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Peer Review File

Worldwide trends in metabolic syndrome from 2000 to 2023: a systematic review and modelling analysis

Corresponding Author: Dr Jean Joel Bigna

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)
The authors have addressed Reviewer 1's comments thoroughly. They provided much clearer information regarding the methodology used for study screening, selection, and analysis. They also explained convincingly why analyses decomposing metabolic syndrome components were not feasible due to insufficient sample size, which would have led to inconsistent and less generalizable findings. This limitation has been appropriately acknowledged in the discussion.

Reviewer #2

(Remarks to the Author)
Global, regional, and national trends in the burden of metabolic syndrome 2 in adults, 2000-2023: a modelling analysis: this manuscript is aimed to estimate temporal trends in Metabolic Syndrome (MetS) prevalence across 198 countries from 2000 to 2023, through conducting a systematic review and Bayesian modelling analysis. There are some issues in the manuscript needed to be addressed or clarified.
1.Could the authors provide further explanation on how to rule out the possibility that setting distinct nodes for males and females stems from variations in the distribution of their respective samples?
2.The manuscript mentions using natural cubic splines to model the non-linear relationship between age and prevalence, which is an excellent approach. However, the flexibility of spline curves is highly dependent on the number and positions of knots. Could the authors clarify whether a sensitivity analysis for knot selection has been conducted?
3.Regarding the interaction term between GDP and representativeness, the authors adopted a prior "centered around a zero effect," which is essentially a strong assumption (i.e., defaulting to no interaction effect). Could the authors elaborate on the substantive rationale for choosing such a relatively strict prior—for instance, whether it is based on the lack of prior literature, theoretical considerations, or other reasons? Furthermore, under such a strong prior, if the results still indicate an interaction effect, the evidence would be quite compelling; however, if no interaction effect is found, might this merely be a consequence of the prior suppressing such an effect?
4.This is a complex model incorporating multilevel random effects and a correlation structure. Could the authors clarify whether the priors they selected have improved the convergence and mixing performance of Markov Chain Monte Carlo (MCMC)? Additionally, is there evidence to demonstrate that these priors have indeed served the purpose of "stabilizing variance estimation"?
5.The choice of priors, particularly the "weakly regularizing" priors for random effect variances and correlations, may have an impact on the results—especially in groups with sparse data. Could the authors clarify whether a prior sensitivity analysis has been conducted?
6.It is suggested that a brief discussion of the posterior estimates of random effect variances could be valuable. For instance, is the random effect variance at the national level significantly larger than that at the regional level? This in itself could shed light on which level is the primary source of variation, thereby enhancing the interpretability of the "borrowing strength" process.
7.To what extent can the model's predictions be considered reliable for countries and regions with no available data? Additionally, could the authors clarify whether any methods have been employed to validate these predictions?

Reviewer #3

(Remarks to the Author)
The manuscript provides important insights on the global epidemiology of metabolic syndrome (MetS), which complements existing evidence by GBD and other large modelling projects that typically focus on single risk factors and conditions. The

more than two-fold increase in MetS prevalence over two decades makes a compelling case for tailored public health interventions. Another noteworthy finding is the higher prevalence of MetS in women than in men, which contrasts with diseases such as diabetes being more prevalent in men than in women globally.

The review and modelling analysis have been rigorously conducted and transparently reported. The claims raised in the discussion section are well borne by the study's findings. The study's largest limitation – namely that data sources from merely 44 countries were used to extrapolate global estimates – is stated and discussed prominently.

I have two suggestions for further improving the manuscript:

First, in the discussion section, the authors only mention public health interventions to curb the rise of MetS globally. To offer a more rounded set of reccomendations and account for evolving technologies, they may also want to dsicuss the role of pharmacological approaches (metformin, GLP-1 receptor agonists, etc) for treating MetS and preventing cardiometabolic disease progression.

Second, I am sceptical that including fixed effects for a survey's level of representativeness is an adequate statistical approach to account for the limitations of using regionally representative data to extrapolate nationally representative estimates. The proposed model is blind to the true prevalence of metabolic syndrome, i.e., whether prevalence in the entire country is higher or lower than in the sub-national region with available data. Instead, if feasible, the authors may want to consider a quality score weighting approach, as is used by the International Diabetes Federation in their 2025 Diabetes Atlas. Here, for countries with more than one data source, nationally representative studies are assigned higher weight than locally representative estimates.

Reviewer #4

(Remarks to the Author)
Thanks for revising the paper. The authors have addressed all of my previous comments as well as those raised by the other reviewers. The revisions have improved the clarity and rigor of the manuscript. I do not have any remaining concerns.

Version 1:

Reviewer comments:

Reviewer #2

(Remarks to the Author)
title：Worldwide trends in metabolic syndrome from 2000 to 2023: a modelling 2 analysis

Thanks for your comprehensive response to my comments and those of other reviewers, as well as the diligent efforts devoted to revising the manuscript. The revised version has achieved a remarkable improvement in quality, and I anticipate the publication of more of your research findings in the future.

Reviewer #3

(Remarks to the Author)
The comments of the other reviewers and myself have been adequately addressed in the revised manuscript and response letter. I have no further comments.

Cover letter – Response to reviewers

Manuscript ID: NCOMMS-25-6544A

Title: ***Worldwide trends in metabolic syndrome from 2000 to 2023: a modelling analysis***

Dear Reviewers,

We sincerely thank you for your thorough evaluation of our manuscript and for the valuable and constructive comments you provided. We have carefully revised the manuscript in response to all points raised. Specifically, we have:

- Addressed each comment in detail, with particular attention to clarifying the robustness and validity of our statistical approaches.
- Revised the text to enhance the clarity and transparency of the modelling framework, adding further explanations of assumptions, sensitivity analyses, and robustness checks.
- Highlighted all revisions in the manuscript using track changes.
- Prepared a comprehensive, point-by-point response document explaining how each comment has been addressed (below). When a suggestion could not be implemented as proposed, we have provided a clear justification.

We are grateful for your insightful feedback, which has greatly helped us strengthen the manuscript and improve its clarity and reproducibility.

Sincerely,

Jean Joel Bigna,

On behalf of all co-authors.

RESPONSE TO REVIEWER COMMENTS

Reviewer #1 (Remarks to the Author):

R1: The authors have addressed Reviewer 1's comments thoroughly. They provided much clearer information regarding the methodology used for study screening, selection, and analysis. They also explained convincingly why analyses decomposing metabolic syndrome components were not feasible due to insufficient sample size, which would have led to inconsistent and less generalizable findings. This limitation has been appropriately acknowledged in the discussion.

Authors: We sincerely thank the reviewer for their careful re-evaluation of our revised manuscript and for recognizing the improvements made in clarifying our methodology and justifying the analytical choices. We are grateful for the acknowledgement that our explanation regarding the infeasibility of decomposing metabolic syndrome components was clear and convincing, and that the limitation has been appropriately addressed in the discussion. We appreciate the reviewer's constructive feedback throughout the process, which has substantially strengthened the clarity and rigor of our work.

Reviewer #2 (Remarks to the Author):

Global, regional, and national trends in the burden of metabolic syndrome 2 in adults, 2000-2023: a modelling analysis: this manuscript is aimed to estimate temporal trends in Metabolic Syndrome (MetS) prevalence across 198 countries from 2000 to 2023, through conducting a systematic review and Bayesian modelling analysis. There are some issues in the manuscript needed to be addressed or clarified.

1.Could the authors provide further explanation on how to rule out the possibility that setting distinct nodes for males and females stems from variations in the distribution of their respective samples?

Authors: We thank the reviewer for this insightful question. The placement of distinct spline knots for men and women was not driven by differences in the distribution of available samples, but rather by epidemiological evidence indicating sex-specific, non-linear age trajectories of metabolic syndrome and its components. Prior studies have shown that the prevalence of metabolic syndrome tends to rise earlier and more steeply in men during midlife, whereas in women the increase is more pronounced after menopause, with inflection points occurring at slightly different ages. To reflect these biological and epidemiological patterns, we specified sex-specific knots (35, 65, and 75 years for men; 40, 60, and 65 years for women), while keeping boundary knots identical (20 and 80 years) to ensure comparability. The spline specification was therefore informed by substantive knowledge of sex-specific age patterns in metabolic syndrome rather than by the empirical distribution of the included studies.

2.The manuscript mentions using natural cubic splines to model the non-linear relationship between age and prevalence, which is an excellent approach. However, the flexibility of spline curves is highly dependent on the number and positions of knots. Could the authors clarify whether a sensitivity analysis for knot selection has been conducted?

Authors: We thank the reviewer for highlighting this important methodological aspect. We agree that the flexibility of spline curves depends on the number and placement of knots. In developing our model, we explored several alternative knot specifications as part of internal sensitivity analyses. These included varying both the number and positions of knots. The resulting prevalence estimates, and age-specific trajectories were highly consistent across specifications, which reassured us that our findings were not driven by arbitrary knot placement.

Ultimately, we selected the final knot positions based on a combination of epidemiological evidence regarding sex-specific age trajectories of metabolic syndrome and its components, and model performance considerations (e.g., convergence, interpretability). While these sensitivity analyses were not detailed in the manuscript, we have now clarified in the revised text (Appendix) that alternative knot placements were tested and yielded robust results.

The following text has been added to the Appendix *"We conducted internal sensitivity analyses using alternative numbers and placements of spline knots (e.g., varying the number of interior knots from two to four, and shifting their positions across different age ranges). These analyses consistently produced similar prevalence estimates and age-specific trajectories, supporting*

the robustness of our results to knot specification. We ultimately retained the final knot positions—35, 65, and 75 years for men, and 40, 60, and 65 years for women, with boundary knots at 20 and 80 years—because they aligned with well-documented epidemiological inflection points in the age-related prevalence of metabolic syndrome and its components (e.g., midlife rise in men, post-menopausal increase in women). In addition, this specification provided stable model convergence and interpretability, balancing epidemiological plausibility with statistical performance."

3.Regarding the interaction term between GDP and representativeness, the authors adopted a prior "centered around a zero effect," which is essentially a strong assumption (i.e., defaulting to no interaction effect). Could the authors elaborate on the substantive rationale for choosing such a relatively strict prior—for instance, whether it is based on the lack of prior literature, theoretical considerations, or other reasons? Furthermore, under such a strong prior, if the results still indicate an interaction effect, the evidence would be quite compelling; however, if no interaction effect is found, might this merely be a consequence of the prior suppressing such an effect?

Authors: We thank the reviewer for this thoughtful observation. Our decision to center the prior for the interaction term between GDP and representativeness around zero was guided by both theoretical and practical considerations. First, there is limited prior empirical evidence to suggest a consistent direction or magnitude of such an interaction across diverse global settings. In the absence of strong prior knowledge, we considered it more appropriate to adopt a conservative, weakly informative prior centered at zero, thereby avoiding the imposition of an assumed positive or negative effect.

Second, the variance of the prior (N(0,0.5)) was deliberately chosen to be wide enough to allow the data to meaningfully update the posterior distribution if an interaction effect were present. In this way, the prior does not "suppress" the possibility of detecting an effect; rather, it regularizes estimation in data-sparse contexts while still permitting substantial deviations from zero when supported by the evidence.

Finally, we agree with the reviewer's point that if an interaction effect emerges despite this conservative prior, the evidence is indeed compelling. Conversely, if no effect is observed, this reflects both the weak prior expectation and the lack of consistent signal in the data, rather than an artifact of the prior overwhelming the likelihood. We have clarified this rationale in the revised Appendix:

"For the interaction term between GDP and study representativeness, we specified a weakly informative prior centered at zero (N(0,0.5)). This choice reflects the absence of strong prior evidence regarding the direction of the interaction, while allowing the data to drive the posterior distribution. The prior was sufficiently wide to permit meaningful deviations from zero when supported by the data, ensuring that any detected interaction effect would represent robust evidence rather than an artifact of prior specification."

4.This is a complex model incorporating multilevel random effects and a correlation structure. Could the authors clarify whether the priors they selected have improved the convergence and mixing performance of Markov Chain Monte Carlo (MCMC)? Additionally, is there evidence

to demonstrate that these priors have indeed served the purpose of "stabilizing variance estimation"?

Authors: We thank the reviewer for this important question. The choice of priors was indeed motivated not only by epidemiological plausibility but also by the need to ensure stable estimation in a complex hierarchical model. In practice, we observed that the use of weakly informative priors for fixed effects and regularizing priors for variance components improved both convergence and mixing of the Markov chains. Specifically, models estimated without these priors occasionally exhibited divergent transitions, poor mixing, or inflated variance estimates for random effects. By contrast, with the chosen priors, all chains converged reliably ($\hat{R} < 1.01$ for all parameters), effective sample sizes were adequate, and trace plots showed good mixing.

Regarding variance stabilization, the regularizing Student-t priors on random effect standard deviations prevented extreme or implausible variance estimates in data-sparse settings, while still allowing sufficient flexibility for heterogeneity to be expressed when supported by the data. This was particularly important at the subregional and national levels, where data density varied considerably. The resulting posterior distributions were narrower and more interpretable compared to models without regularization, indicating that the priors served their intended purpose of stabilizing variance estimation without unduly constraining the results. The Appendix has been revised to reflect this.

5.The choice of priors, particularly the "weakly regularizing" priors for random effect variances and correlations, may have an impact on the results—especially in groups with sparse data. Could the authors clarify whether a prior sensitivity analysis has been conducted?

Authors: We thank the reviewer for raising this important point. We recognize that priors on variance components and correlations can influence results, particularly in data-sparse groups. To address this, we have already conducted internal prior sensitivity analyses by re-estimating the model under alternative specifications for the random effect standard deviations and correlation structures. Specifically, we have compared our chosen weakly regularizing Student-t(3,0,1) priors with broader half-normal and half-Cauchy priors, as well as alternative LKJ priors for correlation matrices (shape parameters 1 and 4). Across these specifications, posterior estimates of prevalence and age-specific trajectories remained highly consistent, and substantive conclusions were unchanged.

These exercises have reassured us that the results were not unduly driven by the prior choices, but rather by the data structure. We have therefore retained the weakly regularizing priors, as they provided the best balance between stabilizing variance estimation in sparse settings and preserving flexibility where data were more abundant.

The following text has been added in the prior section of the Appendix: "*We conducted prior sensitivity analyses by varying the priors on random effect variances (Student-t, half-normal, half-Cauchy) and correlation structures (LKJ priors with different shape parameters). Results were robust across specifications, indicating that our substantive findings were not sensitive to prior choice. We retained weakly regularizing priors as they stabilized variance estimation in sparse data contexts while preserving flexibility in data-rich settings.*"

6.It is suggested that a brief discussion of the posterior estimates of random effect variances could be valuable. For instance, is the random effect variance at the national level significantly larger than that at the regional level? This in itself could shed light on which level is the primary source of variation, thereby enhancing the interpretability of the "borrowing strength" process.

Authors: We thank the reviewer for this insightful suggestion. We agree that examining the posterior estimates of random effect variances provides important information on the main sources of heterogeneity in our model and helps to clarify how the "borrowing strength" mechanism operates.

In our hierarchical specification, random intercepts were estimated at three levels: super-regional, regional, and national. When inspecting the posterior distributions, we observed that the magnitude of variation was generally modest at the super-regional and regional levels, with most estimates clustering around zero and relatively narrow credible intervals. This indicates that, once fixed effects such as GDP, urbanicity, and diagnostic criteria were accounted for, there was limited residual heterogeneity at these broader geographic levels.

By contrast, the national-level random effects displayed greater dispersion, with several countries showing substantial positive or negative deviations from the global mean. For example, countries such as Iraq, Jordan, Palestine, South Africa, and Indonesia exhibited positive intercepts, suggesting higher baseline prevalence than predicted by fixed effects alone. Conversely, countries such as Taiwan, Croatia, France, and Cameroon showed negative deviations, indicating lower prevalence than expected. These findings highlight that the largest share of unexplained variability resides at the country level rather than at the regional or super-regional levels.

This pattern is consistent with the epidemiological reality that national health systems, cultural practices, dietary patterns, and policy environments can differ substantially even within the same region, leading to marked heterogeneity in metabolic syndrome prevalence. The model structure therefore allows estimates for countries with sparse or no data to be informed by both regional trends and the broader super-regional context, while still recognizing that the dominant source of variation lies at the national level.

In practical terms, this means that the "borrowing strength" process primarily operates across countries within the same region: countries with limited or no data benefit from information contributed by neighbouring or socioeconomically similar countries, but the model also preserves the possibility of substantial national-level deviations where data are available. This hierarchical balance ensures that estimates remain coherent across geographic scales while reflecting the true heterogeneity observed in the data.

We have added a paragraph in the Appendix. We discussed both random effect variances and fixed-effect coefficients.

"The fixed-effects estimates were consistent with established epidemiological knowledge. Higher national income (log GDP per capita) and greater urbanicity were both strongly and positively associated with metabolic syndrome prevalence, reflecting the well-documented link between economic development, urban lifestyles, and cardiometabolic risk. The positive coefficients for the Joint Interim Statement (JIS) definitions, particularly the 94 cm cut-off for

men and the 80 cm cut-off for women, indicate that diagnostic thresholds exerted a measurable influence on prevalence estimates, underscoring the importance of harmonized criteria. The significant interaction between subnational representativeness and GDP suggests that subnational studies in wealthier contexts tended to yield higher prevalence estimates than nationally representative surveys, highlighting the need to carefully account for study design when extrapolating to national levels. Finally, the spline terms confirmed the expected non-linear age trajectories, with prevalence rising steeply in midlife and peaking in older age groups, consistent with biological and clinical evidence.

For women, the posterior random effects revealed meaningful heterogeneity across geographic levels. At the super-regional level, negative intercepts were observed in high-income Asia Pacific and high-income Western countries, suggesting lower baseline prevalence than the global average after accounting for fixed effects, whereas regions such as the Middle East and North Africa showed positive deviations. At the regional level, most intercepts were modest and close to zero, indicating limited residual variation once fixed effects were included. By contrast, at the national level, several countries displayed substantial deviations. For example, Iraq, Jordan, Palestine, Morocco, and South Africa showed positive intercepts, consistent with higher-than-expected prevalence, while Taiwan, Croatia, France, Cameroon, and Qatar exhibited negative deviations. These findings suggest that the largest share of unexplained heterogeneity among women resides at the country level, reflecting the influence of national health systems, cultural practices, and lifestyle patterns. The hierarchical structure of the model thus allowed countries with sparse data to benefit from regional information, while preserving the capacity to capture meaningful national-level deviations.

For men, a similar pattern was observed, with the greatest heterogeneity emerging at the national level. At the super-regional scale, high-income Western countries and Sub-Saharan Africa showed negative intercepts, while the Middle East and North Africa displayed positive deviations, consistent with higher prevalence than predicted by fixed effects. Regional-level random effects were again modest, clustering around zero. At the country level, however, marked deviations were evident. Iraq, Jordan, Palestine, Syria, and Indonesia exhibited strong positive intercepts, indicating substantially higher prevalence than expected, whereas Hong Kong, Qatar, Croatia, and the United Kingdom showed negative deviations. These results reinforce the conclusion that national-level variation is the dominant source of heterogeneity in men, as in women. The model's multilevel structure therefore ensured that estimates for countries with limited data were informed by regional and super-regional patterns, while still allowing for substantial country-specific departures where supported by the evidence."

7.To what extent can the model's predictions be considered reliable for countries and regions with no available data? Additionally, could the authors clarify whether any methods have been employed to validate these predictions?

Authors: We thank the reviewer for raising this important point. We acknowledge that the reliability of predictions in countries and regions without primary data is inherently lower than in data-rich settings. In our Bayesian hierarchical framework, estimates for such countries were informed by fixed effects (age structure, GDP per capita, urbanicity, diagnostic criteria) and by random effects at the regional and super-regional levels. This "borrowing strength" approach

enables countries with no data to benefit from information from geographically and socioeconomically similar settings, while the associated uncertainty is explicitly reflected in wider credible intervals.

To assess the robustness of our predictions, we conducted internal validation exercises. Specifically, we performed posterior predictive checks and cross-validation by data exclusion (Appendix, pages 33-41), whereby data from selected countries were temporarily removed and the model's predictions compared against the observed prevalence. These exercises showed that the model was able to reproduce observed prevalence patterns with good accuracy, supporting the reliability of predictions even in data-sparse contexts. In addition, the overall fit of the model was excellent, with pseudo-R^2 values of 99.7% for women and 99.8% for men, indicating that the combination of fixed and random effects explained nearly all of the observed variance (Appendix, page 33). Together, these results provide reassurance that the model yields robust and coherent predictions, while appropriately reflecting greater uncertainty in settings without primary data.

Reviewer #3 (Remarks to the Author):

The manuscript provides important insights on the global epidemiology of metabolic syndrome (MetS), which complements existing evidence by GBD and other large modelling projects that typically focus on single risk factors and conditions. The more than two-fold increase in MetS prevalence over two decades makes a compelling case for tailored public health interventions. Another noteworthy finding is the higher prevalence of MetS in women than in men, which contrasts with diseases such as diabetes being more prevalent in men than in women globally.

The review and modelling analysis have been rigorously conducted and transparently reported. The claims raised in the discussion section are well borne by the study's findings. The study's largest limitation – namely that data sources from merely 44 countries were used to extrapolate global estimates – is stated and discussed prominently.

I have two suggestions for further improving the manuscript:

First, in the discussion section, the authors only mention public health interventions to curb the rise of MetS globally. To offer a more rounded set of reccomendations and account for evolving technologies, they may also want to dsicuss the role of pharmacological approaches (metformin, GLP-1 receptor agonists, etc) for treating MetS and preventing cardiometabolic disease progression.

Authors: We thank the reviewer for this valuable suggestion. In the revised discussion, we have expanded our recommendations to also consider pharmacological strategies alongside public health interventions. Specifically, we now note that pharmacological approaches such as metformin and GLP-1 receptor agonists may play a role in treating metabolic syndrome and preventing progression to cardiometabolic disease. Recent evidence, including a 2024 *Lancet* systematic review and network meta-analysis of randomized controlled trials, has demonstrated that agents such as GLP-1 receptor agonists (particularly semaglutide) and phentermine-topiramate are among the most effective pharmacotherapies for weight reduction in adults with overweight and obesity, with potential downstream benefits for metabolic syndrome management (Shi et al., *Lancet* 2024;403: e21–e31). We have also emphasized, however, that universal testing and pharmacological treatment are unlikely to be feasible or cost-effective at the population level, particularly in low- and middle-income countries, and thus should be considered complementary to, rather than substitutes for, population-wide prevention strategies.

Second, I am sceptical that including fixed effects for a survey's level of representativeness is an adequate statistical approach to account for the limitations of using regionally representative data to extrapolate nationally representative estimates. The proposed model is blind to the true prevalence of metabolic syndrome, i.e., whether prevalence in the entire country is higher or lower than in the sub-national region with available data. Instead, if feasible, the authors may want to consider a quality score weighting approach, as is used by the International Diabetes Federation in their 2025 Diabetes Atlas. Here, for countries with more than one data source, nationally representative studies are assigned higher weight than locally representative estimates.

Authors: We thank the reviewer for raising this important point. We fully agree that the representativeness of primary data is a critical issue in global modelling studies. To address this, we applied strict eligibility criteria and included only population-based studies that used probabilistic sampling methods. We then systematically assessed methodological quality using three core criteria: (1) whether the sample frame was appropriate to capture the target population (restricted to community-based studies of the general population), (2) whether participants were sampled appropriately (all included studies relied on probabilistic sampling), and (3) whether valid methods were used to identify metabolic syndrome. The first two criteria were consistent across all included studies, ensuring a high baseline of representativeness and methodological rigor; only the diagnostic criterion varied.

Within our Bayesian multilevel framework, we further incorporated study representativeness (national vs subnational) as a fixed effect, together with an interaction with GDP per capita, and introduced random effects at national, regional, and super-regional levels. This hierarchical structure allowed us to borrow strength across geographic units while accounting for unmeasured heterogeneity, thereby reducing the risk of systematic bias from subnational data. This approach has been used in other GBD studies (NCD Risk Factor Collaboration (NCD-RisC), *Lancet*. 2016 Apr 9;387(10027):1513–1530; NCD Risk Factor Collaboration (NCD-RisC), *Lancet*. 2024 Mar 16;403(10431):1027-1050)

We acknowledge that alternative approaches, such as quality-score weighting, have been applied in other contexts (e.g., the *International Diabetes Federation Diabetes Atlas*). However, given our stringent inclusion criteria and the need to maintain comparability across 198 countries, we believe our approach provides a robust balance between methodological rigor and global coverage. We have clarified this rationale in the revised discussion.

Reviewer #4 (Remarks to the Author):

Thanks for revising the paper. The authors have addressed all of my previous comments as well as those raised by the other reviewers. The revisions have improved the clarity and rigor of the manuscript. I do not have any remaining concerns.

Authors: We sincerely thank the reviewer for their positive feedback and for recognizing the improvements made in the revised manuscript. We are grateful for their constructive comments during the review process, which have helped us to strengthen the clarity, rigor, and overall quality of the paper.

Cover letter – Response to reviewers

Manuscript ID: NCOMMS-25-6544A

Title: ***Worldwide trends in metabolic syndrome from 2000 to 2023: a systematic review and modelling analysis***

Dear Reviewers,

We sincerely thank you for your thorough evaluation of our manuscript and for the valuable and constructive comments you provided. We are grateful for your insightful feedback, which has greatly helped us strengthen the manuscript and improve its clarity and reproducibility.

Sincerely,

Jean Joel Bigna,

On behalf of all co-authors.

RESPONSE TO REVIEWER COMMENTS

Reviewer #2

title : Worldwide trends in metabolic syndrome from 2000 to 2023: a modelling analysis

Thanks for your comprehensive response to my comments and those of other reviewers, as well as the diligent efforts devoted to revising the manuscript. The revised version has achieved a remarkable improvement in quality, and I anticipate the publication of more of your research findings in the future.

Authors: Thank you very much for your thoughtful feedback and kind words. We truly appreciate your recognition of the efforts made to revise the manuscript. Your comments have been invaluable in improving the quality of our work, and we are grateful for your support. We look forward to sharing more of our research in the future.

Reviewer #3

The comments of the other reviewers and myself have been adequately addressed in the revised manuscript and response letter. I have no further comments.

Authors: Thank you very much for your confirmation and for your careful review throughout the process. We sincerely appreciate your time, thoughtful feedback, and support in improving the manuscript. We're grateful for the opportunity to contribute to the journal and look forward to the next steps.