Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 6 September 2022 doi:10.20944/preprints202209.0084.v1

Article

The CSHQ-DE Questionnaire Uncovers Relevant Sleep Disorders in Children and Adolescents with Long COVID-19.

Sarah Werner[1], Claus Doerfel[1], Richard Biedermann[1], Michael Lorenz[2], Marius Rasche[2], Hans Proquitté[1], Lars Newman[3] and Daniel Vilser[3]*

[1] University Hospital Jena, Germany, Department of Child and Adolescent Medicine, Neonatal and Pediatric Intensive Care Section
[2] University Hospital Jena, Germany, Department of Child and Adolescent Medicine, Respiratory, Allergy and Cystic Fibrosis Section
[3] University Hospital Jena, Germany, Department of Child and Adolescent Medicine, Cardiology Section
* Correspondence: daniel.vilser@med.uni-jena.de

Abstract: Acute SARS-CoV-2 infections in children and adolescents are usually mild. However, they can suffer from ongoing symptoms generally referred as long COVID. Sleep disorders are one of the most frequent complaints in long COVID although precise data are missing. We assessed the sleep behavior of children and adolescents who presented at our outpatient clinic between January 2021 and May 2022 with the Children's Sleep Habits Questionnaire (CSHQ-DE). We compared sleep behavior at three different time points: pre-COVID-19, post-COVID-19 at initial presentation and post-COVID-19 at re-presentation. Data from 45 patients were analyzed. Of those, 64% were female and the median age was 10 years (range 0-18 years). Asymptomatic or mild COVID-19 disease was experienced in 89% of patients, whilst 11% experienced moderate disease. Initial presentation occurred at a median of 20.4 weeks (6 weeks - 14 months) after infection. The CSHQ-DE score increased significantly from pre-COVID-19 (45.82+8.7 points) to post-COVID-19 (49.40+8.3 points; p=<0.01). The score then normalized at re-presentation (46.98+7.8; p=0.1). The greatest changes were seen in the CSHQ-DE subscale score "daytime sleepiness". Our data show that children and adolescents with long COVID often suffer from sleep disturbance. For most children and adolescents these sleep disorders decreased over time without further medical intervention, aside from a basic sleep consultation.

Keywords: long COVID; Post COVID-19 condition; sleep disorders; SARS-CoV-2; Coronavirus; children

1. Introduction

Acute SARS-CoV-2 infection in children and adolescents is usually mild [1]. Similar to adults, children can suffer from ongoing symptoms [2]. This new disease is generally referred as long COVID, Post-COVID-19 condition or Post-COVID-19 syndrome [3]. NICE defines long COVID in children, adolescents and adults as persisting symptoms that develop during or after COVID-19 infection and are present for more than 4 weeks (ongoing COVID-19) or 12 weeks (Post-COVID-19 syndrome) [4]. A slightly different definition exists from WHO which currently only refers to adults [5]. Over 200 Symptoms are described and any organ may be affected [6,7,8,9]. The most frequently described complaints are fatigue, respiratory problems, cognitive dysfunction, cardiac symptoms, abdominal pain and sleep disturbances [10,11,12]. Whilst it is known that sleep disorders have a great impact on the quality of life of children and adolescents [13], precise data, especially longitudinal data relating to the effect of long COVID on sleep in children and adolescents are lacking. Adequate care of sick children and adolescents requires a holistic approach. Therefore we routinely examined the sleep behavior of children and adolescents who presented to our outpatient long COVID clinic.

© 2022 by the author(s). Distributed under a Creative Commons CC BY license.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 6 September 2022 doi:10.20944/preprints202209.0084.v1

2. Materials and Methods

2.1. Cohort Composition

From January 2021 to May 2022 children and adolescents who presented to the interdisciplinary long COVID outpatient clinic of the Children's Hospital of Jena, Germany, were screened for sleeping disorders using the CSHQ-DE. Patients who fulfilled the long COVID diagnostic criteria and consented to the study were included in this analysis. One hundred and two children and adolescents met this criteria, of which 45 completed the questionnaires in full at all three time points and were included in the analysis. The most common reason for exclusion was that the questionnaire was not completed at the time of re-presentation as symptoms had resolved.

2.2. CSHQ-DE

Sleep-related symptoms in patients were assessed using the standardized Children's Sleep Habits Questionnaire (CSHQ-DE) for clinically relevant sleeping issues of school-aged children (4-10 years) [14,15,16]. In this study CSHQ-DE was also used to screen sleep disorders of younger and older children and adolescents (0-18 years). The questionnaire provides a total score and eight subscale scores which reflect the key sleep domains. The clinical cut off for a possible sleep dysfunction is a total score ≥ 41 points. The CSHQ-DE was usually parent-reported, with adolescent patients filling out the questionnaire independently. The CSHQ-DE was completed at three time points: pre-COVID-19 (retrospectively), post-COVID-19 at initial presentation and post-COVID-19 at re-presentation. Only patients in whom the CSHQ was completed at all three time points and whose complaints met the diagnostic criteria for long COVID were included in the analysis. All parents gave their written informed consent to their children's participation in the study. The study protocol was approved retrospectively by the local Ethics Committee (Protocol No. 2022-2614_1-BO).

2.3. Statistical Analysis

Data was analyzed using SPSS 28. Since most of the data was normally distributed, data are presented as mean +/- SD (standard deviation). Groups were analyzed using univariate ANOVA with repeated measures for multiple timepoints. Multiple measurements were corrected using Bonferroni post-hoc analysis. Multivariate Regression between sleep quality indices and symptoms of long COVID were performed. A p-value <0.05 was considered to indicate statistical significance (2-tailed).

3. Results

Data from 45/102 (44.1%) patients presenting for the first time at the long COVID outpatient clinic between January 2021 and May 2022 were analyzed. Of those, 64% were female and the median age was 10 years (range 0 to 18 years). Asymptomatic or mild COVID-19 disease was experienced in 89% of patients, whilst 11% experienced moderate disease. Initial presentation occurred at a median of 20.4 weeks (6 weeks to 14 months) after infection. The test was repeated at the scheduled re-presentation 3 months later (means 14.3 weeks; range 7 weeks to 9 months). At initial presentation 80% of the patients suffered from two or more symptoms (Table 1).

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 6 September 2022 doi:10.20944/preprints202209.0084.v1

Table 1. Predominant symptoms at initial presentation.

Symptoms	In total (%)
Fatigue/stress intolerance	30/45 (62%)
Concentration/learning difficulties	20/45 (44%)
Sleep disorders	19/45 (42%)
Pulmonary symptoms	17/45 (38%)
Headache	16/45 (36%)
Gastrointestinal symptoms	14/45 (31%)
Cardiac symptoms	10/45 (22%)
Dizziness	10/45 (22%)
Muscle and joint symptoms	9/45 (20%)
Neurological symptoms	9/45 (20%)
Smell and taste disorders	9/45 (20%)
Hair loss	6/45 (13%)
Skin changes	4/45 (9%)

On history, 42% of patients reported sleep disorders post-COVID-19. At initial presentation the CSHQ-DE showed that 88.9% suffered from possible sleep dysfunction (total score ≥41); however 66.7% already had a possible sleep dysfunction Pre-COVID-19. 94.7% of patients who self-reported suffering from sleep disorders post-COVID-19 had a total CSHQ-DE score ≥41. Pre-Cov19 the mean CSHQ-DE score of all 45 assessed patients was 45.82±8.7 points, increasing significantly to 49.40±8.3 points (p=<0.01) post-COVID-19. Thereafter, a trend to normalize (46.98±7.8; p=0.1) was observed at re-presentation (Figure 1).

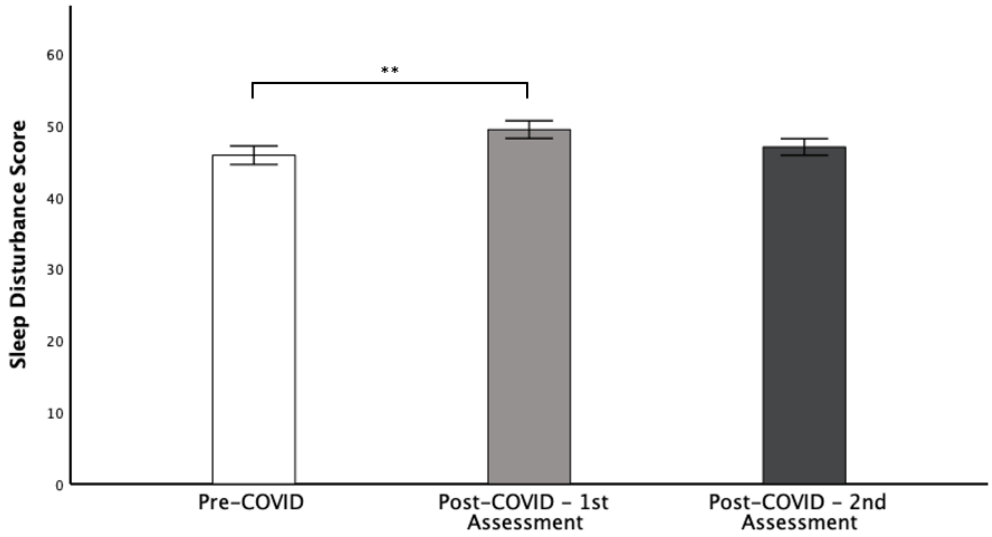

Figure 1. Total CSHQ-DE score pre-COVID-19 vs. post-COVID-19 initial and re-presentation. The sleep disturbance score increased significantly between pre-COVID-19 and 1st Assessment (45.82+8.7 to 49.40+8.3), then decreased following (46.98+7.8). Univariate ANOVA with multiple measurements, post-hoc Bonferroni (**p=<0.01).

Of note, the CSHQ-DE subscale score "daytime sleepiness" significantly increased from pre to post-COVID-19 (13±3.0 vs. 14±3.2; p=<0.001) and significantly decreased again at follow-up (13±3.2; p=0.029) (Figure 2). All other subscale scores of CSHQ-DE did not display a change from pre- to post-COVID-19 (Table 2).

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 6 September 2022 doi:10.20944/preprints202209.0084.v1

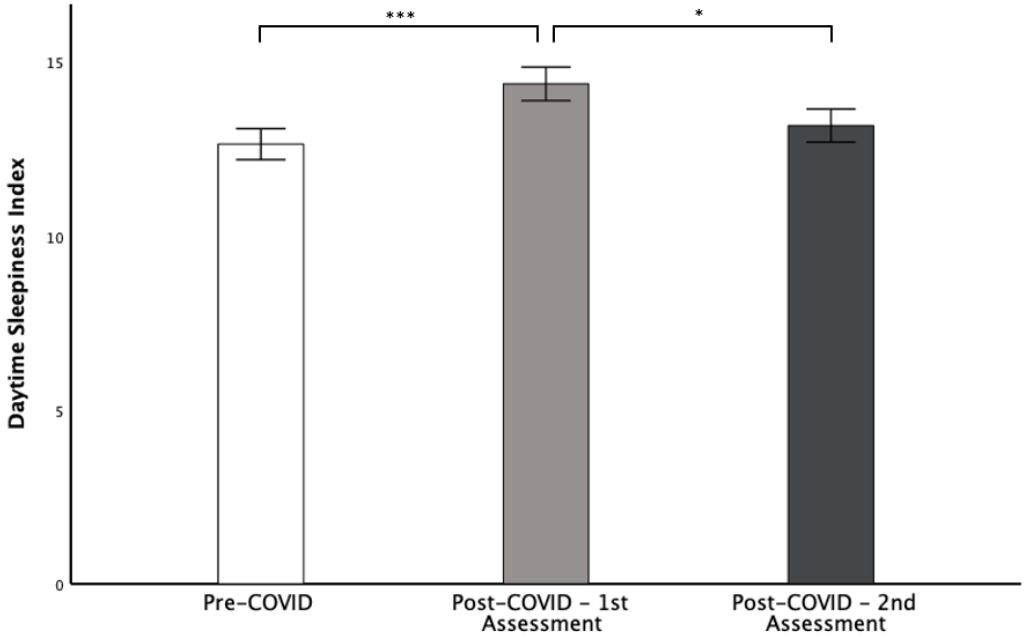

Figure 2. Subscale score "Daytime Sleepiness" pre-COVID-19 vs. post-COVID-19 initial and re-presentation: Significant increase from pre to post-COVID-19 (13±3.0 vs. 14±3.2) and significant decrease at re-presentation (13±3.2). Univariate ANOVA with multiple measurements, post-hoc Bonferroni (*** p=<0.001; *p=0.029).

Table 2. CSHQ-DE Subscales, Mean (SD), ANOVA with multiple measurements, post-hoc Bonferroni.

CSHQ-DE Subscales	Pre-COVID-19	Post-COVID-19 Initial presentation	Post-COVID-19 Re-presentation	p-value
Bedtime resistance	8.2 (±2.7)	8.4 (±2.4)	8.0 (±2.7)	0.495
Sleep Onset Delay	1.8 (±0.9)	2.0 (±0.8)	2.0 (±0.9)	0.239
Sleep Duration	4.1 (±1.3)	4.6 (±1.4)	4.5 (±1.6)	0.150
Sleep Anxiety	5.4 (±2.1)	5.5 (±1.9)	5.3 (±2.2)	0.665
Night Waking	4.0 (±1.6)	4.5 (±1.6)	4.2 (±1.5)	0.130
Parasomnia	9.0 (±2.6)	9.3 (±2.4)	9.1 (±2.4)	0.645
Sleep Disordered Breathing	3.5 (±1.1)	3.5 (±1.0)	3.6 (±1.3)	0.543
Daytime Sleepiness	12.6 (±3.0)	14.4 (±3.2)	13.2 (±3.2)	<0.001

Multivariate regression analysis showed no significant effect of the occurrence of fatigue/stress intolerance, neurological, cardiac or pulmonary long COVID symptoms on either the CSHQ-DE score or daytime sleepiness (Data not shown).

4. Discussion

The presented data shows that sleep disturbances, most notably an increase in daytime sleepiness, occur in children and adolescents with long COVID. As has already been described in adults [17], sleep dysfunction is independent of disease severity. The distribution of symptoms is consistent with other studies of long COVID in children and adolescents, including a female preponderance [3,10,18,19].

Various pathophysiological causes of sleep disturbances secondary to SARS-CoV-2 infection are discussed in the literature [20,21]. Mechanisms include long-term tissue damage, viral persistence, and chronic inflammation. The production of pro-inflammatory cytokines in the central nervous system, in particular the brainstem, can cause post-viral symptoms [22]. Some cytokines and viral envelope proteins are hypnogenic and have specific effects on both NREM and REM sleep. Certain phases of the infection and the strength of the immune response, may be arousal-inducing and cause sleep disruption [23,24]. A

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 6 September 2022 doi:10.20944/preprints202209.0084.v1

long-term consequence is disturbed sleep-wake cycles [25]. Moreover, it appears that the systemic inflammation triggered by the virus and consecutive activation of inflammatory mediators such as interferons and interleukin-6 can impair neuronal function and cause CNS symptoms [26]. Inflammatory mediators may in turn contribute to the manifestation of autoimmune processes [27]. There is evidence for an underlying autoimmune mechanism as shown by persistently elevated antinuclear antibody (ANA) [28] and G-protein coupled receptor antibody titres [29] in long COVID patients. In this regard, the typically high female proportion in long COVID cohorts after mild disease is consistent with the known female predominance in autoimmunity [30].

Differentiating sleep disturbances, especially daytime sleepiness, from fatigue is difficult. The pathogenesis of fatigue after COVID-19 remains unclear and is currently under investigation. COVID-19 related organ damage as well as psychological disturbances can be related to the development of fatigue [31]. Persisting inflammation or an autoimmune response due to antigen mimicry may also play a role [32]. In addition, nonrestorative sleep is associated with daytime sleepiness, which can contribute to fatigue and cognitive dysfunction. Therefore, sleep disturbance in long COVID overlaps with, and is difficult of differentiate from, fatigue and cognitive dysfunction. This highlights the importance of a differentiated assessment of sleep disturbances versus fatigue, with the aim to guide treatment [33].

Furthermore, it remains difficult to separate infectious sequelae of SARS-CoV-2 from those of the broader pandemic (e.g., lockdowns and school closures). There is a paucity of data relating to lockdown´s and school closure´s effect on screen time, social interaction and exercise, which are known risk factors for poor sleep quality. The effect of the broader pandemic, coupled with changes in electronic device and social media behavior, can induce stress, anxiety and weight gain, which in turn exacerbates sleep dysfunction [34].

Two thirds of our patients already had an abnormal CSHQ-DE score Pre-COVID-19 infection. In adult patients, there is evidence that poor sleep is associated with higher susceptibility to SARS-CoV-2 infection as well as worse clinical outcomes [35,36,37]. It is possible that poor sleep results in delayed resolution of symptoms.

The impact of chronically disturbed sleep on the development of long COVID remains unknown. Deficient sleep can contribute to cell stress and consecutive neuronal damage [38]. In addition, sleep disorders can induce mild inflammation causing blood-brain barrier dysfunction, allowing antigens and inflammatory mediators passage into the CNS. In this respect, preexisting sleep disturbances in the context of long COVID could adversely influence the long-term course of COVID-19 disease [33].

5. Limitations

One limitation of this study was the absence of a control group. Further studies on this topic would benefit from a control to correct for confounders of the broader pandemic and non SARS-CoV-2 viral illnesses. It has been demonstrated in adults that sleep disorders were more prevalent among patients who had recovered from COVID-19 than the non-infected control group [39]. A systematic review from 2022 of the effects of coronavirus disease on sleep in children aged 12 years and younger revealed an increase in sleep duration, sleep latency and daytime sleepiness. Reliable data regarding long-term effects on children's sleep and daytime function is lacking [40]. Another limitation is that the Pre-COVID sleep assessment was conducted retrospectively. Due to the nature of the study, a concurrent assessment was not possible.

Our results were limited by the fact that a large proportion of patients who presented to our long COVID outpatients clinic were not included in the study. The study only included patients whom fulfilled the diagnostic criteria for long COVID, which is highly subjective and lacking in objective measurements, such as biomarkers. We used the same diagnostic criteria which was later published in "Recommendation for standardized medical care for children and adolescents with long COVID" of the German Society for Pediatrics (DGKJ) [11]. Of the 102 who presented to the clinic, only 45 families completed the questionnaire at all three time points. The two primary reasons for non-completion were

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 6 September 2022 doi:10.20944/preprints202209.0084.v1

omission of answers to individual questions or, above all, the symptoms has resolved and the parents therefore considered the completion of the questionnaire to be unnecessary. We think the inclusion of the missing questionnaires would have further highlighted the group differences.

5.1. Treatment Recommendations

Our approach to the treatment of sleep disorders was analogous to the recommended treatment of non-organic sleep disorders by the German guideline. [41]. The most important intervention was detailed advice on sleep hygiene (Table 3). A sleep diary should be kept with every attempt at sleep modification to monitor the effectiveness of the intervention.

Table 3. Treatment Recommendations.

• Regular bedtime as part of a regular daily routine, including weekends (or put to bed only when the child is tired)
• Particularly important in smaller children: regular daytime sleep at the same time
• In the evening avoid bright light, especially in the blue-wave range (LCD screens on mobile phones, tablets, TV, etc.)
• Avoidance of media consumption in the evening, especially in the hour before going to bed
• Sufficient physical activity during the day
• No exciting or strenuous activities before falling asleep
• Quiet, dark, warm sleeping environment
• Sleep environment not associated with other activities (gaming, cell phone, television, homework, punishment, etc.)
• Bedtime rituals depending on age (between 15 and 30 min)
• Eating/drinking:
○ Introduction of a behavioral pattern in early childhood: being fed during the day and sleeping at night
○ Avoid excessive amounts of stimulating drinks during the day
○ Avoid stimulating drinks and sweets a few hours before bedtime
○ Not responding to child´s intake wishes which only serve to delay sleep
○ At bedtime avoid hunger and thirst, as well as large meals and significant liquid intake
• Not responding to wishes/demands of the child that only serve to delay sleep
• For older children and adolescents: restrict naps to 20mins and not after 3pm

In cases of severe sleep disorders, pharmacotherapy should be considered. The choice of medication depends on the type of sleep disorder and underlying disease (e.g., depression or panic disorders) [41]. The dose varies greatly between patients and should therefore be implemented carefully. Most of the medications available are prescribed off-label and can therefore only be used as part of an individual treatment regime.

We initiated pharmacotherapy in only four patients. Melatonin was used in increasing doses in three adolescents over a maximum period of six weeks. A 15-year-old boy and 13-year-old girl with issues relating to sleep initiation, sleep maintenance and daytime tiredness experienced significant improvement after four and six weeks respectively, which persisted even after discontinuation. A 17-year-old girl with severe sleep initiation issues with nil improvement. The fourth child (9-year-old girl) had only mild problems with sleep initiation was treated with Dimentinden (Fenistil) primarily due to recurrent urticaria. Both symptoms improved with the medication.

Our first choice for the treatment of moderate and severe sleep disorders secondary to COVID-19 is melatonin. Taken regularly for a few weeks, melatonin restores the regular circadian rhythm [42]. It has antioxidant, anti-inflammatory and immunomodulatory

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 6 September 2022 doi:10.20944/preprints202209.0084.v1

properties [43,44] and thus could potentially have a positive effect on the previously discussed mechanisms of long COVID [6,8,45]. Melatonin accumulates in the mitochondria of endothelial cells resulting in beneficial effects on sepsis-induced mitochondrial dysfunction, oxidative stress, and cytokine response [41].

Endothelial dysfunction occurs in acute COVID-19 infection [46,47,4,8,49,50,51,52]. Endothelial dysfunction caused by persistent endotheliitis could explain many of the symptoms of long COVID [53,54,55,56]. Melatonin activates Nuclear factor erythroid-derived 2-like 2 (NRF2) [37]. NRF2 is the primary regulator of the inducible antioxidant response, which attenuates cellular injury in oxidative stress [53]. Melatonin has been explored as a treatment for other viral infections which produce an excessive inflammatory response [54,55,56]. Its use in COVID-19 has also been proposed [57] and is part of several international trials [58].

We were restrictive in the treatment of sleep disorders with medications. Given the potential of melatonin to have a positive effect on many aspects of the discussed pathogenesis of long COVID, coupled with limited side effects, we are currently considering earlier use. Future studies should focus on melatonin´s effect on clusters of long COVID symptoms and its use independently of sleep disorders.

6. Conclusions

Our results suggest that sleep disturbances are common in children with long COVID and therefore monitoring of sleep behavior should occur in all patients with long COVID. If sleep disturbance does not improve with counselling, medication should be used. In our opinion, melatonin is the first line medication due to potential beneficial effects on underlying long COVID pathophysiology.

Author Contributions: Sarah Werner: writing—original draft preparation, investigation, formal analysis, data curation; **Claus Doerfel**: Conceptualization; **Michael Lorenz:** investigation, project administration; **Hans Proquitté**: writing—review and editing, supervision, resources; **Richard Biedermann:** writing—review and editing, formal analysis; **Marius Rasche:** investigation, data curation; **Lars Newman:** writing—review and editing; **Daniel Vilser**: Conceptualization, investigation, writing—review and editing, funding acquisition, project administration.

Funding: The care of the patients and the evaluation of the data was carried out with the support of the state of Thuringia.

Institutional Review Board Statement: The study protocol was conducted in accordance with the Declaration of Helsinki, and retrospectively approved for studies involving humans by Ethics Committee of University Hospital Jena.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study. Written informed consent has been obtained from the patient(s) to publish this paper.

Data Availability Statement: IPD sharing plan: Study protocol and individual participant data underlying the results reported in the article, after deidentification. Documents will be available 3 months after publication for 3 years for investigators submitting a structured application, after approval by a committee. Data will be made available for all types of analyses that produce results in the approved application. Requests should be sent informally to daniel.vilser@med.uni-jena.de. A data agreement must be signed for access to the data.

Acknowledgments: In this section, you can acknowledge any support given which is not covered by the author contribution or funding sections. This may include administrative and technical support, or donations in kind (e.g., materials used for experiments).

Conflicts of Interest: The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

References

1. Howard-Jones A. et al. COVID-19 in children. II: Pathogenesis, disease spectrum and management. *Journal of Paediatrics and Child Health* **2021**, 58(1), 46-53.
2. Zimmermann P. et al. The Challenge of Studying Long COVID: An Updated Review. *The Pediatric Infectious Disease Journal* **2022**, 41(5), 424-426.
3. Kikkenborg Berg et al. Long COVID symptoms in SARS-CoV-2-positive adolescents and matched controls (LongCOVID-KidsDK): a national, cross-sectional study. *Lancet Child Adolesc Health* **2022,** 6(4), 240–248.
4. COVID-19 rapid guideline: managing the long-term effects of COVID-19. Available online: https://www.nice.org.uk/guidance/ng188/resources/COVID19-rapid-guideline-managing-the-longterm-effects-of-COVID19-pdf-51035515742 (accessed on 22 July 2022).
5. Coronavirus disease (COVID-19): Post COVID-19 condition. Available online: https://www.who.int/news-room/questions-and-answers/item/coronavirus-disease-(COVID-19)-post-COVID-19-condition (accessed on 22 July 2022).
6. Crook H. et al. Long COVID-mechanisms, risk factors, and management. *BMJ* **2021**, 374, n1648.
7. Garg M. et al. The Conundrum of 'Long-COVID-19': A Narrative Review. *International Journal of General Medicine* **2021**, 14, 2491—2506.
8. Nalbandian A. et al. Post-acute COVID-19 syndrome. *Nature Medicine* **2021**, 27(4), 601-615.
9. Nguyen N.N. et al. Clinical patterns of somatic symptoms in patients suffering from post-acute long COVID: a systematic review. *European Journal of Clinical Microbiology & Infectious Diseases* **2022**, 41(4), 515-545.
10. Borch L. et al. Long COVID symptoms and duration in SARS-CoV-2 positive children - a nationwide cohort study. *European Journal of Pediatrics* **2022**, 181(4), 1597-1607.
11. Töpfner N. et al. [Recommendation for standardized medical care for children and adolescents with long COVID]. *Montasschrift Kinderheilkunde* **2022**, 170(6), 539-547.
12. Ashkenazi-Hoffnung L. et al. Long COVID in Children: Observations From a Designated Pediatric Clinic. *The Pediatric Infectious Disease Journal* **2021**, 40(12), e509-e511.
13. Lewandowski A. S. et al. Sleep problems in children and adolescents with common medical conditions. *Pediatr Clin North Am* **2011**, 58(3), 699-713.
14. Schlarb A. et al. Validation and psychometric properties of the German version of the Children's Sleep Habits Questionnaire (CSHQ-DE). *Somnologie* **2010**, 14(4), 260-266.
15. Schwerdtle B. et al. A new diagnostic tool for children with sleep disorders. *Somnologie* **2013**, 17(3), 199-204.
16. Owens J.A. et al. The Children's Sleep Habits Questionnaire (CSHQ): psychometric properties of a survey instrument for school-aged children. *Sleep* **2000**, 23(8), 1-9.
17. van Kessel, S.A. et al. Post-acute and long-COVID-19 symptoms in patients with mild diseases: a systematic review. *FAMPRJ* **2022**, 39(1), 159–167.
18. Asadi-Pooya A.A. et al. Long COVID in children and adolescents. *World Journal of Pediatrics* **2021**, 17(5), 495-499.
19. Stephenson T. et al. Long COVID (post-COVID-19 condition) in children: a modified Delphi process. *Archives of Disease in Childhood* **2022**, 107(7), 674-680.
20. Bhat S.; Chokroverty S. Sleep disorders and COVID-19. Sleep Medicine 2022, 91, 253-261.
21. Semyachkina-Glushkovskaya O. et al. Brain Mechanisms of COVID-19-Sleep Disorders. International Journal of Molecular Sciences 2021, 22, 6917.
22. Yong, S.J. Persistent Brainstem Dysfunction in Long-COVID: A Hypothesis. *ACS chemical neuroscience* **2021**, 12, 573-580.
23. Krueger J. M.; Majde J. A.; Rector D. M. Cytokines in immune function and sleep regulation. *HandbClinNeuro* **2011,** l98, 229–240.
24. Marshall L.; Born J. Brain-immune inter-actionsinsleep. *IntRevNeurobiol* **2002**, 52, 93–131.
25. Mardani, M. Post COVID syndrome. *Arch Clin Infect Dis* **2020,** 15, e108819.
26. Kappelmann N.; Dantzer R.; Khandaker G. M. Interleukin-6 as potential mediator of long-term neuropsychiatric symptoms of COVID-19. *Psychoneuroendocrinology* **2021**. 131, 105295.
27. Novelli, L. et al. The JANUS of chronicinflammatory and autoimmune diseases onsetduring COVID-19—A systematic review of the literature. *JAutoimmun* **2021,** 117, 102592.
28. Seeßle J. et al. Persistent symptoms in adult patients one year after COVID-19: a prospective cohort study. *Clin Infect Dis* **2021**.
29. Quintero O. L. et al. Autoimmune disease and gender: plausible mechanisms for the female predominance of autoimmunity. *J Autoimmun* **2012**, 38(2–3), J109–J119.
30. Wallukat G. et al. Functional autoantibodies against G-protein coupled receptors in patients with persistent Long-COVID-19 symptoms. *J Transl Autoimmun* **2021**, 4, 100100.
31. Gaebler C.; Wang Z.; Lorenzi JCC et al. Evolution of Antibody Immunity to SARS-CoV-2. *bioRxiv* **2020**.
32. Rudroff, T.; Fietsam A.C.; Deters J.R. et al. Post-COVID-19 Fatigue: Potential Contributing Factors. *Brain Sci* **2020**, 10.
33. Schilling C.; Meyer-Lindenberg, A.; Schweiger J. I. Kognitive Störungen und Schlafstörungen bei Long-COVID. *Der Nervenarzt* **2022**; 1-8.
34. Vitti-Ruela B.V.; Dokkedal-Silva V.; Rosa DS et al. Possible sequelae in post-SARS-CoV-2 patients: effects on sleep and general health condition. *Sleep and Breathing* **2020**; 1-2.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 6 September 2022 doi:10.20944/preprints202209.0084.v1

35. Zhang J.; Xu D.; Xie B. et al. Poor-sleep is associated with slow recovery from lymphopenia and an increased need for ICU care in hospitalized patients with COVID-19: a retrospective cohort study. Brain Behav Immun 2020, 88, 50-58.
36. Goldstein C.A.; Rizvydeen M., Conroy D.A. et al. The prevalence and impact of pre-existing sleep disorder diagnoses and objective sleep parameters in patients hospitalized for COVID-19. J Clin Sleep Med 2021, 17, 1039-1050.
37. Huang B.; Niu Y.; Zhao W. et al. Reduced sleep in the week prior to diagnosis of COVID-19 is associated with the severity of COVID-19. Nat Sci Sleep 2020, 12, 999-1007.
38. Coulson R. L. et al. Sleep deficiency as a driver of cellular stress and damage in neurological disorders. *SleepMedRev* **2022**.
39. Al-Ameri L. T., et al. Sleep quality in COVID-19 recovered patients. *Sleep Sci* **2022**, 15(2), 168-171.
40. Camacho-Montano L. R. et al. Effects of COVID-19 home confinement on sleep in children: A systematic review. *Sleep Med Rev* **2022**, 62, 101596.
41. Deutsche Gesellschaft für Kinder- und Jugendpsychiatrie, Psychosomatik und Psychotherapie e.V. (DGKJP). S1-Leitlinie: Nichtorganische Schlafstörungen (F51). Available online: https://www.awmf.org/uploads/tx_szleitlinien/028-012l_S1_Nicht-organische-Schlafstoerungen_2022-01.pdf (accessed on 22 July 2022).
42. Jarrott B. et al. "LONG COVID"—A hypothesis for understanding the biological basis and pharmacological treatment strategy. *Pharmacol Res Perspect* **2022**, 10, e00911.
43. Anderson G.; Reiter R.J. Melatonin: Roles in Influenza, COVID-19, and Other Viral Infections. *Rev. Med. Virol* **2020**, 30, e2109.
44. Lowes D.A. et al. Antioxidants that protect mitochondria reduce interleukin-6 and oxidative stress, improve mitochondrial function, and reduce biochemical markers of organ dysfunction in a rat model of acute sepsis. *British Journal of Anaesthesia* 2013, 110, 472-39.
45. Vilser D. Long COVID / Post-COVID-19-Syndrom bei Kindern und Jugendlichen. *Pädiatrie* **2022**, 34, 20-25.
46. Galley H. F. et al. Melatonin as a potential therapy for sepsis: a phase I dose escalation study and an ex vivo whole blood model under conditions of sepsis. *Journal of Pineal Research* **2014**, 56, 427-38.
47. Evans P.C.; Rainger G.E. et al. Endothelial dysfunction in COVID-19: a position paper of the ESC Working Group for Atherosclerosis and Vascular Biology, and the ESC Council of Basic Cardiovascular Science. *Cardiovascular Research* **2020**, 116, 2177-2184.
48. Varga Z.; Flammer A.J. et al. Endothelial cell infection and endotheliitis in COVID-19. *Lancet* **2020**, 395, 1417-1418.
49. Mejia-Renteria H.; Travieso A. et al. In-vivo evidence of systemic endothelial vascular dysfunction in COVID-19. *International Journal of Cardiology* **2021**, 354, 153-155.
50. Rovas A.; Osiaevi I. et al. Microvascular dysfunction in COVID-19: the MYSTIC study. *Angiogenesis* **2021**, 24, 145-157.
51. Wang X. et al. Coagulopathy, endothelial dysfunction, thrombotic microangiopathy and complement activation: potential role of complement system inhibition in COVID-19. *J Thromb Thrombolysis* **2021**, 51, 657-662.
52. Otifi H.M.; Adiga B.K. Endothelial Dysfunction in COVID-19 Infection. *Am J Med Sci* **2022**, 363, 281-287.
53. Libby P.; Lüscher T. COVID-19 is, in the end, an endothelial disease. *Eur Heart J* **2020**, 41, 3038- 3044.
54. Sashindranath M.; Nandurkar H.H. Endothelial Dysfunction in the Brain: Setting the Stage for Stroke and Other Cerebrovascular Complications of COVID-19. *Stroke* **2021**, 52, 1895-1904.
55. Ergul E.; Yilmaz A.S. et al. COVID 19 disease independently predicted endothelial dysfunction measured by flow-mediated dilatation. *The International Journal of Cardiovascular Imaging* **2022**, 38, 25-32.
56. Oikonomou E.; Souvaliotis N. et al. Endothelial dysfunction in acute and long standing COVID−19: A prospective cohort study *Vascul Pharmacol.* **2022**, 144, 106975.
57. Seitz A.; Ong P. Endothelial dysfunction in COVID-19: A potential predictor of long-COVID? *International Journal of Cardiology* **2022**, 349, 155-156.
58. Gupte A.A.; Lyon C.J.; Hsueh W.A. Nuclear factor (erythroid-derived 2)-like-2 factor (Nrf2), a key regulator of the antioxidant response to protect against atherosclerosis and nonalcoholic steatohepatitis. *Curr Diab Rep* **2013** 13, 362-71.
59. Anderson G. et al. Ebola virus: melatonin as a read-ily available treatment option. *J Med Virol.* **2015**, 87, 537-43.
60. Paemanee A. et al. Screening of melatonin, α-tocopherol, folic acid, acetyl-L-carnitine and resveratrol for anti-dengue 2 virus activity. *BMC Res Notes* **2018**, 11, 307.
61. Elmahallawy E.K. et al. Potential relevance of melatonin against some infectious agents: a review and assessment of recent research. *Curr Med Chem* **2015**, 22, 3848-61.
62. Cross K.M. et al. Melatonin for the early treatment of COVID-19: a narrative review of current evidence and possible efficacy. *Endocr Pract* **2021**, 27, 850-855.
63. International Clinical Trials Registry Platform (ICTRP) - Important information about the COVID-19 outbreak. Available online: https://www.who.int/clinical-trials-registry-platform (accessed on 22 July 2022)