Re: Revision of manuscript "Biopsychosocial and Economic Consequences of Long COVID: A Four-Year Longitudinal Analysis."

Dear Editor,

We thank you and the reviewers for the thoughtful and constructive feedback on our manuscript. We have carefully revised the paper to address all comments. Below, we provide a point-by-point response, indicating how each issue has been handled in the revised version.

All changes have been incorporated into the revised manuscript titled "Biopsychosocial and Economic Consequences of Long COVID: A Four-Year Longitudinal Analysis."

Response to Reviewer 1

Comment 1. Clarity of MEPS description ("national representative" wording).

The Methods currently state that MEPS is a "national representative survey." Please correct/clarify.

Response:
We thank the reviewer for this suggestion. We have revised the description in Section 2.1 (Research Design and Data Source) to read:

"MEPS is a nationally representative survey of the U.S. civilian noninstitutionalized population…"

This corrects the wording and aligns with standard terminology.

Comment 2. Study population and inclusion criteria (need more detail and a flowchart).

Please provide more information on the inclusion/exclusion criteria and how the analytic sample was derived. A flow chart would be helpful.

Response:
We agree and have expanded Section 2.2 (Study Population and Cohort) to provide explicit inclusion and exclusion criteria, including:

- Eligibility of all Panel 24 respondents with a valid COVID-19 history,
- Exclusion of participants with indeterminate COVID-19 status, and
- Exclusion of participants with missing or indeterminate symptom-duration information among those with COVID-19.

We also added a participant flow diagram (Figure 1) summarizing sample inclusion, exclusions, and final cohort assignment. In Section 2.2, we now state:

"Participant inclusion, exclusions, and final cohort assignment are summarized in Figure 1."

Comment 3. Number of repeated measures and potential bias from unequal follow-up.

How many time points were used? Could individuals with more observations bias the results?

Response:
We now clarify in Section 2.3 and 2.4 that:

- Outcomes were modeled annually across four waves (2019–2022), and
- Participants contributed up to four repeated measures.

We explicitly state in Section 2.4 (Statistical Analysis):

"Participants contributed up to four annual observations (2019–2022). Random intercepts and random slopes for time were specified to account for within-person correlation and unequal numbers of observations per participant."

By using hierarchical linear mixed-effects models with random effects and Full Information Maximum Likelihood, unequal follow-up is handled appropriately, and individuals with more observations are not given disproportionate influence beyond what their survey weights imply.

Comment 4. Group differences at baseline (need clearer reporting of significance, e.g., ANOVA).

Is there a significant difference between weighted categories at baseline? A table summarizing demographic differences (e.g., Table 1) would be helpful.

Response:
We have added a comprehensive Table 1 titled:

"Table 1. Baseline demographic characteristics by COVID-19 status group."

Table 1 reports survey-weighted percentages, standard errors, and design-corrected p-values (from survey-adjusted chi-square tests) for sex, race/ethnicity, and insurance status across Long COVID, COVID-recovered, and No COVID groups. In Section 3 (Results) we now explicitly state:

"Significant differences were observed across groups for sex and race/ethnicity, while insurance coverage did not differ significantly across COVID categories (Table 1)."

This directly addresses the request for clearer reporting of group differences using survey-adjusted methods.

Comment 5. Clarify awkward phrasing in the original Results ("this finding that was robust to controlling…").

The sentence describing findings "robust to controlling for…" is unclear.

Response:
We have removed the awkward phrasing and replaced it with clearer language in Section 3.1 (Escalating Economic Burden). The relevant sentence now reads:

"The persistence of the Time × COVID status interaction after adjustment for baseline health and comorbidities indicates that escalating healthcare utilization among individuals with Long COVID is not fully explained by pre-pandemic medical vulnerability or socioeconomic status, and is consistent with a unique longitudinal burden associated with post-acute sequelae."

This preserves the substance of the finding without the confusing wording.

Comment 6. Reference group for race/ethnicity.

Why was "multiple races" used as the reference group? This seems non-standard.

Response:
We appreciate this important point and have updated the modeling strategy. In the revised manuscript, race/ethnicity is modeled with Non-Hispanic White as the reference group, in line with standard practice in U.S. population analyses. This is now explicitly stated in Section 2.3 (Covariates):

"Race/ethnicity was modeled as a categorical variable with Non-Hispanic White as the reference group to enhance interpretability and statistical stability in U.S. population analyses (Heeringa et al., 2017)."

We also updated Table 2 and all related text in the Results to reflect this reference category (e.g., "Black (vs White), Asian/NHPI (vs White)").

Comment 7. Interpretation of primary findings – concern about overclaiming causality.

The original Discussion and Conclusion seemed to draw "definitive" conclusions from observational data and a single interaction term. Please soften causal language.

Response:
We agree and have carefully revised both the Discussion (Section 4) and Conclusion to avoid causal language and overstatement. Key changes include:

- Replacing phrases such as "demonstrates that" and "definitive evidence" with more cautious terms such as "provides evidence," "indicates," and "is consistent with."
- Reframing statements about Long COVID's impact on expenditures to emphasize associations rather than causation.

For example, in the Discussion we now write:

"…indicating that Long COVID is associated with elevated long-run healthcare costs beyond pre-existing vulnerability…"

and in the Conclusion:

"…Long COVID was independently associated with escalating healthcare costs."

We believe these revisions fully address the concern about overclaiming and bring the interpretive tone into line with the observational design.

Comment 8. Role of baseline health and multimorbidity as predictors of outcomes.

Please clarify that baseline health status and comorbidity burden are major drivers of observed symptom differences.

Response:
We have strengthened this point in Section 4 (Discussion). We now write:

"A key and potentially counterintuitive finding of this study is that baseline health status and multimorbidity burden were the primary predictors of perceived health and psychological distress across all COVID-19 groups. After adjustment, COVID-19 status itself did not independently explain longitudinal symptom deterioration."

We also connect this to existing literature on risk concentration and pre-existing vulnerability (Sudre et al., 2021; Thompson et al., 2022), situating our findings in the broader evidence base.

Comment 9. Insurance status as a covariate and confounding.

Including insurance in the model does not fully mitigate confounding by access to care. Please avoid wording that suggests this.

Response:
We agree and have revised the relevant language in the Strengths and Limitations section. Instead of implying that insurance "mitigates" confounding, we now state:

"MEPS does not provide information on COVID viral variants or the severity of the acute episode, and therefore, residual confounding is probable even after statistical adjustment. … Insurance status was included as a covariate, but residual confounding related to access to care and health-seeking behavior may persist."

This acknowledges the limitation and avoids overstating the role of insurance adjustment.

Comment 10. Clarification of limitations regarding self-report and measurement.

Please elaborate on the limitations of self-reported COVID status, symptom duration, and perceived health.

Response:
We have expanded the Strengths and Limitations section to more fully discuss measurement limitations. We now note that:

- COVID-19 infection status, symptom presence and duration, and perceived health are self-reported and subject to recall and reporting bias.
- Long COVID is not clinically verified in MEPS; some misclassification may arise from respondents attributing pre-existing symptoms to Long COVID.

We also note that nondifferential misclassification would tend to bias group differences toward the null, making our estimates of economic burden conservative.

Response to Reviewer 2

Comment 1. Self-selection and attrition bias across the four-year panel.

The limitations section is well addressed, but could expand slightly on self-selection and attrition bias in MEPS.

Response:
We appreciate this comment and have explicitly addressed self-selection and attrition in the Strengths and Limitations section. We now write:

"Attrition bias, particularly subsequent attrition, is likely if individuals with greater illness burden or socioeconomic instability are less likely to remain under observation. Longitudinal surveys such as MEPS are also subject to self-selection bias, as those who agree to continued participation may differ from non-participants. Although survey weighting and model-based estimation mitigate these concerns, selective attrition may lead to underrepresentation of individuals with severe illness or high healthcare utilization, which would tend to attenuate group differences and make the estimated economic burden associated with Long COVID conservative."

This directly addresses the reviewer's concern and clarifies the likely direction of any residual bias.

We again thank the reviewers and the editorial team for their insightful comments, which have substantially strengthened the manuscript. We hope that the revisions now fully address all concerns and that the paper will be suitable for publication.