**Point by point response**

Reviewer comments: written in **bold black**

Author response: written in plain blue

Quotations of the revised manuscript: Written in *cursive red*

**Comments from Editors:**

**The major issue for me is**  
  
**1) Lead time biases that might underestimate mortality and other clinical endpoint differences and overestimate comorbidity imbalances. Some of the sarcomere positive cases may have been picked up by screening of affected family members and they would have earlier/milder phenotype. Can they do a sensitivity analysis excluding "gene first" diagnoses?**

**Author response:**

Thank you for this important point. We agree that including patients identified through genotype-first screening may introduce lead-time bias. However, our analysis was designed to minimize this bias in several ways:

* First, we used age as the underlying time scale in all survival and event models, aligning individuals by biological age rather than by time since diagnosis.
* Second, we implemented left-truncation at the time of study entry, ensuring individuals only contribute risk time after observation begins.
* Third, we calculated age-standardized incidence rates for key outcomes (e.g., AF, ventricular arrhythmias, LVSD), which controls for differences in age distributions between sarcomeric and non-sarcomeric HCM.

To further address this concern, we now present a sensitivity analysis excluding individuals diagnosed through genotype-first screening as suggested (see page XX).

**Changes made:**

We have added results from out sensitivity analyses throughout the manuscript.

In line XX (in a section investigating patient characteristics) we have added the following text ”*Differences in the risk of cardiovascular co-morbidities and adverse events remained significant after adjustment for age and sex in multiple logistic regression (****Supplementary Figure S1a****) and in sensitivity analysis excluding patients diagnosed through family screening (****Supplementary Figure S1b****).*” In line XX (comparing incidence of atrial fibrillation and ventricular arrhythmias) we have added the following ”*In sensitivity analysis excluding patients diagnosed through family screening the ASI ratio of atrial fibrillation was 1.43 (CI: 1.29 to 1.59) and for ventricular arrhytmias 1.50 (CI: 1.26 to 1.77).*”. From Line XX where we investigate differenced in mortality, the following sentence has been added ”*In sensitivity analysis excluding patients diagnosed through family screening the difference in RMST was 4.0 years (CI: 2.4 to 5.6, p<0.001).*” We added a new sensitivity analysis excluding “gene-first” cases in the Supplement (Figure Sx), and a description of these results in the Results and Discussion sections (page XX).

**2. Figure 1 and all the comorbidity data, are heavily confounded by age. to make statements about differences in HTN, obesity, etc between sarcomere + and negative, age and sex adjustment are needed**

**Author response:**

Thank you for highlighting this. We performed additional logistic regression analyses adjusted for age and sex, confirming that sarcomeric HCM remains associated with lower odds of hypertension, obesity, septal reduction, and obstruction (see alternate figure 1 below).

Et billede, der indeholder tekst, skærmbillede, nummer/tal, menu

AI-genereret indhold kan være ukorrekt.

**Changes made:**

We have added the following text to the results “ *Differences in the risk of cardiovascular co-morbidities and adverse events remained significant after adjustement for age and sex in multiple logistic regression (****Supplementary Figure S1a****).*” In addition, we have added a supplementary figure with this analysis (the one attached above).

**Interesting manuscript but I have not seen that treatments, particularly septal reduction therapies (surgical or transcatheter) were considered as modifiers of those trajectories. How do they know whether the endpoints that they see would be different if the septal reduction would have not happened? I think they should include that variable as a time dependent covariate?**

**Author response:**

Thank you for this suggestion. We agree and have now included septal reduction therapy as a time-dependent covariate in Cox models for studied outcomes (heart failure, arrhythmias, death). Results were robust to this adjustment.

**Changes made:**

The section describing the Cox models in Methods (Page XX Line xx) now reads ”*We used Cox proportional hazards modeling with age as the timescale with delayed entry (i.e., left-truncated at the time of the first SHaRe visit). Time-varying covariates (modifiers) included obesity, hypertension, LV obstruction, atrial fibrillation and LV systolic dysfunction. We adjusted for sex, age at diagnosis with HCM, and whether septal reduction therapy had been performed (as a time-varying covariate), and applied Bonferroni correction for multiple testing.*”

In Results, the first section in the subheading on clinical trajectories (Page XX, line xx) now reads ”*We investigated associations between potential disease modifiers (obesity, hypertension, LV obstruction, atrial fibrillation, and LV systolic dysfunction) on the rate of subsequent outcomes, to identify exposure-outcome pairs (****Figure 5****), on the overall cohort of both sarcomeric and non-sarcomeric HCM (including septal reduction therapy as a time-varying covariate due to potential disease modification).*” The associated hazard ratios have also been changed in the manuscript and Figures 5 and 6 updated according to this analysis.

**They included LA diameter (if this measured on M-mode, it has many limitations and it would have been better to include the LA volume) and it is different between sarcomeric and non-sarcomeric. This variable is highly associated with AF but yet they include in the analysis LVSD (figures 5 and 6). Could they include the variable LA dimension?**

**Author response:**

Thank you for this suggestion. LA size was measured via 2D echocardiography in the parasternal long-axis view, not M-mode. LA dimension is routinely collected as part of standard HCM evaluation, given its relevance to risk stratification (e.g., inclusion in the ESC SCD risk calculator). Unfortunately, LA volume was not consistently available across the cohort and could not be reliably included in analyses. Given the dynamic nature of LA size and its role as a mediator, we did not include it as a covariate in trajectory models.

**Changes made:**

None at this point.

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**Reviewer #1:  
  
  
This is a well-designed study examining the clinical trajectories of sarcomeric and non-sarcomeric HCM. Main findings were that sarcomeric HCM patients present at younger ages, have higher incidence of arrhythmias and heart failure with shorter life-spans, and higher HCM-related mortality rates. The presence of Afib or LV dysfunction have higher impacts on development NYHA III-IV symptoms and death in sarcomeric HCM patients when compared to non-sarcomeric HCM patients. Despite higher comorbidity burden in non-sarcomeric HCM patients, they had comparably less severe outcomes.  
  
  
- Can the authors describe the time frame between genetic testing and data capture? Could any variants have been re-classified in the interim if testing was done in a non-contemporary era?  
Author response:**

Thank you for this thoughtful question. The SHaRe registry includes patients diagnosed and genotyped across 12 international HCM centers. Variant curation was initially performed locally at each center but subsequently harmonized through central review by the SHaRe Variant Curation Committee. All pathogenic/likely pathogenic classifications used in this study reflect consensus interpretations made according to ACMG/AMP guidelines, minimizing the risk of misclassification due to reanalysis.

**Changes made:**

We

**- In regard to figure 6- it would be important to know which examined exposure-outcome pairs did not have a significant genetic interaction. This should be added to the text.  
Author response:**

Thank you for this suggestion. In Figure 6, we presented only the exposure-outcome pairs with statistically significant interactions between genotype and clinical trajectory. In total, we tested 16 such interactions, and the significant ones are shown. For transparency, we have now added the non-significant interaction estimates in a supplementary figure, we refer to in the manuscript.

**Changes made:**

We refer to the supplementary table including all tested interactions in the results section on page XX line XX ” ***Figure 6*** *shows the time-adjusted hazard ratios for modifier-outcome pairs, stratified by genotype, and using age as the time-scale (left-truncated at the first visit at a SHaRe site). Only pairs in which genetic status had a significant interaction are included. Tested interaction terms with non-significant results are shown in* ***Supplementary table S1****.*”

**- The authors describe that prior studies have shown LVOT obstruction is linked to higher rates of SCD, stroke, and death. However, in the present study, LVOT obstruction was not independently associated with these outcomes. Could there be any era-specific factors to consider in the registry that could account for these differences? Can the authors display the eras in which the patients were first seen at their respective HCM centers and if there is a disproportionate number of patients in one era over another?  
Author response:**

Thank you for this question. Many earlier studies did not adjust for key confounders—particularly age, which is closely linked to both obstructive physiology and event risk. In contrast, our models incorporated age as the underlying time scale and used left-truncation at study entry,, allowing for a more rigorous accounting of age-related confounding. Once this adjustment is made, obstruction does not independently predict the studied outcomes in our cohort. In terms of era, the vast majority of patients in SHaRe have contemporary follow-up (i.e., has been evaluated at one of the participating centers within the last 10 years), complicating comparisons of era-specific management.

**Changes made:**

None at this point.

**- Aside from more aggressive anticoagulation, which is mentioned, could there be any other treatment related factors that may mitigate some of the results- perhaps more widespread use of SGLT2i, GLP-1 agents, or more aggressive lipid control? While they list limitations as not having access to medical therapy- this could be inferred from assessing eras in which patients were first seen for HCM care.  
Author response:**

We appreciate the reviewer’s thoughtful suggestion. While treatment patterns for cardiovascular risk factors has evolved over time, there is currently no accepted disease-modifying medical therapy for hypertrophic cardiomyopathy itself. As noted, our dataset does not include detailed medication data across centers, which precludes robust assessment of lipid-lowering therapy, SGLT2 inhibitors, or GLP-1 receptor agonists. We agree that temporal treatment trends may have influenced comorbidity profiles or cardiovascular risk mitigation. While some patients included in SHaRe may have received their diagnosis decades ago, they would have had their last clinical work-up performed in the few years leading up to 2016 (the first inclusion year of the registry) at the very latest, with the vast majority of patients having more contemporary follow-up.

**Changes made:**

Since septal reduction therapy is a potential disease-modifier, we have added that as a time-varying covariate to our Cox models (please see our answer to the third point raised by the editors).

**- Are there any sub-analyses of the 700 patients who were diagnosed in childhood? It would be important to see if these patients have disproportionate risk and/or difference exposure-outcome pairs with genetic interaction.  
Author response:**

Thank you for this important suggestion. We agree that childhood-onset HCM represents a clinically distinct subgroup. In total, 725 patients in our cohort were diagnosed before age 18, of whom 550 (76%) had sarcomeric HCM.

We performed a subgroup analysis limited to childhood-onset HCM and recreated the exposure–outcome association heatmap (analogous to Figure 5, shown below). Although this subgroup had fewer events, especially among non-sarcomeric cases, the overall pattern of associations was very similar to that observed in the full cohort. Please note that these models were not corrected for multiple comparisons due to reduced power.

Regarding genetic interaction, we explored interaction terms between genotype (sarcomeric vs non-sarcomeric) and each exposure variable in this childhood-onset subgroup. However, due to limited sample size and event counts, especially in the non-sarcomeric group, these analyses were underpowered and did not yield statistically significant interactions.

Subgroup heatmap for childhood-onset HCM patients is provided here:

**Changes made:**

To preserve manuscript focus and length, we have chosen not to include these additional analyses in the main text but are happy to provide them upon request.

**- Female sex in prior studies has been shown to be associated with higher adverse outcome risk and possibly higher rate of sarcomeric variants. In the present study, there was a significant difference in rate of females in the sarcomeric group. Can the authors comment on if they believe female sex has the potential for significant genetic interaction in exposure-outcome pairs?  
Author response:**

Thank you for this insightful comment. To specifically address potential effect modification by sex, we tested three-way interactions between sex, genotype, and exposures on adverse outcomes. No significant interactions were found, suggesting that female sex did not modify genotype-related outcome trajectories in our cohort.

**Changes made**

To preserve manuscript focus and length, we have chosen not to include these additional analyses in the main text but are happy to provide them upon request.  
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**Reviewer #3:  
  
  
The authors on a multicenter longitudinal cohort study of genotyped children and adults in the Sarcomeric Human Cardiomyopathy Registry. Patients were classified as sarcomeric HCM (pathogenic/likely pathogenic sarcomere variant) or non-sarcomeric HCM. The influence of genetic classification, and comorbidities, on the sequence of cardiovascular events were assessed in time-varying Cox proportional hazards models. Sarcomeric HCM patients had earlier disease onset, worse outcomes including earlier death, and with lower prevalence of obstruction. Obesity and hypertension were more prevalent in non-sarcomeric HCM patients. Atrial fibrillation was associated with subsequent heart failure, ventricular arrhythmias, stroke and death with worse outcomes in sarcomeric HCM patients.  
  
The study comes from an experienced group, is multicenter and has a clear presentation. I have several major and specific comments.  
  
  
Major Comments**  
  
**1-The absence of an age matched group with comorbidities but without HCM limits the ability to draw inferences about the contribution of HCM per se in addition to the comorbidities in causing the clinical events observed in the study.  
Author response:**

Thank you for this important point. SHaRe is a disease-specific registry without matched controls and as such our study focuses on differences within the HCM population. We acknowledge that an age-matched comparator group without HCM would enhance interpretability of the role of comorbidities on cardiovascular disease trajectories, but, this was not feasible within the structure of the SHaRe registry. However, our use of age-standardization and age-specific incidence analyses allowed us to partially account for age-related confounding in evaluating the role of comorbidities such as hypertension and obesity.

**Changes made:**

We have added a statement to the Discussion (page XX) acknowledging the absence of an external non-HCM comparator group as a limitation and clarifying our approach to mitigate this.

**2-Clinical implications are somewhat limited as regular clinical evaluation, imaging, and Holter monitoring is recommended in all HCM patients whether they have (P/LP) mutations or not. Aggressive management of hypertension and obesity is indicated in all patients, whether they have HCM or not, and is recommended across the board.  
Author response:**

We agree that guideline-recommended care applies to all HCM patients. However, our findings support risk refinement: e.g., sarcomeric HCM may warrant earlier rhythm surveillance, while non-sarcomeric patients may benefit from intensive comorbidity control. We see this not as replacing standard care but as refining risk stratification and prioritization.

**Changes made:**

None at this point.

**3-The impact of medications on clinical events was not examined and is clinically important since they are known to affect cardiac function, blood pressure control, and outcomes in many patient populations.  
Author response:**

We agree and regret that longitudinal medication data were not consistently collected across sites, limiting our ability to evaluate treatment effects. This limitation is now more clearly acknowledged.

**Changes made:**

We have added the following sentence in the Discussion section (Line XX on pageXX) ””

**4-The presence of hyperlipidemia and CAD was not evaluated and HCM patients with CAD have worse clinical outcomes than HCM patients without CAD (Sorajja et al Circulation. 2003 Nov 11;108(19):2342-8).  
Author response:**

Thank you for this comment. Information on the presence of coronary artery disease, defined as a myocardial infarction or significant stenosis as assessed on imaging (CT or perfusion testing), was available for patients. We have added these data to the revised manuscript along with information on diabetes.

**Changes made:**

We

**5-There are no data on LV scar burden by CMR  
Author response:**

Correct — late gadolinium enhancement and LV fibrosis burden by cardiac MRI were not consistently available in this cohort and were therefore not included. We agree that this is a critical phenotype and could further refine risk stratification.

**Changes made:**

We have added the following sentence in the Discussion section (Line XX on pageXX) ””

Specific Comments  
  
**1-How did SHaRe variant curation committee decide on variants with conflicting classification?  
Author response:**

Variants with conflicting interpretation were adjudicated centrally by the SHaRe Variant Curation Committee. Only variants classified as P/LP by consensus were included.

**Changes made:**

We

**2-How was the presence hypertension ascertained? Did authors take note of the control of hypertension?**  
**Author response:**

Hypertension was defined based on either a documented clinical diagnosis at any visit or the use of antihypertensive medications. Blood pressure recordings from clinical visits were available in approximately 74% of patients; however, these were not collected in a standardized manner across centers and time points. As such, we were unable to reliably assess longitudinal blood pressure control or treatment efficacy, and therefore did not include measures of hypertension control in the analysis.

**Changes made:**

None at this point.

**3-Was cardiac function and remodeling determined at each site or through core laboratory? Was EF measured or was it a visual estimate? Authors report LA diameter, how about LA volumes which is now standard recommendation for assessing LA size.  
Author response:**

Cardiac imaging was performed and interpreted locally at each participating center. LV ejection fraction was typically based on quantitative methods (Simpson’s or biplane), but in some cases was estimated visually. LA volume was not consistently reported across sites, while LA dimension is routinely collected as part of standard HCM evaluation, given its established relevance to risk stratification in HCM We agree that LA volume, in general, is a more robust metric, but due to incomplete data capture on this measure, we chose not to report this.

**Changes made:**

We have clarified that results from cardiac imaging were determined locally in Methods (line XX) ”*Cardiac remodeling and function: Left ventricular (LV) ejection fraction (EF), LV outflow gradient (with a gradient >30 mmHg defined as obstruction) and maximal LV wall thickness (from imaging performed and interpreted at locally at participating sites).*”

**4-Please state how were sudden death and aborted sudden defined.  
Author response:**

We have added definitions of sudden cardiac death and aborted sudden cardiac death in the manuscript as suggested.

**Changes made:**

The section describing arrhythmias in the revised Methods now reads (Line XX) ” *sudden cardiac death (defined as sudden unexpected death of presumed cardiac origin within an hour of symptom onset in witnessed cases, or within 24 hours of last seen alive and well in unwitnessed cases), aborted sudden cardiac death (defined as successful resuscitation following cardiac arrest), sustained ventricular tachycardia and appropriate implantable cardioverter-defibrillator (ICD) therapy (including both antitachycardia pacing and shocks).*”

**5-Was Holter monitor obtained on a yearly basis in the study?  
Author response:**

Yearly Holter monitoring is part of routine care in patients with HCM, and as such was performed at participating sites. Arrhythmic events from Holter monitoring (e.g., non-sustained ventricular tachycardia, atrial fibrillation etc.) were registered in SHaRe.

**Changes made:**

To preserve manuscript focus and length, we have not included a statement indicating specific testing performed at participating sites, but are happy to provide them upon request.

**6-Was anti-tachycardia pacing for sustained VT taken note of?  
Author response:**

Yes, thank you for this question. The SHaRe registry captures ICD therapies including whether sustained ventricular tachycardia was treated with anti-tachycardia pacing or shock. In the composite ventricular arrhytmia outcome both ICD therapy types (ATP and shock) were included.

**Changes made:**

We have clarified that both ATP- and shock therapy was registered in SHaRe in Methods as (Please see last sentence of revised text in our answer to question 4).

**7-How did the excluded patients compare with patients included in the study?  
Author response:**

We excluded patients with known phenocopies, those with variants of uncertain significance and participants with missing genotype or phenotype data. Baseline characteristics of excluded vs included patients are now provided in Supplementary Table X. In general, excluded patients were XXXX.

**Changes made:**

We

**8-Page 10: “HCM. Patients with sarcomeric HCM were less likely to have hypertension 185 (RR 0.51 [CI 0.48-0.55]), obesity (RR 0.72 [CI 0.67-0.79])” This is expected given the younger age at diagnosis for patients with sarcomeric mutations (38 vs 54 yrs), and the association of comorbidities with older age in the general population.  
Author response:**

Thank you for this comment! We have in the revised manuscript added analysis in which we correct for differences in age and sex of the two groups, with consistent results.

**Changes made:**

Et billede, der indeholder tekst, skærmbillede, nummer/tal, menu

AI-genereret indhold kan være ukorrekt.

**Changes made:**

We added the following text to the Results (Line XX) ”*Differences in the risk of cardiovascular co-morbidities and adverse events remained significant after adjustment for age and sex in multiple logistic regression (****Supplementary Figure S1a****)* “ and added a supplemetary figure with this updated analysis

**9-Obstructive physiology having lower prevalence in patients with sarcomeric mutations has been noted before by HCMR registry (Neubauer et al JACC 2019 Nov 12;74(19):2333-2345)  
Author response:**

Correct — thank you for the reference. We now cite this study in the Discussion when noting our finding.

**Changes made:**

The article has been cited in this sentence of the Discussion section (Line XX on page XX) ”*As reported previously, we found that patients with non-sarcomeric HCM were more likely to have common cardiovascular comorbidities (hypertension and obesity) and obstructive physiology.*”

**10-Page 11: “Regarding adverse events, patients with sarcomeric HCM were more likely to experience ventricular arrhythmias etc.” this has been shown before by the investigators (reference 4) and by others (reference 5).  
Author response:**

We agree and appreciate the opportunity to clarify that our study builds on prior work by confirming these associations in a genotype-based framework and expands these findings by focusing on temporal trajectories and interaction effects.

**Changes made:**

None at this point.

**11-Do the authors have data on the frequency of SCD and aborted SCD in patients with sarcomeric mutations who have had ICD implantation and those who do not have an ICD? This would directly address the question of the impact of ICD implantation on SCD in this patient population (HCM patients with sarcomeric mutations)  
Author response:**

Thank you

**Changes made:**

We

**12-How was cardiac mortality defined? Was this ascertained by a committee that reviewed all events or was it determined at each center?  
Author response:**

Cause of death was adjudicated at each site by local investigators based on clinical records or autopsy findings where available. Cardiac mortality was defined as sudden cardiac death, heart failure death, periprocedural death during/after cardiac procedures or surgery, death from myocardial infarction, fatal stroke and death from major vascular events (pulmonary embolism and aortic dissection).

**Changes made:**

Definition added to Methods.

**13-Do the cardiac mortality results remain significant if stroke is excluded from the cardiac mortality definition?  
Author response:**

Yes — results remained significant after exclusion of fatal strokes (and also other major vascular causes). Significantly higher rates of death due to SCD or heart failure (HR 1.52 [CI: 1.10–2.11], p=0.012) was found in sarcomeric HCM.

**Changes made:**

None at this point.

**14-Did the authors look at cardiac function and remodeling in obese versus non-obese patients?  
Author response:**

In preparing the revised manuscript, we looked into features from echocardiographic examinations at baseline in these two groups. We have attached results in a table format here. While results are significant, the absolute differences are quite small.

|  | **Not obese**, N = 3,510 | **Obese**, N = 1,547 | **p-value** |
| --- | --- | --- | --- |
| **Max LV wall thickness** | 17.8 ± 6.4 | 18.2 ± 5.3 | <0.001 |
| **LV ejection fraction** | 64.8 ± 9.4 | 65.6 ± 9.8 | <0.001 |
| **LA dimension, mm** | 40.1 ± 9.6 | 44.1 ± 8.8 | <0.001 |
| **Indexed LA dimension, mm/m2** | 21.7 (18.8, 24.7) | 20.2 (17.8, 22.6) | <0.001 |
| **LV internal diameter in diastole, mm** | 43 (39, 48) | 44 (40, 49) | <0.001 |
| **Indexed LV internal diameter in diastole, mm/BSA** | 23.5 (21.0, 26.1) | 20.2 (18.2, 22.5) | <0.001 |
| **Max LV outflow gradient, mmHg** | 10 (9, 40) | 19 (10, 65) | <0.001 |
| Format is: n (%); Median (IQR); Mean ± SD | | | |
|  | | | |

**Changes made:**

To preserve manuscript focus and length, we have chosen not to include additional analyses on the impact of obesity on cardiac function and remodeling.

**15-There are no data on diabetes in table 1. Was this diagnosis looked for?  
Author response:**

Thank you for this question. We have now included diabetes (along with CAD and previous MI) in Table 1 of the revised manuscript.

**Changes made:**

Table 1 has been revised on Page XX. We have attached the first four rows of the section on comorbidities of table 1 here.

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Sarcomeric HCM** | **Non-sarcomeric HCM** |  |
| **Co-morbidities and medical history** |  |  |  |
| Hypertension | 628 (20%) | 1,345 (44%) | <0.001 |
| Diabetes | 146 (4.7%) | 321 (11%) | <0.001 |
| Coronary artery disease | 69 (2.2%) | 291 (9.6%) | <0.001 |
| Myorcardial infarction | 28 (0.9%) | 60 (2.0%) | <0.001 |

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**Reviewer #4:**  
  
  
**1. Please clarify whether results in Figures 5 and 6 are from the same models or not, i.e., whether the interaction term was always included, and justify it?  
Author response:**

Thank you for this important clarification request. Figures 5 and 6 represent results from distinct, but related, time-varying Cox models.

* Figure 5 shows the association between clinical modifiers (e.g., AF, LVSD) and subsequent outcomes within each genetic group, using stratified models without an interaction term.
* Figure 6 shows formal interaction analyses with sarcomeric status as a multiplicative interaction term, allowing us to assess whether the association between each modifier and outcome differed significantly by genotype.

We have updated the Methods section to explicitly explain this distinction and justify the use of both modeling approaches: Figure 5 provides clinical interpretability within each group, while Figure 6 formally tests for heterogeneity of effect.

**Changes made:**

We

**2. “The code for statistical analysis and creating figures can be found online”—as of August 14, I couldn’t access the link** [**https://github.com/christoffervi/sarc\_nonsarc**](https://github.com/christoffervi/sarc_nonsarc)**.**

**Author response:**

Thank you for alerting us. The GitHub repository was private during the initial review. It is now publicly accessible and contains key scripts used for data cleaning, statistical modeling, and figure generation.

**Changes made:**

We