nature portfolio

Peer Review File

SSRI/SNRI and Long COVID in children and adolescents with neuropsychiatric conditions: a cohort study from the RECOVER Initiative

Corresponding Author: Dr Yong Chen

This file contains all reviewer reports in order by version, followed by all author rebuttals in order by version.

Version 0:

Reviewer comments:

Reviewer #1

(Remarks to the Author)
This paper is well written and addresses an important knowledge gap using the large-scale RECOVER Initiative cohort.

Comments:
1. Page 10, lines 207–209:
"The temporal sequencing in this study, defined exposure to SSRIs/SNRIs prior to SARS-CoV-2 infection, mitigates reverse causation and strengthens the plausibility of a pharmacologic effect during or after infection."
The rationale for the second part "strengthens the plausibility of a pharmacologic effect during or after infection" is unclear, even with the example provided in the following sentence. Please elaborate on this.
2. Page 15, "Long COVID Outcome Definitions":
Please provide the ICD codes used to define the listed symptoms and clinical conditions associated with long COVID.
3. Page 15, lines 322–323:
"These outcomes were assessed during the follow-up period and were restricted to patients without prior documentation of the same conditions during the baseline period."
What is the time window used for the baseline period when assessing prior conditions?
4. Page 16, lines 340–341:
"For each outcome, incidence rates were calculated by dividing new cases during the follow-up period by the total number of at-risk patients (excluding individuals with the condition at baseline)."
Given the unequal follow-up times in EHR data, this approach could introduce bias. Please clarify whether any adjustment for differential follow-up time was applied.
5. Page 16, lines 350–351:
How was the severity of acute COVID-19 defined using the EHR data? Please provide criteria or codes used in this classification.

Minor Comments:
1. Page 9, line 188:
Change:
"Negative control outcome analysis for twenty-seven yielded no significant associations …"
To:
"Negative control outcome analysis for twenty-seven negative control outcomes yielded no significant associations …"
2. Page 13, lines 274–275:
Original:
"This difference may limit generalizability but reflects the study's targeted population."
Consider revising for clarity. If the intention is to acknowledge the limited generalizability while highlighting the coverage of targeted population, a better phrasing could be:
"This difference may limit generalizability, but it reflects the study's intended target population."

(Remarks on code availability)

I was able to run the code using the demo dataset. However, the package "ParallelLogger" is required but not included in the code. It can be loaded by adding library(ParallelLogger).

Disclaimer: Since the dataset used is synthetic and not the real data referenced in the manuscript, I cannot verify the analytical results.

Reviewer #2

(Remarks to the Author)
Description of study:
The study utilized retroactive analysis of data from over 110,000 youth ages 5-20 years from 37 sites across the US to evaluate the relationship between long-COVID symptoms and SSRI/SNRI use. Results suggest that SSRI/SNRI use in those with long-COVID was related to a decreased risk of fever, chills, and hair loss, but an increased risk of thromboembolic effects, cognitive dysfunction, elevated liver enzymes, and generalized pain.

Methodology:
Cohort selection:
• Methodological decision for cohort definition is justified, including the stipulation of enrollment by 179 days before study cut-off.
• I am concerned that the stark differences in rates of neuropsychiatric symptoms between the SSRI/SNRI and comparison group are not fully accounted for through the temporal sequencing used in the study. For example, encephalopathy was included as pre-existing neuropsychiatric condition and was much more prevalent in the SSRI/SNRI cohort. This condition includes symptoms that overlap with long-covid and have been shown to increase following COVID-19 infection regardless of SSRI use. Given that it is very common that symptoms of encephalopathy wax and wane, changes in symptoms may not be robustly accounted for with the temporal sequencing of the study design.
• How was severity of COVID-19 symptoms operationalized?

Statistical design.
• The overall statistical design is appropriate.
• I question whether impetigo should be used as a negative control variable. Group A strep has also been shown to be related to post-infectious sequalae of neuropsychiatric symptoms, including cognitive dysfuncton(eTable 1).
• Selection and statistical handling of patient specific characteristics was appropriate.

Results.
• Tables represent that data and findings well.
• Results are clearly articulated.

Conclusions/Discussion.
• I am pleased to see that you highlighted two important points that could have easily been overlooked: getting ahead of potential misinterpretation of rates of vaccination between the populations compared (Line 235) and how this work further reflects known health-care disparities (Line 248).
• The strengths and limitations of the methodology are clearly articulated.

Misc considerations:
• Reference included are appropriate
• No inflammatory language

Overall.
The authors have presented a very important and powerful study to help both clinicians and individuals evaluate the potential relationship between SSRI/SNRI used and long-COVID in youth. The sample, although not representative of the general US population, capitalizes on a large cohort that allows for the analyses of this specific question that would not be achieved without such a robust and collaborative effort. The authors also present their work in a very clear, succinct manner and present limitations that could not be reasonably addressed given methodological and cohort-constraints. The authors appropriately draw conclusions from the data available.

(Remarks on code availability)

Version 1:

Reviewer comments:

Reviewer #1

(Remarks to the Author)
Thank you for addressing my comments.

(Remarks on code availability)

Reviewer #2

(Remarks to the Author)
The authors fully addressed both my comments and the comments of reviewer 1.

(Remarks on code availability)

Response to Reviewer #1:

This paper is well written and addresses an important knowledge gap using the large-scale RECOVER Initiative cohort.

Our response: We thank the reviewer for this encouraging feedback. We aimed to present the study clearly and rigorously, and we appreciate the recognition that the manuscript effectively communicates its findings. We are also grateful that the reviewer acknowledges the importance of addressing this knowledge gap and the value of leveraging the RECOVER Initiative's large-scale, multi-site pediatric cohort. This affirmation reinforces the relevance and potential impact of the work.

Comments:

1. **Page 10, lines 207-209: "The temporal sequencing in this study, defined exposure to SSRIs/SNRIs prior to SARS-CoV-2 infection, mitigates reverse causation and strengthens the plausibility of a pharmacologic effect during or after infection." The rationale for the second part "strengthens the plausibility of a pharmacologic effect during or after infection" is unclear, even with the example provided in the following sentence. Please elaborate on this.**

   Our response: We appreciate this thoughtful comment. We agree that the rationale for the statement "strengthens the plausibility of a pharmacologic effect during or after infection" required further clarification. In response, we have expanded the explanation in the Discussion section to better articulate the temporal and biological basis for this point. The revised text now appears at lines 214-218 in the clean version of the manuscript (all line numbers in our responses refer to the clean revised manuscript; a tracked-changes version marking all revisions is also provided):

   "*The temporal sequencing in this study, where exposure to SSRIs/SNRIs precedes SARS-CoV-2 infection, mitigates reverse causation and ensures that medication effects were present during the acute and early post-acute phases when long-COVID-related biological processes emerge. This timing strengthens the plausibility that SSRIs/SNRIs could influence downstream symptom development through their known immunomodulatory and autonomic effect*."

2. **Page 15, "Long COVID Outcome Definitions": Please provide the ICD codes used to define the listed symptoms and clinical conditions associated with long COVID.**

   Our response: Thank you for this helpful suggestion. We have now added a supplemental table that lists all ICD-10-CM codes used to define each symptom and clinical condition associated with long COVID. These codes are provided in the revised Supplement as **eTable 1**, which improves transparency and reproducibility of the outcome definitions.

3. **Page 15, lines 322-323: "These outcomes were assessed during the follow-up period and were restricted to patients without prior documentation of the same conditions during the baseline period." What is the time window used for the baseline period when assessing prior conditions?**

   Our response: We appreciate the reviewer's helpful observation. The baseline period used to assess prior conditions was defined as the 24 months to 7 days before SARS-CoV-2 infection. We have now explicitly stated this in the revised Methods section (lines 311-312):

   "Individuals were required to have at least one healthcare encounter during a baseline period (24 months to 7 days before SARS-CoV-2 infection)…"

4. **Page 16, lines 340-341: "For each outcome, incidence rates were calculated by dividing new cases during the follow-up period by the total number of at-risk patients (excluding individuals with the condition at baseline)." Given the unequal follow-up times in EHR data, this approach could introduce bias. Please clarify whether any adjustment for differential follow-up time was applied.**

   Our response: Thank you for raising this important point regarding potential bias from unequal follow-up times in EHR-based studies. In our design, the follow-up period was intentionally standardized to 28-179 days after the index date, which is a fixed window and consistent for all individuals. Incidence was calculated as the proportion of at-risk patients with a new diagnosis during this period. Under this design, person-time denominators would be equivalent across participants and would not change the interpretation of incidence estimates.

   To improve clarity, we have revised both the Methods and Results sections to explicitly state the use of a harmonized follow-up window in the revised manuscript:

   - Lines 140-142: "*Long COVID outcomes were evaluated during a standardized 28-179-day period after infection to ensure equal observational time across participants.*"

   - Lines 166-167: "*The incidence of long COVID was expressed as the proportion of at-risk individuals who developed each outcome within the fixed follow-up window.*"

   - Lines 338-341: "*These outcomes were assessed during the harmonized follow-up period of 28-179 days after the index date and only among patients without prior documentation of the same conditions during the baseline period.*"

   - Lines 359-363: "*The incidence of long COVID outcomes was calculated for the SSRI/SNRI and control groups as the proportion of at-risk patients (excluding those with the condition at baseline) who develop the outcome during follow-up. Because all participants*

contributed data over a fixed observation window and outcomes were based on clinician-documented events, this approach would not alter the interpretation of incidence."

5. **Page 16, lines 350-351: How was the severity of acute COVID-19 defined using the EHR data? Please provide criteria or codes used in this classification.**

   Our response: Thank you for this clarification question. Acute COVID-19 severity was classified using structured EHR indicators, following the pediatric framework described by Forrest et al. [1] and the validated definitions from the PEDSnet COVID-19 Severity repository (GitHub: PEDSnet/COVID19_Severity).

   We categorized severity as asymptomatic, mild, moderate, or severe based on the combinations of COVID-19-related hospitalization, intensive care unit (ICU) admission, respiratory support procedures (e.g., supplemental oxygen, non-invasive ventilation, mechanical ventilation), and diagnosis codes indicating respiratory acute COVID-19 complications. Patients were assigned the highest severity level recorded within 14 days of the index date. This classification reflects clinically meaningful stratification of pediatric acute COVID-19 and aligns with prior EHR-based research [2-4]. We have added this clarification and the citation to the Methods section in the revised manuscript as follows (lines 354-357):

   "…*severity of acute COVID-19 (categorized as asymptomatic, mild, moderate, or severe) based on COVID-19-related hospitalization, intensive care unit (ICU) admission, respiratory support procedures, and diagnosis codes indicating respiratory acute COVID-19 complications within 14 days of the index date;*[59]*…*"

Minor Comments:

6. **Page 9, line 188: Change "Negative control outcome analysis for twenty-seven yielded no significant associations …" to "Negative control outcome analysis for twenty-seven negative control outcomes yielded no significant associations …"**

   Our response: Thank you for the suggestion to clarify the wording of this sentence. We have revised this accordingly, and the sentence has been updated in the revised manuscript to read (lines 194-196)

   "*Negative control outcome analysis for twenty-six negative control outcomes yielded no significant associations …*"

7. **Page 13, lines 274-275: Original: "This difference may limit generalizability but reflects the study's targeted population." Consider revising for clarity. If the intention is to acknowledge the limited generalizability while highlighting the coverage of targeted population, a better phrasing could be: "This difference may limit generalizability, but it reflects the study's intended target population."**

   Our response: Thank you very much for the helpful suggestion. We have rephrased the sentence as suggested by the reviewer to improve clarity. The updated text now reads (lines 283-284):

   "*This difference may limit generalizability, but it reflects the study's intended target population.*"

8. **Remarks on code availability:**
   I was able to run the code using the demo dataset. However, the package "ParallelLogger" is required but not included in the code. It can be loaded by adding library(ParallelLogger). Disclaimer: Since the dataset used is synthetic and not the real data referenced in the manuscript, I cannot verify the analytical results.

   Our response: Thank you for your valuable comments. We have updated the Code Ocean capsule to explicitly load the "*ParallelLogger*" package, consistent with the reviewer's suggestion. The reproducible environment has been resubmitted for peer review and is fully operational with the demo dataset. The analytic results reported in the manuscript are based on detailed individual-level patient data compiled as part of the RECOVER program. Due to the high risk of reidentification based on the number of unique patterns in the data, patient privacy regulations prohibit us from releasing the data publicly.

Response to Reviewer #2:

Description of study:

1. **The study utilized retroactive analysis of data from over 110,000 youth ages 5-20 years from 37 sites across the US to evaluate the relationship between long-COVID symptoms and SSRI/SNRI use. Results suggest that SSRI/SNRI use in those with long-COVID was related to a decreased risk of fever, chills, and hair loss, but an increased risk of thromboembolic effects, cognitive dysfunction, elevated liver enzymes, and generalized pain.**

   Our response: We appreciate the reviewer's thoughtful summary of the study and are grateful for the recognition of the scale and scope of this analysis. We also appreciate the reviewer's attention to the differential risk patterns observed across symptom domains, which reflects a central contribution of this work. We have ensured that the revised manuscript continues to present these findings clearly and emphasizes the clinical relevance of both the protective and risk-enhancing associations identified.

Methodology:

Cohort selection:

2. **Methodological decision for cohort definition is justified, including the stipulation of enrollment by 179 days before study cut-off.**

   Our response: We thank the reviewer for acknowledging the rationale behind our cohort selection strategy. The requirement that participants enter the cohort at least 179 days before the study cutoff ensured that all individuals had a complete and standardized follow-up window of 28-179 days after cohort entry for assessing long COVID outcomes. We appreciate the reviewer's recognition of this methodological strength. To enhance clarity, we have added the following sentence to the Methods section (lines 307-309):

   "*This study spanned from March 1, 2020, to March 19, 2024. Cohort entry occurred between March 1, 2020, and September 22, 2023, allowing a minimum of 179 days of follow-up for long COVID assessment.*"

3. **I am concerned that the stark differences in rates of neuropsychiatric symptoms between the SSRI/SNRI and comparison group are not fully accounted for through the temporal sequencing used in the study. For example, encephalopathy was included as pre-existing neuropsychiatric condition and was much more prevalent in the SSRI/SNRI cohort. This condition includes symptoms that overlap with long-covid and have been shown to increase following COVID-19 infection regardless of SSRI use. Given that it is very common that symptoms of encephalopathy wax and wane, changes in symptoms may not be robustly accounted for with the temporal sequencing of the study design.**

Our response: Thank you for bringing this important concern to our attention. We agree that preexisting neuropsychiatric conditions, particularly encephalopathy, may fluctuate over time and overlap with symptoms attributed to long COVID, raising the possibility of residual misclassification.

Our study design mitigates (although cannot fully eliminate) this issue in several ways. First, we restricted each long COVID outcome to incident diagnoses by excluding patients with the same condition documented during the baseline period. Second, propensity score stratification was applied for all preexisting neuropsychiatric conditions, including encephalopathy, which helped to balance baseline conditions. Third, negative control outcome analyses did not show evidence of systematic bias that would be expected if waxing-waning symptoms were driving observed associations.

However, we acknowledge that episodic neuropsychiatric conditions may still be imperfectly captured in EHR data, and symptom recurrence after infection may occasionally be indistinguishable from true new-onset long COVID manifestations. We have added text to the Discussion to clarify this limitation and note its relevance when interpreting neurologic and autonomic findings (lines 284-290):

"*Although our design excluded patients with documented baseline symptoms from outcome-specific analyses and adjusted for all preexisting neuropsychiatric diagnoses, we acknowledge that some conditions, such as encephalopathy, exhibit fluctuating courses that may not be fully captured in EHR data. As such, symptom recurrence after infection may be difficult to distinguish from true incident post-COVID manifestations, and this limitation may partially contribute to the differential risks observed for neurologic and autonomic outcomes.*"

4. How was severity of COVID-19 symptoms operationalized?

Our response: We appreciate this clarification question. Acute COVID-19 severity was classified using structured EHR indicators, following the pediatric framework described by Forrest et al. [1] and the validated definitions from the PEDSnet COVID-19 Severity repository (GitHub: PEDSnet/COVID19_Severity).

We categorized severity as asymptomatic, mild, moderate, or severe based on the combinations of COVID-19-related hospitalization, intensive care unit (ICU) admission, respiratory support procedures (e.g., supplemental oxygen, non-invasive ventilation, mechanical ventilation), and diagnosis codes indicating respiratory acute COVID-19 complications. Patients were assigned the highest severity level recorded within 14 days of the index date. This classification reflects clinically meaningful stratification of pediatric acute COVID-19 and aligns with prior EHR-based research [2-4]. We have added this clarification and the citation to the Methods section in the revised manuscript as follows (lines 354-357):

"*…severity of acute COVID-19 (categorized as asymptomatic, mild, moderate, or severe) based on COVID-19-related hospitalization, intensive care unit (ICU) admission, respiratory support procedures, and diagnosis codes indicating respiratory acute COVID-19 complications within 14 days of the index date;*[59] *…*"

Statistical design:

5. **The overall statistical design is appropriate.**

   Our response: We appreciate the reviewer's positive assessment of the statistical design.

6. **I question whether impetigo should be used as a negative control variable. Group A strep has also been shown to be related to post-infectious sequalae of neuropsychiatric symptoms, including cognitive dysfunctón(eTable 1).**

   Our response: Thank you for raising this important point. Upon re-evaluation, we agree that impetigo may potentially share post-infectious neuropsychiatric symptoms and therefore does not fully satisfy the assumptions required of a negative control outcome. We have removed impetigo from the negative control outcome set and revised the manuscript and Supplement to reflect this change.

   In the revised manuscript, the Results section now reads (lines 194-196):
   "*Negative control outcome analysis for twenty-six negative control outcomes yielded no significant associations …*"

   The Methods section has been updated to state (line 379):
   "*A set of 26 negative control outcomes…*"

   In the supplement, "impetigo" has been removed from the former **eTable 1** (now **eTable 2**), and the table title has been updated to indicate that 26 negative control outcomes were included.

7. **Selection and statistical handling of patient specific characteristics was appropriate.**

   Our response: We thank the reviewer for highlighting the appropriateness of the patient-specific characteristics selection and statistical handling.

Results:

8. **Tables represent that data and findings well.**

   Our response: We appreciate the reviewer's positive assessment of the results presentation. We are grateful that the reviewer found them effective.

9. **Results are clearly articulated.**

   Our response: We appreciate the reviewer's recognition that the results are clearly communicated.

Conclusions/Discussion:

10. **I am pleased to see that you highlighted two important points that could have easily been overlooked: getting ahead of potential misinterpretation of rates of vaccination between the populations compared (Line 235) and how this work further reflects known health-care disparities (Line 248).**

    Our response: We appreciate the reviewer's thoughtful and encouraging feedback. We intentionally addressed the potential for misinterpretation of vaccination differences to prevent unwarranted inferences about vaccine-related risk, given the public health implications. We also appreciate the reviewer's acknowledgement of our discussion of healthcare disparities, which we view as essential context for interpreting differential SSRI/SNRI prescribing patterns and long COVID outcomes. We appreciate the reviewer's recognition that these points strengthen the discussion.

11. **The strengths and limitations of the methodology are clearly articulated.**

    Our response: We thank the reviewer for the positive assessment of how the manuscript presents the methodological strengths and limitations. We appreciate that the reviewer found the discussion clear and appropriately framed.

Misc considerations:

12. **Reference included are appropriate**

    Our response: We appreciate the reviewer's recognition that the references are appropriate.

13. **No inflammatory language**

    Our response: We thank the reviewer for noting the balanced and objective tone of the manuscript.

Overall:

14. **The authors have presented a very important and powerful study to help both clinicians and individuals evaluate the potential relationship between SSRI/SNRI used and long-COVID in youth. The sample, although not representative of the general US population, capitalizes on a large cohort that allows for the analyses of this specific question that would not be achieved without such a robust and collaborative effort. The authors also present their work in a very clear, succinct manner and present limitations that could not be reasonably addressed given methodological and cohort-constraints. The authors appropriately draw conclusions from the data available.**

    Our response: We sincerely thank the reviewer for this generous and thoughtful assessment of our manuscript. We really appreciate the reviewer's recognition of the study's contribution to understanding the complex relationship between SSRI/SNRI use and long COVID in pediatric populations, as well as the value of leveraging a large, multi-institutional cohort through the RECOVER initiative. We are grateful that the clarity of presentation, balanced interpretation of findings, and transparent discussion of methodological constraints were well received. We also appreciate the reviewer's acknowledgment that the conclusions appropriately reflect the available data. This important feedback is greatly encouraging and affirms the scientific and clinical relevance of our work.

References for Responses:

[1] Forrest, C. B. et al. Severity of Acute COVID-19 in Children <18 Years Old March 2020 to December 2021. Pediatrics 149, (2022).

[2] Zhou, T. et al. Body Mass Index and Postacute Sequelae of SARS-CoV-2 Infection in Children and Young Adults. JAMA Netw Open 7, e2441970 (2024).

[3] Lu, Y. et al. Risk of neuropsychiatric and related conditions associated with SARS-CoV-2 infection: a difference-in-differences analysis. Nat Commun 16, 6829 (2025).

[4] Zhang, B. et al. Long COVID associated with SARS-CoV-2 reinfection among children and adolescents in the omicron era (RECOVER-EHR): a retrospective cohort study. Lancet Infect Dis https://doi.org/10.1016/S1473-3099(25)00476-1 (2025) doi:10.1016/S1473-3099(25)00476-1.

Reviewer comments:

Reviewer #1 (Remarks to the Author):
Thank you for addressing my comments.

Our response: We thank the reviewer for the positive feedback and for taking the time to review our manuscript.

Reviewer #2 (Remarks to the Author):
The authors fully addressed both my comments and the comments of reviewer 1.

Our response: We thank the reviewer for the positive feedback and are pleased that our revisions have addressed the reviewer's comments as well as those of Reviewer 1.