately, there does not currently exist a "gold standard tool" for evaluating the severity of fatigue in children with FMF [18]. There does, however, exist a treatment which has shown efficacy in helping to prevent it. It is suggested that Colchicine, the first-line therapeutic defence for FMF, helps to reduce the symptoms of FMF, facilitating improved sleep outcomes in child and adolescent patients [23,24]. Its therapeutic success serves as an important reminder that healthcare practitioners should be continually assessing sleep problems among paediatric FMF patients. Ultimately, the management and control of this disorder's symptoms are needed to address the impact of FMF on sleep quality [17]. Otherwise, children with FMF may display behavioural and neurocognitive impairments.

Cognitive Development

Adequate sleep is a core component of cognitive function in adolescents [25]. During this critical period in development, sleep is a strong predictor of typical brain development, neurocognitive outcomes, and mental health [26-28]. This puts children with FMF at a significant risk for cognitive impairment given that they experience more frequent sleep disturbances [11]. As such, we have chosen to describe three outcomes heavily influenced by sleep. Given the gravity of sleep disturbances that children with FMF have in comparison to their typical counterparts, they are particularly vulnerable to deficits in neuroplasticity, lesser academic outcomes, and comorbidities [11,26,32,34]. Though this connection is understudied, further research should be done to establish a better understanding of the relationship between children with FMF and sleep-related cognitive impairments.

Neuroplasticity:

Neuroplasticity or neural plasticity, as defined by the National Institutes of Health, refers to the process by which the brain undergoes functional and structural changes, allowing the nervous system to respond to intrinsic or extrinsic stimuli by reorganising its structure, functions, or connections [29]. Sufficient sleep is crucial for neuroplasticity, especially in the refining of neural connections through the process of synaptic pruning [26]. This process streamlines neural circuits, facilitating increased cognitive skills [30], such as memory consolidation and integration [31]. However, sleep deprivation and poor sleep quality, both of which are prominent in children with FMF, pose a significant challenge to neuroplasticity. It can lead to a reduction in spine density and disrupt neuronal connectivity in the hippocampal CA1 region, a region of the hippocampus heavily involved with memory formation and retrieval of hippocampal-dependent memories [32]. Notably, Rapid Eye Movement (REM) sleep—a sleep cycle phase where brain activity, breathing, heart rate, and blood pressure increase, and the eyes move rapidly while closed—is incredibly important for neural plasticity [32,33]. REM is thought to play an important role in brain development and memory consolidation; this understanding is supported by the heightened formation and elimination of synapses in mice models [26]. Studies have also concluded that deprivation of REM sleep can cause the inhibition of hippocampal synaptic plasticity by affecting the amount of apical and basal dendritic spines present, as well as hippocampal long-term potentiation [32]. The intricate relationship between sleep and neuroplasticity highlights the essential role of sufficient sleep in refining neural connections and promotion of REM as well as underscores that sleep deprivation poses significant challenges to these processes. These complex relationships highlights the importance of addressing sleep-related challenges in FMF to support optimal brain development in affected children.

Academic Outcomes:

The foundation for understanding the association between sleep and academic outcomes stems from neurocognitive skills and their pivotal role in achieving academic success. Research has shown that sleep fragmentation, late bedtimes, and disrupted sleep significantly impact a child's learning ability, school performance and neurobehavioral functioning [27]. To succeed in the classroom, students are required to complete complex tasks which require creativity, abstract thought and integration [27]. Sleep disruptions weaken these cognitive skills by decreasing motivation, engagement, concentration, reasoning and problem-solving [34]. As elucidated earlier, these implications extend to structural and functional changes in the brain associated with memory– without sufficient sleep, the brain cannot undergo the structural changes required for memory consolidation [26,32] which hinders a child's ability to recall learned information. Furthermore, sleep deprivation has been shown to impact concentration negatively [35]. A study The foundation for understanding the association between sleep and academic outcomes stems from neurocognitive skills and their pivotal role in achieving academic success. Research has shown that sleep fragmentation, late bedtimes, and disrupted sleep significantly impact a child's learning ability, school performance and neurobehavioral functioning [27]. To succeed in the classroom, students are required to complete complex tasks which require creativity, abstract thought and integration [27]. Sleep disruptions weaken these cognitive skills by decreasing motivation, engagement, concentration, reasoning and problem-solving [34]. As elucidated earlier, these implications extend to structural and functional changes in the brain associated with memory– without sufficient sleep, the brain cannot undergo the structural changes required for memory consolidation [26,32] which hinders a child's ability to recall learned information. Furthermore, sleep deprivation has been shown to impact concentration negatively [35]. A study that assessed the relationship between quality of sleep and learning concentration in

children found that 58.5% of children with low sleep quality had a middle learning concentration level and 30.2% had a low concentration level, with a p-value indicating a statistically significant correlation [36]. Moreover, research has shown that children with FMF miss significantly more school than their peers, which may hinder their ability to keep up with coursework and negatively impact their academic performance [37]. Ultimately, the negative effect of insufficient sleep on attention, learning and memory has been deemed to be one of the primary causes of children's failure to thrive in school settings [38], obstructing their ability to achieve academic success.

Comorbidities:

Adequate sleep plays a pivotal role in resetting our brains and protecting overall cognitive health [39]. On the other hand, insufficient sleep can give rise to a range of comorbidities. Namely, sleep deprivation places children at a heightened risk for developing mental health disorders such as anxiety, depression, attention deficit and hyperactivity disorder (ADHD) [28,40]. Research suggests a bidirectional correlation between lack of sleep and mental health disorders, demonstrating high rates of sleep problems among children with psychiatric conditions and reports of youth complaining of insomnia meeting the criteria for a mental health diagnosis [41]. Notably, lack of sleep has been found to further exacerbate mental illness. For example, depressed youth who suffer from insomnia and hypersomnia experience longer depressive episodes and more severe symptomatology [41]. Interestingly, studies reveal that almost 50% of children with ADHD also suffer from sleep disturbances, reinforcing the relationship between sleep quality and mental illness [41]. Prioritising sleep inchildren aged 8-15 is crucial to maintain overall cognitive health but also serves to prevent the development and progression of mental health disorders in youth. This relationship is particularly relevant for children with FMF, as research has found that they are more likely to suffer from anxiety and depression [42]. Given their increased susceptibility to both sleep disturbances and mental health disorders, prioritizing sleep in children with FMF may also play a role in mitigating the development of comorbidities.

Therapeutic Interventions

In addressing sleep disturbances, much of the existing literature focuses on the diagnosis and management of insomnia in the general population. The typical treatment process of insomnia begins with a comprehensive assessment of causes and triggers, followed by an exploration of interventions, including sleep hygiene routines, behavioural therapy, and pharmacological treatment [41]. Given the effectiveness of these interventions for treating insomnia in the broader population, exploring their potential benefits for children with FMF who suffer from sleep disturbances could be valuable. However, there is limited research on treatment options specifically tailored to paediatric FMF patients experiencing sleep issues, highlighting a gap in targeted interventions for these children.

Sleep Hygiene:

Educating children with FMF and their caregivers on sleep hygiene routines was noted to be an important start to treatment, as children with FMF are more prone to sleep disturbances that can impact their overall well-being. [43,44]. Important aspects of sleep hygiene include consistency in sleep and wake-up times, dietary factors such as caffeine intake, minimization of overstimulation prior to established bedtimes, and environmental factors such as ventilation and temperature in a child's bedroom [43].

Behaviour Therapy:

Furthermore, the goal of behavioural therapy would be to remove negative associations that may result in sleep disturbances like insomnia, which are prevalent among children with FMF [43]. Some behavioural techniques include cognitive restructuring techniques, positive routines, and stimulus control; their benefits include improvement in sleep quality and quantity [43,44]. Given that children with FMF frequently experience disrupted sleep, techniques like Cognitive Behavioural Therapy for Insomnia (CBT-I), were noted to be more effective than other insomnia therapies and beneficial in mitigating sleep-related challenges [45].

Pharmacological Therapy:

In the treatment of sleep disturbances, behavioural therapy should be considered a first-line treatment [44]. Medication would typically be introduced when behavioural therapies are ineffective, or when children and their caregivers struggle to adapt to them [43,44]. Rather than pursuing medication on its own, a combination therapy of both pharmacologic and behavioural intervention has been noted to be an effective strategy [44]. To determine suitable pharmacological therapies, the following guidelines must be considered: the therapy should target symptoms and be developmentally appropriate for the child, the primary sleep disorder should be addressed prior to pursuing insomnia medication, and benefits should outweigh potential side effects [43]. Some examples of pharmacological therapies include melatonin, iron, and antihistamines [43]. In the context of treatment in patients with FMF, an important consideration is the potential of medications negatively interacting with or being involved in the fever's pathways. For instance, a study conducted by Musabak et al. found that melatonin may be involved in the pathogenesis of FMF; this may affect the safety of the medication in care [46]. As such, further understanding of the safety and efficacy of medications would be required before prescribing pharmacological therapy to treat FMF.

Additional Supports:

In addition to therapeutic interventions, Corkum et al. noted an association between later start times in school with a higher number of students meeting sleep duration

recommendations and a lower number of students experiencing morning fatigue [47]. Though no mandate was shared to change start times in Canada, informal reports across some school boards have shared success in implementing the aforementioned strategy [47].

DISCUSSION

Existing literature suggests that children diagnosed with FMF are at greater risk of experiencing poor sleep quality [11]. This poor sleep quality manifests as and is defined through sleep disturbances, increased bedtime resistance, sleep-onset delay, sleep anxiety, night wakings, parasomnias, and sleep-disordered breathing [11,19]. This narrative review demonstrates a correlation between FMF-associated poor sleep quality and cognitive development in children ages 8-15. A lack of sufficient sleep caused by bedtime resistance and other psychological obstacles associated with FMF poses significant challenges to the optimal development of neuroplasticity in children. Furthermore, sleep disruptions also weaken cognitive skills students require to succeed in the classroom, including attention, learning and memory [38]. Lastly, as a result of insufficient sleep, children with FMF are at a heightened risk of developing mental health disorders.

Although this narrative review presents promising findings, further research needs to be conducted to also synthesise findings regarding the impact of poor sleep quality caused by FMF on neuroplasticity, learning in academic settings, and other associated comorbidities in children aged 8-15 diagnosed with FMF. Conducting future research would help devise additional treatment and community supports for children with FMF. Given that FMF is the most common monogenic autoinflammatory disorder, new research has the potential to positively impact many lives. Most existing treatments for children with this diagnosis aid them in dealing with more well-known symptoms of their disorder. Furthermore, research has not been conducted on how to support children with FMF experiencing poor sleep quality as a result of their diagnosis and not due to a separate condition, like insomnia. Further research into these connections is essential to address the unique challenges faced by children with FMF, particularly as they suffer with the under-recognized symptom of poor sleep quality. Such efforts would pave the way for tailored support systems to enhance their quality of life

CONCLUSION

The impact of FMF on sleep is multifaceted and warrants careful consideration from paediatric healthcare providers. Research suggests that FMF not only disrupts sleep patterns directly through pain and discomfort associated with the condition but also indirectly through its effects on psychological well-being and cognitive development. Children with FMF often experience a range of sleep disturbances, including bedtime resistance, sleep-onset delay, and night wakings, which can significantly affect their quality of life. Poor sleep quality among FMF patients has been linked to increased levels of anxiety and depression, as well as cognitive deficits which may impede academic performance. Addressing sleep problems in children with FMF requires a comprehensive approach, including strategies such as sleep hygiene education, behavioural therapy, and, when necessary, pharmacological intervention. Additional investigation is warranted to confirm the relationship between FMF symptoms and sleep quality, and its influence on cognitive development in children and adolescents.

1. Bhatt H, Cascella M. Familial mediterranean fever. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2024. Available from: http://www.ncbi.nlm.nih.gov/books/NBK560754/
2. Ben-Chetrit E. Clinical manifestations and diagnosis of familial Mediterranean fever. Wolters Kluwer. 2024; Available from: https://www.uptodate.com/contents/clinical-manifestations-and-diagnosis-of-familial-mediterranean-fever/print#
3. Westwell-Roper C, Niemietz I, Tucker LB, Brown KL. Periodic fever syndromes: beyond the single gene paradigm. Pediatr Rheumatol. 2019;17(1):22. Available from: https://doi.org/10.1186/s12969-019-0324-7
4. Arpacı A, Doğan S, Erdoğan HF, El Ç, Cura SE. Presentation of a new mutation in FMF and evaluating the frequency of distribution of the MEFV gene mutation in our region with clinical findings. Mol Biol Rep. 2021;48(3):2025–33. Available from: https://doi.org/10.1007/s11033-020-06040-y
5. Blackwell CK, Hartstein LE, Elliott AJ, Forrest CB, Ganiban J, Hunt KJ, et al. Better sleep, better life? How sleep quality influences children's life satisfaction. Qual Life Res. 2020;29(9):2465–74. Available from: https://doi.org/10.1007/s11136-020-02491-9
6. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res. 1989;28(2):193–213.
7. Paavonen EJ, Räikkönen K, Pesonen AK, Lahti J, Komsi N, Heinonen K, et al. Sleep quality and cognitive performance in 8-year-old children. Sleep Medicine. 2010;11(4):386–92. Available from: https://www.sciencedirect.com/science/article/pii/S1389945710000596
8. Chaput JP, Gray CE, Poitras VJ, Carson V, Gruber R, Olds T, et al. Systematic review of the relationships between sleep duration and health indicators in school-aged children and youth1. Applied Physiology, Nutrition, and Metabolism. 2016; 41(6):S266–82. Available from: https://journals.scholarsportal.info/details/17155312/v41i0006/s266_srotrbiiscay.xml
9. Short MA, Blunden S, Rigney G, Matricciani L, Coussens S, M. Reynolds C, et al. Cognition and objectively measured sleep duration in children: a systematic review and meta-analysis. Sleep Health. 2018; 4(3):292–300. Available from: https://www.sciencedirect.com/science/article/pii/S2352721818300135
10. Buxton OM, Chang AM, Spilsbury JC, Bos T, Emsellem H, Knutson KL. Sleep in the modern family: protective family routines for child and adolescent sleep. Sleep Health. 2015;1(1):15–27. Available from: https://www.sciencedirect.com/science/article/pii/S2352721814000060
11. Makay B, Kiliçaslan SK, Anik A, Bora E, Bozkaya Ö, Çankaya T, et al. Assessment of sleep problems in children with familial Mediterranean fever. Int J of Rheum Dis. 2017; 20(12):2106–12. Available from: https://onlinelibrary.wiley.com/doi/10.1111/1756-185X.12339
12. Colrain IM, Baker FC. Changes in Sleep as a Function of Adolescent Development. Neuropsychol Rev. 2011 Mar;21(1):5–21.

13. Ozdogan H, Ugurlu S. Familial mediterranean fever. La Presse Médicale. 2019; 48(1, Part 2):e61–76. Available from: https://www.sciencedirect.com/science/article/pii/S075549821830486X
14. Majeed HA, Al-Qudah AK, Qubain H, Shahin HM. The clinical patterns of myalgia in children with familial Mediterranean fever. Elsevier. 2000;30(2):138–43. Available from: https://www-sciencedirect-com.libaccess.lib.mcmaster.ca/science/article/pii/S004901720088097X?via%3Dihub
15. Valrie CR, Bromberg MH, Palermo T, Schanberg LE. A systematic review of sleep in pediatric pain populations. Journal of Developmental & Behavioral Pediatrics. 2013;34(2):120. Available from: https://journals.lww.com/jrnldbp/abstract/2013/02000/a_systematic_review_of_sleep_in_pediatric_pain.7.aspx
16. Lautenbacher S, Kundermann B, Krieg JC. Sleep deprivation and pain perception. Sleep Medicine Reviews. 2006;10(5):357–69. Available from: https://www.sciencedirect.com/science/article/pii/S1087079205000754
17. İncesu Ç, Kayaalp GK, Demirkan FG, Köker O, Çakmak F, Akgün Ö, et al. The assessment of fatigue and sleep quality among children and adolescents with familial Mediterranean fever: A case-control and correlation study. Eur J Pediatr. 2024; Available from: https://doi.org/10.1007/s00431-024-05442-5
18. Saraç DC, Metin S, Demir BK, Gücenmez ÖA, İnanç İ, Akar İ, et al. Assessing fatigue and related factors in adolescents with familial Mediterranean fever (Fmf): psychometric properties of the PedsQL Multidimensional Fatigue Scale. Turk J Pediatr. 2023;65(4):630–9.
19. Durcan G, Yildiz M, Kadak MT, Barut K, Kavruk Erdim N, Sahin S, et al. Increased frequency of sleep problems in children and adolescents with familial Mediterranean fever: The role of anxiety and depression. Int J of Rheum Dis. 2020;23(10):1396–403. Available from: https://onlinelibrary.wiley.com/doi/10.1111/1756-185X.13941
20. Fredriksen K, Rhodes J, Reddy R, Way N. Sleepless in chicago: tracking the effects of adolescent sleep loss during the middle school years. Child Development. 2004;75(1):84–95. Available from: https://journals.scholarsportal.info/details/00093920/v75i0001/84_sictteldtmsy.xml
21. Friman PC, Schnoes CJ. Pediatric Prevention. Elsevier. 2020;67(3):559–71. Available from: https://www.clinicalkey.com/#!/content/playContent/1-s2.0-S0031395520300237?
22. Freeman KA. Treating bedtime resistance with the bedtime pass: a systematic replication and component analysis with 3-year-olds. Journal of Applied Behavior Analysis. 2006 ;39(4):423–8. Available from: https://journals.scholarsportal.info/details/00218855/v39i0004/423_tbrwtbracaw3.xml
23. Özcakar ZB, Yalçinkaya F, Yüksel S, Acar B, Ekim M, Gökmen D. Possible effect of subclinical inflammation on daily life in familial Mediterranean fever. Clinical Rheumatology. 2006;25(2):149–52. Available from: https://journals.scholarsportal.info/details/07703198/v25i0002/149_peosiodlifmf.xml
24. Slobodnick A, Shah B, Krasnokutsky S, Pillinger MH. Update on colchicine, 2017. Rheumatology (Oxford). 2018;57(Suppl 1):i4–11. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5850858/
25. Brooks SJ, Katz ES, Stamoulis C. Shorter duration and lower quality sleep have widespread detrimental effects on developing functional brain networks in early adolescence. Cereb Cortex Commun. 2021;3(1):tgab062. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8759437/
26. Weiss JT, Donlea JM. Roles for sleep in neural and behavioral plasticity: reviewing variation in the consequences of sleep loss. Frontiers in Behavioral Neuroscience. 2022;15. Available from: https://www.frontiersin.org/articles/10.3389/fnbeh.2021.777799
27. Dewald JF, Meijer AM, Oort FJ, Kerkhof GA, Bögels SM. The influence of sleep quality, sleep duration and sleepiness on school performance in children and adolescents: A meta-analytic review. Sleep Medicine Reviews. 2010;14(3):179–89. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1087079209001002
28. Merrill RM, Ashton MK, Angell E. Sleep disorders related to index and comorbid mental disorders and psychotropic drugs. Ann Gen Psychiatry. 2023;22(1):23. Available from: https://annals-general-psychiatry.biomedcentral.com/articles/10.1186/s12991-023-00452-3
29. Puderbaugh M, Emmady PD. Neuroplasticity. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2024. Available from: http://www.ncbi.nlm.nih.gov/books/NBK557811/
30. Feinberg I. Scientific American. 2017. Why is synaptic pruning important for the developing brain? Available from: https://www.scientificamerican.com/article/why-is-synaptic-pruning-important-for-the-developing-brain/
31. Tononi G, Cirelli C. Sleep and synaptic down-selection. In: Buzsáki G, Christen Y, editors. Micro-, Meso- and Macro-Dynamics of the Brain. Cham (CH): Springer; 2016. Available from: http://www.ncbi.nlm.nih.gov/books/NBK435759/
32. Jiao Q, Dong X, Guo C, Wu T, Chen F, Zhang K, et al. Effects of sleep deprivation of various durations on novelty-related object recognition memory and object location memory in mice. Behavioural Brain Research. 2022;418:113621. Available from: https://www.sciencedirect.com/science/article/pii/S016643282100509X
33. NCI Dictionary of Cancer Terms. 2011. National Cancer Institute. Available from: https://www.cancer.gov/publications/dictionaries/cancer-terms/def/rapid-eye-movement-sleep
34. Diaz A, Berger R, Valiente C, Eisenberg N, VanSchyndel S, Tao C, et al. Children's sleep and academic achievement: the moderating role of effortful control. Int J Behav Dev. 2017;41(2):275–84. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5327793/
35. Hosokawa R, Tomozawa R, Fujimoto M, Anzai S, Sato M, Tazoe H, et al. Association between sleep habits and behavioral problems in early adolescence: a descriptive study. BMC Psychol. 2022;10:254. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9636702/
36. Novianti SW, Andriyani M, Hastuti D. The relationship between the quality of sleep and learning concentration among school-age children. JNC. 2022;5(3). Available from: http://jurnal.unpad.ac.id/jnc/article/view/33360
37. Press J, Neumann L, Abu-Shakra M, Bolotin A, Buskila D. Living with a child with familial Mediterranean fever: does it affect the quality of life of the parents? Clin Exp Rheumatol. 2000;18(1):103–6.
38. Buckhalt JA. Insufficient sleep and the socioeconomic status achievement gap. Child Development Perspectives. 2011;5(1):59–65.
39. Eugene AR, Masiak J. The neuroprotective aspects of sleep. MEDtube Sci. 2015 Mar;3(1):35–40. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4651462/
40. Colten HR, Altevogt BM, Research I of M (US) C on SM and. Extent and health consequences of chronic sleep loss and sleep disorders. In: Sleep Disorders and Sleep Deprivation: An Unmet Public Health Problem. National Academies Press (US); 2006. Available from: https://www.ncbi.nlm.nih.gov/books/NBK19961/
41. Alfano CA, Gamble AL. The role of sleep in childhood psychiatric disorders. Child Youth Care Forum. 2009;38(6):327–40. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2786210/
42. Lidor I, Tiosano S, Sharif K, Amital H, Cohen AD, Amital D. The risk of depression and anxiety in patients with familial mediterranean fever – a cross-sectional study. Journal of Affective Disorders. 2021 Sep;292:695–9.
43. Nunes ML, Bruni O. Insomnia in childhood and adolescence: clinical aspects, diagnosis, and therapeutic approach. Jornal de Pediatria. 2015;91(6, Supplement 1):S26–35. Available from: https://www.sciencedirect.com/science/article/pii/S0021755715001308

44. Veeravigrom M, Chonchaiya W. Insomnia. Eslevier. 2021;17(1):67–76. Available from: https://www.clinicalkey.com/#!/content/playContent/1-s2.0-S1556407X21000783
45. Werner-Seidler A, O'Dea B, Shand F, Johnston L, Frayne A, Fogarty AS, et al. A smartphone app for adolescents with sleep disturbance: development of the sleep ninja. JMIR Ment Health. 2017;4(3):e28. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5554352/
46. Musabak U, Kilciler G, Uygun A, Kantarcıoglu M, Polat Z, Sagkan RI, et al. Melatonin and its day and night rhythm of alterations in familial mediterranean fever: a brief research letter. Open Rheumatol J. 2011;5:13–7. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3087213/
47. Corkum P, Weiss S, Hall W, Brown C, Chambers C, Constantin E, et al. Assessment and treatment of pediatric behavioral sleep disorders in Canada. Sleep Medicine. 2019;56:29–37. Available from: https://www.clinicalkey.com/#!/content/playContent/1-s2.0-S1389945718309043