**Peer Review File**

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**Reviewer A**

**Comment 1**:Abstract: It's very unclear from your abstract what you're reviewing in this paper. The abstract seems like you will be reviewing all literature pertaining to COVID19. If you are only reviewing "long COVID," then your abstract should clearly reflect that. Background should relate to long COVID. Findings and conclusions should be about long COVID. Also, if this is a review paper, you should report in your abstract how many studies were found with your initial search, how many met your search criteria, how many studies you finally ended up reviewing.

**Reply 1**: Thank you for your suggestions and questions. Your professional comments have been very helpful to the improvement of our review, and we have revised the background and results and conclusions of the summary based on your comments. We have made our content more focused on long COVID and removed some content about COVID-19 infection. We are so sorry for the problem of article selection. We did not provide the total number of literatures selected because this article is not a meta-analysis or systematic review. Although we did not use software to evaluate literature quality, we can ensure that we have tried our best to select literatures with high credibility, new publication time and high compatibility with the content of the review. If the data in the search article is necessary for the publication of the article, we will try to retrieve the original search data and provide relevant analysis data. We hope that our sincere apologies and answers will be recognized by you. (see Page2, line23)

**Change in the text**:Line:23: Background: In the context of the global pandemic of COVID-19, more than 700 million infections and millions of deaths have occurred in countries around the world. Currently, two main sequelae of this disease are considered to occur in children, namely, multi-system inflammatory syndrome in children and long COVID. Among these two, the incidence of long COVID is higher and its impact on the population is more extensive, which is the focus of us. However, due to the lack of relevant studies and the limitations of most studies, the studies on sequelae of COVID-19 infection lag behind those of adults, but they have begun to attract the attention of some clinicians and researchers.

Line35: Results: This review summarizes the latest researches on epidemiology, pathogenesis, clinical manifestations, prevention and treatment of long COVID in children. Based on the existing research data, we summarized and analyzed the characteristics of long COVID in children, helping pediatricians and researchers to better understand long COVID in children.

Line40: We aim to summarize existing research on long COVID in children and

help pediatricians and government agencies quickly understand the disease so that it can be used for clinical diagnosis, treatment and prevention in the population.

**Comment 2**:Introduction - There have already been multiple studies (systematic reviews) on long COVID in children (Pellegrino et all J of Pediatrics 2020; Lopez-Leon et all, Sci Rep 2022). How is this paper different? Does your paper bring anything new to the literature? Does it review anything that has not already been reviewed or do it in a way that has not already been done?

**Reply 2**: Thank you for your question. Your questions made us think more deeply about the content of our review, and the two articles you mentioned are also in our references. Comparing our review with these two, we believe that we have collected more updated data to describe long COVID in children, including pathogenesis and epidemiology and clinical manifestations. In addition, we also summarized the latest research on COVID-19 from the perspective of treatment and prevention, expanding the clinical significance of our review.

**Comment 3**: Epidemiology of long COVID - Is this paper reviewing long COVID in adults or children or both? It's not clear at all what you're reviewing here. It should clearly describe what we know about long COVID in adults, followed clearly by what we do or do not know about long COVID in children.

**Reply 3**: Thank you for your questions. We refer to the analogy and contrast between children and adults in this section, and we sincerely apologize for the ambiguity. Indeed, our intention was to highlight the epidemiological characteristics of children by comparing them with adults. All content in this paragraph has been revised to come from clinical studies in children and we have modified some of the content including the latest research progress and expanding cited data. (see Page6, line106)

**Change in text**: Line106: The morbidity of long COVID ranges from 1.6% to 70%, corresponding with the prevalence of countries, population vaccination coverage, and the reliability and comprehensiveness of relevant statistics (3,7-12).

Line112: Moreover, the latest study in children has found the function of SARS-CoV-2 vaccine in reducing the morbidity of long COVID (11,14).

**Comment 4**: Pathogenesis of long COVID - Again, I assume that the studies you're reviewing in this section are all relating to long COVID in adults? This should clearly be explained. Comment 5: Children are mentioned twice in this section, but you should clearly distinguish what is know about long COVID based on studies in adults versus what has been studied in children.

**Reply 4**: Thank you for your suggestions and questions. We sincerely apologize for not making it clear at the beginning of this paragraph whether the study was on adults or children. In fact, most of the current studies on the mechanism come from adults, but the clinical evidence behind the mechanism can also be found in children. So we want to prove that the mechanism is similar in both cases through limited data in children. Otherwise, when we refer to children, we mean that research evidence comes from children. (see Page6, line121)

**Change in text**: Line121: Both in adult and children, the underlying pathogenesis of long COVID remains unclear. The current studies on the mechanism of COVID-19 predominantly rely on adult clinical studies due to ethical considerations, limited availability of tests, and the relatively smaller number of studies involving children. However, some limited clinical studies have found similar results in children and adults, suggesting that the pathogenesis of COVID-19 may be similar in both age groups.

**Comment 5**: Clinical manifestation of long COVID in different systems - line 123 - is this study about adults or children?

**Reply 5**: Thank you for your questions. We are so sorry that our expression is not clear, or the previous content may have affected your understanding of this part of the content. All the content of this part comes from the clinical research of children, and we have revised the expression of this part, hoping to make you and readers understand more clearly. (see Page8, line160)

**Change in the text**: Line160: The clinical manifestations of long COVID in children closely resemble those observed in adults, exhibiting a diverse range of symptoms that can affect multiple bodily systems. These symptoms may include fatigue, headache, hyposmia, hypogeusia, muscle or joint pain, insomnia, cough, cognitive difficulties, fever, dizziness, abdominal pain, dyspnea, post-exertional malaise, and decreased exercise tolerance (7,34-38) (Table 2).

**Comment 6**: Prospect - This is not a typically used section heading in English review papers. Discussion or conclusions would be more common. This section in particular needs a lot of language editing. "The variation of viral strain" is not a sentence. "The sample size differences" is not a sentence. "The recall bias" is not a sentence. These are all fragments which need to be taken out or made into sentences.

**Reply 6**: Thank you for your suggestions. We apologize for our carelessness and revise the manuscript accordingly. So we have revised the part you mentioned and polished the discussion of this paragraph. (see Page18, line349)

**Change in the text**: Line348: These factors can contribute to discrepancies

between long COVID studies, particularly when comparing studies conducted at different times and in different regions, thereby increasing the difficulty of analysis.

Line351: The variation in sample sizes among studies can introduce interference when conducting overall analyses.

Line356: The issue of recall bias is another concern to consider, as many of the studies conducted were retrospective in nature.

Line357: The format of the studies, particularly in their early stages of the COVID-19 pandemic, primarily relied on questionnaires.

Line364: Limited epidemiological data is available on children, and existing studies often suffer from small sample sizes that are not statistically significant.

**Comment 7**: I do not see any section in this paper where you explain what methods were used for selecting papers to review. What kind of studies were included? What were your inclusion and exclusion criteria? How many studies were found? How many were finally reviewed?

**Reply 7**: Thank you for your question. The type of our article is narrative review, so we have provide our search strategy in table as journal requirement in table 1. The types of articles we reviewed include narrative review, meta analysis, case report, case series, original article. We are so regretful that we did not count the types of included articles and use software to evaluate the quality of included articles. However, we have selected the latest published articles that are closely related to the content of this review, and screened the articles with large sample size and rigorous research methods. If the data in the search article is necessary for the publication of the article, we will try to retrieve the original search data and provide relevant analysis data. We hope that our sincere apologies and answers will be recognized by you.

**Reviewer B**

**Comment 1**: The topic is highly interesting, however the material of the review article is insufficient to gain scientific recognition and complete the knowledge in this sector.

**Reply 1**: Thank you for your comment. We are so sorry that our content does not meet your high requirements. We have done our best to collect, collate and summarize the latest research in the field of COVID-19 in children and provide a comprehensive review. We have modified the content of the paper with the suggestions of reviewers and editors, combined with the latest research

literature, to provide clearer expression and more correct understanding. We sincerely hope that our articles can get your recognition and get your valuable comments.

**Reviewer C**

**Comment 1**: This is a nice summary of a complicated topic. Below more details comments. In general, I think this paper is missing some tables or figures.

**Reply 1**: Thank you for your kindly suggestions. Your valuable suggestions have been very helpful in improving the content richness and conciseness of our review. We have added a table on clinical symptoms to the article based on your suggestions. (see Page10, line186)

**Change in the text**: Line186:

Table 2 The clinical manifestation

| Systems | Symptoms | Mechanisms |
|---|---|---|
| Respiratory system | Dyspnea, chest tightness or pain, cough, exercise intolerance, post-exertional malaise | Vagus nerve disorder<br>Virus persistence |
| Circulatory system | Chest tightness or pain, palpitation, arrhythmia , myocarditis, post-exertional malaise | Autonomic dysfunction<br>Virus persistence |
| Hematologic System | Thrombosis, autoimmune thrombocytopenic purpura | Immune dysregulation<br>Coagulation dysfunction<br>Vascular endothelium damages |
| Mental health and nervous systems | Dizziness, insomnia, hyposmia, hypogeusia, headache, brain fog, fatigue | Impact of pandemic<br>Brain infection<br>Neuroinflammation<br>Autoimmune reaction |
| Digestive system | Abdominal pain, dyspnea, nausea, irritable bowel syndrome | Virus persistence<br>Autonomic dysfunction<br>Intestinal microbiome abnormality |
| Motor system | Fatigue, muscle or joint pain, post-exertional malaise | Autoimmune reaction<br>Chronic inflammatory |

**Comment 2**: EPIDEMIOLOGY: this section should include a better discussion providing perspective about case controlled studies, which showed less prevalence of long covid, or a danish study showing on a national level a prevalence of 0.1% of all infected children. About risk factors, the authors should refer to this prospective study made through assessments in person of patients (PMID: 37073325).

**Reply 2**: Thank you for your kindly suggestions. We consulted additional literature, including large clinical studies, systematic reviews, and the article you mentioned, and we revised the prevalence range to 1.6-66% (see Page 6, line106)

**Change in the text**: Line106: The morbidity of long COVID ranges from 1.6% to 70%, corresponding with the prevalence of countries, population vaccination coverage, and the reliability and comprehensiveness of relevant statistics (3,7-12).

**Comment 3**: PATHOGENESIS: as the authors properly mention viral persistence, they should refer to this major study demonstrating viral persistence thourght the body in children (PMID: 37385286)

**Reply 3**: Thank you for your kindly suggestions. We have carefully reviewed the references you provided, and we found that this study has important support for our proposed mechanism of the long-term existence of the virus in vivo, and we have added it to the references. We put the changes to the manuscript and added references in the subsequent section. (see Page7, line127)

**Change in the text**: Line127: In clinical studies in children and adults, viral RNA and protein can still be detected 2 months after acute infection in some patients, and there is a certain correlation with the symptoms of long COVID (16-19).

Line442: 19. Buonsenso D, Martino L, Morello R, et al. Viral persistence in children infected with SARS-CoV-2: current evidence and future research strategies. The Lancet Microbe 2023;4:e745-e56.

**Comment 4**: RESPIRATORY SYMPTOMS: the authors may find helpful this detailed recent review (PMID: 37844017), plus may take inspiration to include some tables, currently missing in this form

**Reply 4**: Thank you for your kindly suggestions. We have carefully read this literature, and this systematic review of respiratory system puts forward some latest research progress of respiratory system, which will be of great help for us to draw the table according to your suggestions.

**Comment 5**: MENTAL AND CNS: the authors properly discuss several points, in my opinion there are quite a few studies showing abnormal brain metabolism in some children, in italy and france. I am reporting two studies, but the authors can also extend to other papers cited in these papers (PMID: 37303754 ; PMID: 35839175 )

**Reply 5**: Thank you for your kindly suggestions. According to the references and suggestions you provided, we have reviewed these two articles and other

relevant literatures related to brain metabolic changes in them. We ended up adding two additional references and modifying the manuscript. We are pleased with your suggestions to make our manuscript expression more credible and to improve the universality of evidence sources. We put the changes to the manuscript and added references in the subsequent section. (see Page14, line269)

**Change in the text**: Line269: As for the mechanism of occurrence of psychoneurotic symptoms and mental health impairment, several case studies of children have found that children with neuropathy-related symptoms of long COVID may have cerebral metabolism, which may be related to smell and taste decrease or neurocognitive problems (68-70).

Line563: 69. Morand A, Campion J-Y, Lepine A, et al. Similar patterns of [18F]-FDG brain PET hypometabolism in paediatric and adult patients with long COVID: a paediatric case series. European Journal of Nuclear Medicine and Molecular Imaging 2022;49:913-20.

Line566: 70. Cocciolillo F, Chieffo DPR, Giordano A, et al. Case report: Post-COVID new-onset neurocognitive decline with bilateral mesial-temporal hypometabolism in two previously healthy sisters. Frontiers In Pediatrics 2023;11:1165072.

**Comment 6**: PREVENTION: vaccines have been found to reduce, but not eliminate, the risk of long covid. there are at least two papers, one here, one cited in the discussion of the same paper (PMID: 37073325)

**Reply 6**: Thank you for your kindly suggestions. We sincerely thank you for your reminding. We have included these two references in the article and modified the description of the effects of the vaccine as follows: decrease but not eliminate (see Page16, line308)

**Change in the text**: Line308: Vaccination can effectively reduce the rate of severe illness, which is conducive to the disease recovery of children with severe illness, and decrease but not eliminate the morbidity of long COVID additionally (11,13,14),

**Reviewer D**

**Comment 1**: The authors revised literature studies on “long COVID” in paediatric samples conducted after 2019. Considering the impact of COVID-19 pandemic on mental health, the research theme is interesting and valuable. I have some major suggestions that the authors may consider introducing in their paper.
Introduction is not well documented on COVID-19; my suggestion would be to document on the COVID-19 pandemic as well, particularly on its clinical

presentation and on the two main long-term complications of SARS-CoV-2 infection, Multisystem Inflammatory Syndrome in Children (MIS-C), and long COVID.

**Reply 1**: Thank you for your kindly suggestions. While we appreciate your valuable advice, there is less mention of the pandemic in our article, especially with regard to children's mental health, which is a major impact of the pandemic on children. As you mentioned in comment 5, we have supplemented the mental health and nervous system-related symptoms of the article according to your suggestions, as shown in comment 5.

**Comment 2**: In addition, the cellular and molecular mechanisms underlying the various clinical spectrum of long COVID are poorly described. The proposed pathophysiological mechanisms for the development of long COVID seems to be include: hyperinflammatory state, chronic immune activation, renin-angiotensin system dysfunction leading to central and peripheral circulatory abnormalities, mast cell activation, virus persistence and organ damage, interference with fibrinolysis and promotion of microthrombi, and the development of autoantibodies. Lastly, infections or post-infections autoimmune effects post-SARS-CoV-2 might play an important role. I suggest to expand this section to include more information regarding the pathophysiology of this condition.

**Reply 2**: Thank you for your kindly suggestions. Thank you so much for providing us with a relatively complete pathophysiological framework of COVID-19, which helps us to better understand the deficiencies in the part of pathogenesis. By comparison, we found that most of the content and pathogenesis have overlapping parts. We are very sorry that one of the important mechanisms of autonomic dysfunction is not mentioned, so we have expanded this content at your suggestion. (see Page8, line154)

**Change in the text**: Line154: In addition, autonomic dysfunction has been suggested as a potential mechanism for the development of cardiovascular symptoms and symptoms resembling myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) in individuals experiencing long COVID (31-33).

**Comment 3**: I think that it would be optimal to better specify in the method section how they proceeded to the extraction of data, and inclusion and exclusion criteria for the research strategy. It would be good to know how many papers they screened, and how many papers were excluded from the review based on inclusion and exclusion criteria.

**Reply 3**: Thank you for your kindly suggestions. We did not provide the total number of literatures selected because this article is not a meta-analysis or systematic review. Although we did not use software to evaluate literature quality,

we can ensure that we have tried our best to select literatures with high credibility, new publication time and high compatibility with the content of the review. If the data in the search article is necessary for the publication of the article, we will try to retrieve the original search data and provide relevant analysis data. We hope that our sincere apologies and answers will be recognized by you.

**Comment 4**: Furthermore, I think that the manuscript would benefit from a more expanded literature review of studies focusing on the impact of COVID 19 on children. Despite of adults, long COVID has been poorly studied in children. A very low number of studies concerning the long-term effects of SARS-CoV-2 infection in the first years of age has been conducted, with conflicting results. Please, consider also including more literature data on the neuropsychiatric symptoms, that seem to be the most common impairment in children and adolescents with long COVID.

**Reply 4**: Thank you for your questions. We apologize for any ambiguity caused by the misrepresentation here. The conclusion you mentioned that the psychological impact of older children is less than that of younger children is quite acceptable to us, which seems to conflict with our expression here. We review the source literature and limit the impact here to intellectual development, which is more closely related to the original text. We added citations to the section on brain metabolism. In addition, in this paragraph, we have added a reference to pandemics based on your suggestions. (see Page14, line261)

**Change in the text**: Line246: …, and the negative impact of brain fog symptoms on the intellectual development of school-age children may be accompanied lifelong (64).

Line270: …, several case studies of children have found that children with neuropathy-related symptoms of long COVID may have cerebral metabolism, which may be related to smell and taste decrease or neurocognitive problems (68-70).

**Comment 5**: Regarding the mental and nervous system's disfunctions, the authors reported that the influence related to virus infection is more serious and far-reaching under the age of 12. Conversely, development of mental health disfunctions was found more common in older children and adolescents, in females and in those with previously diagnosed psychological problems, in agreement with what has been reported for pediatric long COVID, further suggesting that most of the clinical manifestations characterizing long COVID depend on the pandemic and not directly on the infection [Esposito S, Principi N, Azzari C, Cardinale F, Di Mauro G, Galli L, Gattinara GC, Fainardi V, Guarino A,

Lancella L, Licari A, Mancino E, Marseglia GL, Leonardi S, Nenna R, Zampogna S, Zona S, Staiano A, Midulla F. Italian intersociety consensus on management of long covid in children. Ital J Pediatr. 2022;48(1):42. https:// doi. org/ 10. 1186/ s13052- 022- 01233-6.].
Instead, this section may be expanded. Increased behavioural symptoms are reported during the global pandemic caused by SARS-CoV-2 infection in pediatric patients with neuropsychiatric disorders (Pasca L, Zanaboni MP, Grumi S, Totaro M, Ballante E, Varesio C, de Giorgis V. Impact of COVID-19 pandemic in pediatric patients with epilepsy with neuropsychiatric comorbidities: a telemedicine evaluation. Epilepsy Behav. 2021;115:107519). Similarly, in another study conducted by Raffagnato et al. (2021), 25% of families reported during home quarantine the exacerbation of some behavioral problems, such as more frequent and intense episodes of non-collaboration, indifference, physical/verbal aggression, poorly targeted/organized play, screaming/crying, social isolation, provocative attitudes towards others, attempts to escape, and self-cutting ideation. In a meta-analysis conducted on 80,879 children (Racine et al., 2021), the pooled prevalence of depression and anxiety symptoms during pandemic has doubled compared to prepandemic estimates. Finally, minor edits in the main text are necessary.

**Reply 5**: Thank you for your kindly suggestions. Your in-depth understanding of the impact of the pandemic on the mental health of children with COVID-19 has been a great help in expanding our content. Based on your suggestions and the references provided, we have included and added a section on the important impact of the pandemic on mental health. (see Page15, line276)

Change in the text: Line276: Among these factors, the impact of the pandemic on mental health problems stands out as particularly critical. Numerous studies have indicated that the COVID-19 pandemic may exert a significant influence on children's manifestations of abnormal mental states like anxiety and depression (62,72-74). Additionally, it may have an even more severe impact on children who already have existing mental illnesses (75,76).

**Reviewer E**

**Comment 1**: It is useful to summarise the research but there are many aspects missing from this review and it does not feel like there is clinical experience coming through.

**Reply 1**: Thank you for your kindly suggestions. We are so sorry for our lack of clinical experience, and the content of the article is not fully consistent with the actual clinical background. We will search for more literature based on your suggestion to supplement the content of the article.

**Comment 2**: There is a lot of adult data given and nor much pediatric. I do think the search was not thorough as missed out post COVID syndrome as a search term and children should include adolescents and young people as search terms please. Methods
Should have included paediatric( English spelling) and post covid syndrome as well as long covid.

**Reply 2**: Thank you for your kindly suggestions. We apologize for the large amount of adult research in my content. Indeed, your suggestions on searching are so beneficial for us, and our detection strategy have included teenagers, children, adolescents and young people. So we supplemented the search term part in the methods. (see Page2, line32)

**Changes in the text**: Line32: Methods: We reviewed all the studies on "long COVID", pediatric, children, adolescent, post covid syndrome in PubMed published after 2019.

**Comment 3**: The abstract massive infections needs qualifying as a sentence eg massive numbers or severity?

**Reply 3**: Thank you for your comment about the lack of accuracy in the presentation of our content. We have revised the content according to the latest data provided by WHO in accordance with your request. (see Page2, line23)

**Change in the text**: Line23: In the context of the global pandemic of COVID-19, more than 700 million infections and millions of deaths have occurred in countries around the world.

**Comment 4**: Line 55 should include eg wacks et al paper Wacks M, Wortley E, Gregorowski A, Segal TY, Whittaker E. Fifteen-minute consultation: Managing post-COVID-19 syndrome (long COVID) in children and young people [published online ahead of print, 2023 Apr 20]. Arch Dis Child Educ Pract Ed. 2023;edpract-2022-324950. doi:10.1136/archdischild-2022-324950 and this gives the other definitions too.

**Reply 4**: Thank you for your kindly suggestions. Thanks for your reminder, this article does also propose the definition of COVID-19 in children, so we have added this article as a reference for the article. ( see Page 4,line 72)

**Changes in the text**: Line72: Long COVID is a multi-system syndrome characterized by fatigue, headache, mood disorders, reduced sense of smell and other symptoms (3,5).

Line409: 5. Wacks M, Wortley E, Gregorowski A, et al. Fifteen-minute

consultation: Managing post-COVID-19 syndrome (long COVID) in children and young people. Archives of Disease In Childhood Education and Practice Edition 2023.

**Comment 5**: Line 96 is there a reference for the ebv theory?

**Reply 5**: Thank you for your kindly suggestions. We sincerely apologize that we did not clearly state the source of the citation here, so we added additional references to supplement our review to provide evidence. (see Page7, line130)

**Changes in the text**: Line130: Furthermore, the activation of herpes virus such as EBV from latent state may also be one of the potential mechanisms (20).

Line444: 20. Klein J, Wood J, Jaycox JR, et al. Distinguishing features of long COVID identified through immune profiling. Nature 2023;623:139-48.

**Comment 6**: Line 109- "Many investigations have shown that the levels of D-dimer, 108 IL-6, IL-1 and other cytokines in children with long COVID are elevated, suggesting the risk of 109 inflammation and thrombosis in their bodies(1,2,23–25)"
this is not reported in reference 1.
Reference 2 "Children with long-COVID had higher leukocytes, neutrophils, monocytes, basophils, platelets, and D-dimer when compared with patients without long-COVID ($p < 0.001$). Leukocytes, neutrophils, monocytes, platelets, and D-dimer had the highest AUC in the ROC analysis (0.694, 0.658, 0.681, 0.667, and 0.612, respectively) and were statistically significant."
This was a retrospective analysing initial blood tests as predictors of long covid and they had symptoms at initial infection. I do not think you can extrapolate to say that this suggests a risk of thrombosis in their bodies. You could potentially say that reference 2 shows that retrospectively the markers of inflammation etc are higher than controls as the time of infection and this poses the question of whether there may be a possible link to inflammation/chronic endothelial damage( 23) being a factor in causation.
Most of the levels in reference 23 are normal and the only significant difference is ddimer and most are in the normal range.

**Reply 6**: Thank you for your kindly suggestions. I feel so sorry for my negligence in selecting reference articles. We found that reference 1 does not contain this content and the research purpose of reference 2 is not consistent with what we want to prove, so we have deleted both reference 1 and 2. As for reference 23(now is 25), the association between D-Dimer and thrombotic inflammation is mentioned in the original text. We believe that at least this article can support the part of thrombosis so it can be retained in the references for evidence, although there was no significant increase in other indicators related to thrombosis and

inflammatory in this study. (see Page8,line147)

**Changes in the text**: Line147: Many investigations have shown that the levels of D-dimer, IL-6, IL-1 and other cytokines in children with long COVID are elevated, suggesting the risk of inflammation and thrombosis in their bodies (1,2,27-29). (25-27 means 23-25 in original manuscript)

**Comment 7**: 4 clinical manifestations, post exertional malaise is missing.
Could reference
Newlands, F.; Goddings, A.-L.; Juste, M.; Boyd, H.; Nugawela, M.D.; Pinto Pereira, S.M.; Whelan, E.; Whittaker, E.; Stephenson, T.; Heyman, I.; et al. Children and Young People with Long COVID—Comparing Those Seen in Post-COVID Services with a Non-Hospitalised National Cohort: A Descriptive Study. Children 2023, 10, 1750. https://doi.org/10.3390/children10111750

**Reply 7**: Thanks for your kindly suggestions. We sincerely apologize for not adding post exertional malaise to the clinical symptoms as a primary symptom. We have revised the content of this section and added the references you provided. (see Page8, line161)

**Change in the text**: Line161: These symptoms may include fatigue, headache, hyposmia, hypogeusia, muscle or joint pain, insomnia, cough, cognitive difficulties, fever, dizziness, abdominal pain, dyspnea, post-exertional malaise, and decreased exercise tolerance (7,34-38).

**Comment 8**: Grammar in lines 127-129 can be improved.

**Reply 8**: Thanks for your kindly suggestions. Thanks for your reminding, we realize that the presentation of this paragraph needs to be improved. Therefore, we have embellished this paragraph based on the original text. (see Page9, line166)

**Change in the text**: Line166: These symptoms implicate multiple systems, and their severity is influenced by various risk factors. A survey conducted in Italy revealed that 92 percent of patients with long COVID experienced difficulties in their daily lives to varying degrees, with 29 percent of them requiring assistance from a multidisciplinary team (35).

**Comment 9**: 4.1 The major finding is dysfunctuional breathing and thought to have aetiology in autonomic dysfunction
These should be mentioned. Byt may be unpublished fiundings so far.

**Reply 9**: Thank you for your friendly reminder. Under your suggestion, we have checked relevant literature and found that there is a correlation between vagus

nerve and respiratory symptoms of long COVID7 in adult studies, especially cough itself is regulated by vagus nerve. However, it is a pity that we did not find relevant research among children. We have added relevant content to the original text and made a clear explanation. (see Page11, line192)

**Change in the text**: Line207: Additionally, clinical studies have found vagus nerve inflammation in adults following COVID-19 infection, which is correlated with cough and other respiratory symptoms of long COVID (43,44). However, there is a paucity of relevant studies investigating this phenomenon in children.

**Comment 10**: 4.2 The main finding in children clinically is pots and inappropriate tachycardia and autonomic dysfunction. dysautonomia and this is not mentioned. Too much on adults does not give a full picture.

**Reply 10**: Thank you for your suggestions . We are so sorry for not including the concept of autonomic symptoms in the section on circulatory system, so at your suggestion we have added content related to autonomic disorders to this section. However, autonomic symptoms are a group of syndromes and the pathogenesis of more specific symptoms, so we decided to describe their significance in the cardiovascular system in terms of pathogenesis. (see Page12, line227)

**Change in the text**: Line227: Moreover, autonomic dysfunction may serve as a potential mechanism for circulatory system-related symptoms, including postural hypertension, fatigue discomfort, and syncope (32,49). The functioning of the autonomic nervous system is closely intertwined with the circulatory system (50), and several studies have indicated a potential association between primary COVID-19 infection and the development of autonomic nervous system disorders (51,52). Furthermore, in studies on long COVID, there has been evidence of autonomic nervous dysfunction contributing to associated clinical symptoms, which may have a strong genetic correlation in patients (53-55).

**Comment 11**: 4.3 there is a Cochrane review on coagulation and covid that should be referenced

**Reply 11**: Thanks for your kindly suggestions. Thank you for your suggestion. We have searched the relevant literature and found that the topic of this review is about coagulopathy and acute phase of COVID-19, which may not be particularly suitable as evidence of coagulopathy in long COVID.

**Comment 12**: 4.4 Mental system is not a term that is used. Emotional wellbeing or mental health. Or mind
236- mental health effects

**Reply 12**: Thank you for your kindly suggestions. We are sorry for this unusual

expression error, our original intention is to use systematic classification to make the whole article more orderly. With your suggestion, we have revised all the “mental systems” appearing in the article to “mental health”. (see Page14, line252)

Change in the text: Line252: 4.4 Mental health and nervous systems

Line255: In the filed of mental health,…

Line269: As for the mechanism of occurrence of psychoneurotic symptoms and mental health impairment,…

Line276: Among these factors, the impact of the pandemic on mental health problems stands out as particularly critical.

Line301: …,and establishing local mental health centers to provide psychological counselling and communication services for children and adolescents.

**Comment 13**: Gastro system not mentioned and clinically is important

**Reply 13**: Thank you for your kindly suggestions. Indeed, when we were writing the first draft, we discussed whether the absence of the digestive system would make the article less complete. In the section of 4 clinical manifestations, we also mentioned abdominal pain as the main symptom ( Page , line ). Additionally, digestive system symptoms include diarrhea, liver dysfunction and so on. Due to the limited amount of reference available, we are unable to accurately describe the mechanism and incidence of digestive system symptoms, etc. Therefore, we regrettably choose to delete the content of this part.

**Comment 14**: 245- what are you postulating about actrually giving metformin and to whom?

**Reply 14**: Thank you for your kindly questions. Thank you for asking us to revisit the implications of this clinical study. As the first published clinical study on long COVID prophylaxis, it lacks data in children to support its routine clinical use in children. We are so sorry that we only limited its adaptive scope as a diabetes drug in the manuscript, and we have modified and supplemented this section in our manuscript.(see Page17, line328)

**Change in the text**: Line328: Currently, there is insufficient research regarding the use of metformin in children as a preventive measure for long COVID. The use of metformin in children should only be considered for those who are 10 years old and above, aligning with its established usage as a medication for diabetes. However, it is crucial that parents or guardians provide informed consent. Given that this study focuses on adults, there is a limited availability of clinical data for

children, thereby making it difficult to endorse the routine use of metformin as a preventive drug for long COVID in pediatric patients.

**Comment 15**: There is nothing on treatment in this article

**Reply 15**: Thank you for your questions. The section of treatment in our review is from line267 to 288. We understand exactly what you mean by this question, indeed, our review of treatment is based on speculation and empirical advice from a number of clinical studies. In clinical practice, the current treatment for COVID-19 is only symptomatic medication but not specific therapy. Our purpose is to provide summative recommendations for clinical research and practical application, and these existing findings may be converted into a part of clinical guidelines in future studies.