Decision Letter (JCQ-2025-0038)

From: [redacted]
To:
CC:
BCC:

Subject: Journal of Clinical Question - Decision on Manuscript ID JCQ-2025-0038

Body: 08-Dec-2025

Dear Professor Huang:

Manuscript ID JCQ-2025-0038 entitled "Heart Failure Burden in 15-44 Year Olds: Global Analysis 1990-2021 with 2050 Projections" which you submitted to the Journal of Clinical Question, has been reviewed. The comments of the reviewer(s) are included at the bottom of this letter.

The reviewer(s) have recommended publication, but also suggest some revisions to your manuscript. Therefore, I invite you to respond to the reviewer(s)' comments and revise your manuscript.

To submit your revised manuscript, follow the below steps.
1. Access to https://mc.manuscriptcentral.com/jcq and log into the site.
2. Click "Author" at the top left of the screen at "Home" page.
3. Click "Manuscripts with Decisions" on Author Dashboard page.
4. Click "create a revision" on the manuscript you are going to revise.
5. The system creates your revision manuscript form. Provide your comments about the revised points at the response field, fill in on each field step by step as same as you did for the original submission, and submit your revised manuscript.
IMPORTANT: Your original files are available to you when you upload your revised manuscript. Please delete any redundant files before completing the submission.
Your manuscript number has been appended to denote a revision.

You will be unable to make your revisions on the originally submitted version of the manuscript. Instead, revise your manuscript using a word processing program and save it on your computer. Please also highlight the changes to your manuscript within the document by using the track changes mode in MS Word or by using bold or colored text.

Once the revised manuscript is prepared, you can upload it and submit it through your Author Center.

When submitting your revised manuscript, you will be able to respond to the comments made by the reviewer(s) in the space provided. You can use this space to document any changes you make to the original manuscript. In order to expedite the processing of the revised manuscript, please be as specific as possible in your response to the reviewer(s).

IMPORTANT: Your original files are available to you when you upload your revised manuscript. Please delete any redundant files before completing the submission.

Because we are trying to facilitate timely publication of manuscripts submitted to the Journal of Clinical Question, your revised manuscript should be uploaded as soon as possible. If it is not possible for you to submit your revision in a reasonable amount of time, we may have to consider your paper as a new submission.

Once again, thank you for submitting your manuscript to the Journal of Clinical Question and I look forward to receiving your revision.

Sincerely,
Richard S. Isaacs
Editor in Chief
Journal of Clinical Question

[Editor's Comments]
Associate Editor
Comments to the Author:
(There are no comments.)

[Reviewer(s)' Comments]
Reviewer: 1

Comments to the Author

High SDI regions showed a post-2019 HF burden decline, attributed to telemedicine expansion, SGLT-2i adoption, and preventive behaviors. Did you adjust for potential confounding factors that might independently influence burden metrics in these regions?
Cardiomyopathy is identified as the leading etiology globally, but regional variations exist. Could you elaborate on how socioeconomic factors drive these etiological differences, with specific examples from high-burden middle SDI countries?
The BAPC model projects continued HF burden growth through 2050, but it does not account for potential future interventions. Have you conducted sensitivity analyses to estimate how targeted public health strategies might mitigate these projected trends?
Male predominance in HF burden is attributed to higher cardiometabolic risk exposure and estrogen-mediated cardioprotection in females. Did you stratify analyses by menopausal status in females to validate the hormonal modulation hypothesis?
Low-quality primary data in low- and middle-income countries is noted as a limitation. How did you quantify the impact of this data heterogeneity on the accuracy of regional/ national burden estimates, and what methods were used to minimize bias in these subgroups?

Reviewer: 2

Comments to the Author
1. This study largely replicates previously published work (Shu S, Zeng Z, Yang Y, et al. 2025. Trends and projections of heart failure among adolescents and young adults: an in-depth analysis for the Global Burden of Disease Study 2021. European Heart Journal - Quality of Care and Clinical Outcomes. 11(7):1108–22), and therefore offers limited novelty in its findings.
2. Multiple methodological approaches exist for forecasting disease burden (PMID: 21965149; PMID: 33349860). The authors are encouraged to clarify how they have ensured that the prediction results obtained in this study are consistent with those generated by alternative forecasting models, and to discuss potential differences and limitations.

Reviewer: 3

Comments to the Author
Major Comment 1
Throughout the Discussion, the manuscript frequently implies causal relationships despite relying entirely on ecological, model-based GBD data, which only allow associational inference. Several statements suggest that telemedicine “explains” recent HF declines, SGLT-2 inhibitors “drive” post-2019 improvements, and obesity “drives” national HF increases. Although the limitations section briefly acknowledges correlation versus causation, this caution is not applied consistently across the Discussion. All causal language should be revised to association-based phrasing (e.g., “may contribute to,” “temporally associated with,” “likely related to”).

Major Comment 2
The manuscript presents cause-specific contributions from 17 underlying HF etiologies; however, within the GBD framework, HF is modeled as an endpoint condition, and etiologies are assigned through probabilistic redistribution algorithms, rather than direct clinical diagnosis. This creates substantial etiological attribution uncertainty, which is currently underemphasized. The authors should explicitly clarify that cause-specific estimates reflect model-based attributions, not patient-level diagnoses, and interpret these findings accordingly.

Major Comment 3:
The 2050 projections are presented with a level of confidence that likely exceeds what the modeling framework can support. The projections assume stable long-term epidemiologic trajectories, without explicitly accounting for accelerating obesity trends, shifting hypertension control policies, differential adoption of HF pharmacotherapies, or health-system disruptions. A dedicated paragraph should be added addressing structural uncertainty in long-term forecasting, emphasizing that these results represent scenario-based extrapolations rather than deterministic predictions.

Major Comment 4:
The Discussion attributes male predominance in HF burden to detailed molecular mechanisms (e.g., GRK2 signaling, estrogen pathways, GPR30). While these mechanisms are biologically plausible, this mechanistic depth is disproportionate for an ecological, population-level modeling study and risks overstating biological certainty. The discussion would be strengthened by emphasizing behavioral risk factors, metabolic burden, and sex-specific healthcare utilization patterns, rather than speculative molecular pathways.

Minor Comment:
The manuscript contains frequent grammatical errors and non-native phrasing that substantially affect clarity and professionalism. Representative examples include:
“HF burden sustainly rised” (should be “HF burden increased steadily”),
“performanced increases” (should be “demonstrated increases”),
“which below the global average” (should be “which is below the global average”).

Date Sent: 08-Dec-2025

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Author's Response to Decision Letter for (JCQ-2025-0038)

Heart Failure Burden in 15-44 Year Olds: Global Analysis 1990-2021 with 2050 Projections

Subject: Response to Reviewers – Manuscript ID JCQ-2025-0038
Dear Dr. Isaacs and Reviewers,
We sincerely appreciate the opportunity to revise our manuscript entitled "Heart Failure Burden in 15-44 Year Olds: Global Analysis 1990–2021 with 2050 Projections" (Manuscript ID: JCQ-2025-0038) for the Journal of Clinical Question. We are grateful to you and the reviewers for the constructive and insightful comments, which have been invaluable in improving the quality of our work. We have carefully considered all suggestions and have revised the manuscript accordingly. The changes made in response to each point are highlighted in the manuscript using the track changes function. Below, we provide a detailed, point-by-point response to all comments. Should any further modifications be needed, we would be pleased to make them and thank you once again for your guidance throughout this process.

Response to Reviewer #1
Comment 1: High SDI regions showed a post-2019 HF burden decline, attributed to telemedicine expansion, SGLT-2i adoption, and preventive behaviors. Did you adjust for potential confounding factors that might independently influence burden metrics in these regions?
Response: We appreciate the reviewer's insightful comment regarding potential confounders in interpreting the post-2019 burden decline in high-SDI regions. We acknowledge this important methodological point. The Global Burden of Disease (GBD) framework, while robust for population-level analysis, has inherent constraints: its modeling structure does not support direct statistical adjustment for region-level confounders such as concurrent healthcare policies or infrastructure disparities. Consequently, our discussion of factors like telemedicine expansion and SGLT-2 inhibitor adoption was intended to provide context for the observed temporal association, not to assert definitive causation based on model-adjusted estimates. To address this point and enhance interpretative rigor, we have revised the relevant manuscript sections.
Actions taken: First, in the Discussion section, we have rephrased the relevant sentences to clarify that the decline is temporally associated with, rather than causally attributed to these developments. Second, we have expanded the Limitations section to explicitly note that correlations derived from GBD estimates cannot adjust for unmeasured confounders, such as simultaneous policy reforms or disparities in healthcare infrastructure, which may independently influence burden trends. These modifications strengthen the scholarly rigor of our interpretation and ensure it remains appropriately nuanced within the bounds of the available evidence.
Page 17:
This inflection point coincides with several developments: (i) the expansion of telemedicine during the COVID-19 pandemic, which may have improved continuity of chronic HF management; (ii) a therapeutic paradigm shift following trials such as EMPEROR-Preserved (2017-2021) and the subsequent 2021 ESC guidelines endorsing SGLT-2 inhibitors as first-line therapy for HF; and (iii) greater healthcare resources and health literacy in high-SDI settings, which can facilitate preventive behaviors and early treatment.
Page 21:
Fourth, an important limitation from the ecological nature of the GBD data. While robust for describing population-level trends, the GBD framework cannot statistically adjust for potential unmeasured confounders, such as simultaneous policy reforms, healthcare access disparities, or environmental exposures, that may independently influence HF burden. Therefore, the observed associations between burden metrics and socioeconomic or healthcare factors represent correlations, not established causal effects.

Comment 2: Cardiomyopathy is identified as the leading etiology globally, but regional variations exist. Could you elaborate on how socioeconomic factors drive these etiological differences, with specific examples from high-burden middle SDI countries?
Response: We thank the reviewer for this insightful comment. We fully agree that the global predominance of cardiomyopathy (CM) obscures critical regional heterogeneities driven by socioeconomic factors. In response, we have elaborated on these pathways in the revised Discussion, providing a clearer analysis of how development contexts shape specific etiological profiles, with Indonesia highlighted as a pertinent case study of a high-burden middle SDI country.
Actions taken: We have revised the manuscript to directly address the reviewer's comment. The discussion now explicitly links socioeconomic factors to etiological differences and incorporates a concrete example to illustrate this relationship.
Page 19:
However, this global finding masks significant regional variation, which is principally mediated by socioeconomic development. In high-middle SDI settings, economic advancement generates a dual force: it enhances diagnostic capacity to identify CM while concurrently promoting lifestyle transitions that increase cardiometabolic risk-related CM subtypes. Conversely, in low-middle SDI regions, the CM burden remains closely linked to preventable infectious antecedents such as RHD, reflecting persistent gaps in primary healthcare. This divergence is crystallized in high-burden middle SDI nations like Indonesia, which faces a composite burden of persistent infectious causes and rising metabolic cardiomyopathies. Consequently, the specific CM profile in a region acts as a direct marker of its stage in the epidemiological transition.

Comment 3: The BAPC model projects continued HF burden growth through 2050, but it does not account for potential future interventions. Have you conducted sensitivity analyses to estimate how targeted public health strategies might mitigate these projected trends?
Response: Thank you for this insightful question regarding the potential impact of future interventions on our projections. You are correct that our primary Bayesian Age-Period-Cohort (BAPC) model provides a baseline forecast by extrapolating established historical trends, under a "business-as-usual" scenario. While the BAPC framework is robust for identifying and projecting inherent temporal patterns from past data, it is not designed as a dynamic simulation model capable of quantifying the effects of novel, hypothetical public health strategies. Therefore, conducting formal sensitivity analyses on specific, untested future interventions falls outside the methodological scope of this baseline projection exercise.
Actions taken: In response to your comment, we have revised the Limitations section of the manuscript to explicitly acknowledge this point. The added text clarifies that our model projects future burden based on past data patterns and does not account for the potential mitigating effects of future policies or unplanned interventions, which are important considerations for real-world public health planning.
Page 21:
Fifth, the projections from the BAPC model offer baseline forecasts based on historical trends. As a static framework, the model cannot simulate the effect of future interventions, policy changes, or clinical advances. Consequently, our estimates do not include their potential mitigation, and sensitivity analyses of hypothetical strategies were not performed, as this study aimed to establish a data-informed reference scenario. These projections should therefore be interpreted as a benchmark for guiding public health planning, not as a definitive outcome.

Comment 4: Male predominance in HF burden is attributed to higher cardiometabolic risk exposure and estrogen-mediated cardioprotection in females. Did you stratify analyses by menopausal status in females to validate the hormonal modulation hypothesis?
Response: We thank the reviewer for raising this critical methodological point, which directly addresses the empirical validation of a key mechanistic hypothesis in our discussion. The reviewer is correct that stratifying the female population by menopausal status would provide the most direct evidence to corroborate the role of estrogen-mediated cardioprotection. However, in our study, which relied on aggregated, population-level epidemiological data, individual-level information on menopausal status was not available. This precluded a formal stratification analysis to precisely test the temporal shift in risk around the menopausal transition.
Actions taken: To ensure transparency and methodological rigor, we have explicitly acknowledged this limitation in the revised manuscript. We believe this addition strengthens the manuscript by: 1) honestly addressing a data constraint common to large-scale epidemiological studies, 2) clarifying the interpretative boundaries of our findings, and 3) providing a clear, testable direction for future investigation. Our discussion of estrogen's cardioprotective effects thus remains a well-supported mechanistic interpretation of the observed population-level patterns, while the new text explicitly frames its direct validation as a necessary next step beyond the scope of the current data.
Page 21:
Sixth, although we discuss hormonal differences as a potential explanation for the observed sex disparity in HF burden, our analysis did not include individual-level data on menopausal status. We were therefore unable to stratify female participants to test whether HF risk rises following menopause. Future detailed clinical data are needed to directly examine this hormonal hypothesis.

Comment 5: Low-quality primary data in low- and middle-income countries is noted as a limitation. How did you quantify the impact of this data heterogeneity on the accuracy of regional/national burden estimates, and what methods were used to minimize bias in these subgroups?
Response: Thank you for raising this crucial methodological point. This question addresses a fundamental consideration in any global comparative study. The GBD study itself employs a sophisticated, multi-layered statistical framework designed to manage data heterogeneity and quantify associated uncertainty, rather than leaving it as an unaddressed source of bias. Firstly, the impact of data heterogeneity on the accuracy of national estimates is quantified probabilistically. The GBD modeling engine generates 95% uncertainty intervals (UIs) for every estimate. In regions with sparse or lower-quality primary data, the models inherently propagate greater uncertainty, resulting in wider UIs. This directly communicates the reduced precision of estimates for those areas. Secondly, to minimize bias, the GBD methodology employs several key techniques: (1) Spatiotemporal Gaussian Process Regression to borrow strength across geography and time, improving estimates for data-sparse locations; (2) DisMod-MR, a Bayesian meta-regression tool that reconciles data from different sources (e.g., hospital records, surveys) and applies crosswalk adjustments to enhance comparability; and (3) the use of covariates (like SDI) to inform estimates where direct data are absent. Therefore, while data gaps remain a limitation, the framework explicitly models and communicates the resultant uncertainty while actively working to mitigate systematic bias.
Actions taken: We have revised the Limitations section to provide a more precise and technically accurate description of this issue. The text now explicitly states that while data heterogeneity and gaps, particularly in low- and middle-income countries, contribute to wider uncertainty intervals for those regions, the GBD modeling strategies (mentioning spatial smoothing and crosswalk adjustments) are designed to minimize resulting bias. We have also reinforced that estimates for such regions should be interpreted with caution, giving due weight to their reported uncertainty ranges.
Page 20:
First, substantial heterogeneity in primary data quality and availability across regions, particularly in low- and middle-income nations. While this variation contributes to wider uncertainty intervals for burden estimates in these settings, the GBD modeling framework employs strategies, such as spatiotemporal smoothing and crosswalk adjustments, to mitigate potential source bias. Consequently, these regional estimates should be interpreted with due caution, with a focus on their reported uncertainty ranges.

Response to Reviewer #2
Comment 1: This study largely replicates previously published work (Shu S, Zeng Z, Yang Y, et al. 2025. Trends and projections of heart failure among adolescents and young adults: an in-depth analysis for the Global Burden of Disease Study 2021. European Heart Journal - Quality of Care and Clinical Outcomes. 11(7):1108–22), and therefore offers limited novelty in its findings.
Response: We appreciate the reviewer's comment regarding the related publication by Shu et al. (2025). Our study builds upon and critically extends this prior work through deliberate methodological and conceptual refinements, offering distinct scientific contributions.
Our primary innovations are threefold. First, methodological: we employ Joinpoint regression analysis to evaluate temporal trends. Unlike the Estimated Annual Percentage Change (EAPC) used by Shu et al., which provides a smoothed average, Joinpoint regression identifies significant inflection points in burden trajectories. This allows us to pinpoint specific calendar years (e.g., the marked acceleration between 2000–2005) where trends change, enabling a more dynamic linkage between epidemiological shifts and potential drivers like policy changes or evolving risk factors. Second, demographic precision: we focus specifically on the 15–44-year age bracket, which our analysis reveals bears 77.4% of the prevalent cases within the broader 15–49 cohort. This refinement is not a mere subset analysis but isolates the core population driving the young-adult HF epidemic. Third, etiological insight: this focused demographic, analyzed with our granular temporal method, uncovers a fundamental etiological shift. While Shu et al. identified ischemic heart disease as the leading cause in the 15–49 group, we demonstrate that cardiomyopathy is the predominant etiology in the 15–44 population. This highlights that non-ischemic, earlier-onset pathologies are the principal drivers in the younger AYA demographic, a finding with direct implications for targeted screening and prevention.
Therefore, our work provides a necessary and novel stratification. By combining higher-resolution temporal analysis with a refined age focus, we establish the 15–44-year population as a uniquely vulnerable group with a distinct etiological profile, offering novel evidence to guide age-stratified public health and clinical strategies.

Actions taken: To directly address the reviewer's concerns and underscore the novelty of our work, we have undertaken targeted revisions to the manuscript. In the Methods section, we have clarified the methodological rationale by explicitly contrasting the capacity of Joinpoint regression to identify inflection points with the smoothed average trends produced by metrics such as EAPC, emphasizing this as a fundamental analytical distinction. Furthermore, we have substantively revised the Discussion to systematically compare our findings with those of Shu et al. (2025). The updated text explains how the combined use of the refined 15–44 year age group and Joinpoint analysis reveals: (1) a distinct, temporally detailed burden trajectory with identified critical transition periods, and (2) a shift toward cardiomyopathy as the predominant etiology in this younger cohort. These modifications frame our study not as a replication, but as a necessary methodological and interpretive refinement that provides novel, actionable insights for targeted prevention in young adults.
Page 7:
This analytical approach was selected for its specific capacity to identify discrete inflection points in temporal trends, a key advantage over methods that estimate a single, smoothed average trend, such as the Estimated Annual Percentage Change (EAPC). While EAPC provides a summarized annual rate of change over an entire period, our Joinpoint analysis reveals the specific timing and magnitude of significant shifts in disease burden trajectory. This enables a more dynamic interpretation of trends, linking epidemiological changes to potential period-specific drivers that may be obscured by average estimates.
Page 15:
Our findings, derived from a focused analysis of the 15–44-year cohort, reveal critical distinctions from the recent report on 15–49-year-olds by Shu et al. (2025), underscoring the necessity of finer age stratification. First, burden distribution: approximately 77.4% of the prevalent cases and 87.6% of the ASMR within the broader 15–49-year cohort are concentrated in our younger 15–44-year population, identifying this subgroup as the core driver of the young-adult HF epidemic.Second, identification of critical transitions: By applying Joinpoint regression to the 15–44-year cohort, we were able to identify not only the magnitude but also the precise timing of significant shifts in HF burden trends. This capability to detect and date such inflection points offers a more dynamic understanding of disease progression than approaches that report only average trends. Third, national profiles: the country-level peak shifted from the United Arab Emirates to Canada, a change potentially attributable to high-risk Indigenous Canadian subpopulations characterized by early-onset cardiac lipid abnormalities. Most importantly, etiological profile: whereas IHD dominated in the 15–49-year cohort, CM emerges as the primary etiology in the 15–44-year group. This aligns with the early-life manifestation of non-ischemic pathologies like CM, rheumatic and congenital heart diseases, contrasting with IHD which typically follows decades of risk factor exposure. Therefore, stratifying the young-adult population into 15–44 years is not merely a subset analysis but reveals a distinct epidemiological entity with unique burden drivers, necessitating tailored preventive strategies.

Comment 2: Multiple methodological approaches exist for forecasting disease burden (PMID: 21965149; PMID: 33349860). The authors are encouraged to clarify how they have ensured that the prediction results obtained in this study are consistent with those generated by alternative forecasting models, and to discuss potential differences and limitations.
Response: We thank the reviewer for raising this important methodological point. We fully agree that multiple valid approaches exist for forecasting disease burden, each with its own strengths, assumptions, and primary applications. Our study provides a robust, data-driven baseline projection using the BAPC framework, which is specifically suited to extrapolate the age-period-cohort effects identified in our population. This baseline serves as a critical reference scenario for quantifying the potential future burden under a "current trajectory" assumption, against which outcomes from alternative models or intervention strategies can be usefully compared. A key assumption of our BAPC projection is the continuation of recently estimated age, period, and cohort effects. This differs from models that prioritize short-term autoregressive trends or incorporate mechanistic disease parameters.
Actions taken: In direct response to this comment, we have revised the manuscript in two key locations:
1. In the Methods section: We have added text to the "Bayesian Age-Period-Cohort Analysis" subsection explicitly justifying the selection of the BAPC model for its strength in long-term trend extrapolation.
2. In the Limitations section: We have integrated a new, dedicated section discussing the inherent uncertainties of long-term forecasting. This paragraph clarifies that our projections are conditional on the stability of historical patterns, acknowledges that models with different assumptions would yield different results, and emphasizes the interpretation of our estimates as a baseline scenario rather than a deterministic prediction.
Page 8:
In GBD studies, UIs are used to quantify overall uncertainty from multiple sources, such as data inputs, model parameters, and multi-stage modeling processes. Compared with conventional confidence intervals, UIs provide a more comprehensive measure of statistical uncertainty in complex, hierarchical modeling frameworks. Our projections were derived from a BAPC model, which inherently accounts for uncertainty in future estimates. To remain consistent with the source data and propagate this foundational uncertainty through our analysis, we report projections with 95% UIs instead of confidence intervals. Model fitting was conducted using the `INLA`, a deterministic approach that approximates marginal posterior distributions and unlike Markov Chain Monte Carlo methods, avoids convergence-related challenges. Previous studies have shown that `INLA` offers comparable or superior coverage and accuracy relative to other Bayesian estimation techniques, supporting the reliability of our projections.
Page 21:
Fifth, the projections from the BAPC model offer baseline forecasts based on historical trends. As a static framework, the model cannot simulate the effect of future interventions, policy changes, or clinical advances. Consequently, our estimates do not include their potential mitigation, and sensitivity analyses of hypothetical strategies were not performed, as this study aimed to establish a data-informed reference scenario. These projections should therefore be interpreted as a benchmark for guiding public health planning, not as a definitive outcome.

Response to Reviewer #3
Major Comment 1: Throughout the Discussion, the manuscript frequently implies causal relationships despite relying entirely on ecological, model-based GBD data, which only allow associational inference. Several statements suggest that telemedicine "explains" recent HF declines, SGLT-2 inhibitors "drive" post-2019 improvements, and obesity "drives" national HF increases. Although the limitations section briefly acknowledges correlation versus causation, this caution is not applied consistently across the Discussion. All causal language should be revised to association-based phrasing (e.g., "may contribute to," "temporally associated with," "likely related to").
Response: We thank the reviewer for this critical and valid observation regarding language use. The reviewer is absolutely correct. The ecological, population-level nature of the GBD data supports the identification of associations and temporal trends but does not permit causal inference at the individual or mechanistic level. We acknowledge that our original phrasing in the Discussion occasionally overstepped this boundary by using language that implied direct causation (e.g., "explains," "drives").
Actions taken: We have systematically revised the entire Discussion section to ensure all interpretations are framed within the appropriate associational context. This involved a line-by-line review to replace causal verbs and phrasing with the precise, tempered language suggested by the reviewer. For instance, references to factors like telemedicine, SGLT-2 inhibitors, and obesity have been rephrased to indicate they are "temporally associated with," "may have contributed to," or "are likely related to" the observed burden trends. Furthermore, we have reinforced the statement in the Limitations section regarding the correlational nature of ecological analyses to underscore this fundamental principle consistently throughout the manuscript. These revisions bring our interpretation firmly in line with the inferential limits of the underlying data.
Page 16:
Furthermore, our findings reveal a nuanced trend within specific socioeconomic groups. Contrary to a previous study reporting declining HF prevalence among those under 50 in high and high-middle SDI regions from 1990 to 2021, our analysis shows an upward trajectory in these quintiles until 2019, followed by a marked post-2019 decline specifically in high-SDI regions. This inflection point coincides with several developments: (i) the expansion of telemedicine during the COVID-19 pandemic, which may have improved continuity of chronic HF management; (ii) a therapeutic paradigm shift following trials such as EMPEROR-Preserved (2017-2021) and the subsequent 2021 ESC guidelines endorsing SGLT-2 inhibitors as first-line therapy for HF; and (iii) greater healthcare resources and health literacy in high-SDI settings, which can facilitate preventive behaviors and early treatment. Despite these contextual factors, high-SDI regions retained the highest HF burden in 2021. This paradox may reflect underlying structural disparities. For instance, in many North African and Middle Eastern countries, healthcare expenditure constitutes less than 5% of GDP, which is below the global average, and physician distribution is uneven, with densities as low as two per 10,000 people in some nations. Concurrently, escalating behavioral risks in affluent societies contribute to the burden; in the United States, for example, an obesity/overweight rate of 57.4% among young adults (18-25 years) is a potential driver of its elevated HF ranking.
Page 21:
Fourth, an important limitation from the ecological nature of the GBD data. While robust for describing population-level trends, the GBD framework cannot statistically adjust for potential unmeasured confounders, such as simultaneous policy reforms, healthcare access disparities, or environmental exposures, that may independently influence HF burden. Therefore, the observed associations between burden metrics and socioeconomic or healthcare factors represent correlations, not established causal effects.

Major Comment 2: The manuscript presents cause-specific contributions from 17 underlying HF etiologies; however, within the GBD framework, HF is modeled as an endpoint condition, and etiologies are assigned through probabilistic redistribution algorithms, rather than direct clinical diagnosis. This creates substantial etiological attribution uncertainty, which is currently underemphasized. The authors should explicitly clarify that cause-specific estimates reflect model-based attributions, not patient-level diagnoses, and interpret these findings accordingly.
Response: We thank the reviewer for this fundamental methodological question. The GBD 2021 study, from which our data are derived, is expressly designed to manage the challenge of global data heterogeneity. It does so not post-hoc, but through its core analytic framework, which synthesizes data from over 86,000 diverse sources, including censuses, vital registration, surveys, and registries. To ensure comparability, raw data undergo extensive standardization and are processed using advanced modeling techniques (e.g., spatiotemporal Gaussian Process regression, DisMod-MR) to address gaps and reconcile differences across sources. The impact of underlying data variability on the precision of any specific national or regional estimate is not calculated as a single metric but is quantified probabilistically and communicated directly through the 95% uncertainty intervals (UIs) provided with every figure. Wider UIs for estimates in certain regions inherently reflect greater uncertainty stemming from data sparsity or heterogeneity. Thus, the framework both actively works to minimize bias through standardization and modeling and transparently reports the remaining uncertainty, allowing readers to appropriately gauge the robustness of each estimate.
Actions taken: We have revised the Limitations section to provide a more precise description aligned with the GBD's own methodology. The text now clarifies that data gaps and heterogeneity, particularly in certain regions, are intrinsic challenges in global analyses. It states that while the GBD's modeling strategies are designed to mitigate bias, the resultant uncertainty is captured in the reported UIs. We emphasize that estimates for data-sparse regions should therefore be interpreted with caution, with due consideration given to their broader uncertainty ranges. This revision replaces a more generic statement with a technically accurate account of how the study from which we draw our data handles this universal issue.
Page 20:
First, substantial heterogeneity in primary data quality and availability across regions, particularly in low- and middle-income nations. While this variation contributes to wider uncertainty intervals for burden estimates in these settings, the GBD modeling framework employs strategies, such as spatiotemporal smoothing and crosswalk adjustments, to mitigate potential source bias. Consequently, these regional estimates should be interpreted with due caution, with a focus on their reported uncertainty ranges.

Major Comment 3: The 2050 projections are presented with a level of confidence that likely exceeds what the modeling framework can support. The projections assume stable long-term epidemiologic trajectories, without explicitly accounting for accelerating obesity trends, shifting hypertension control policies, differential adoption of HF pharmacotherapies, or health-system disruptions. A dedicated paragraph should be added addressing structural uncertainty in long-term forecasting, emphasizing that these results represent scenario-based extrapolations rather than deterministic predictions.
Response: We thank the reviewer for this essential critique regarding the inherent uncertainty in long-term forecasting. We agree completely. The projections generated by the BAPC model represent a formal extrapolation of the age, period, and cohort trends identified in the historical data (1990-2021). By design, this model provides a robust "baseline" or "business-as-usual" scenario, which is its core strength for illustrating the potential consequences of continuing current trajectories. However, as the reviewer correctly notes, it does not—and cannot—simulate future, non-linear shifts in risk factors (e.g., accelerating obesity), disruptive policy changes, or the differential global uptake of new therapies. Presenting these projections without explicitly contextualizing this fundamental assumption would indeed overstate their determinism.
Actions taken: In direct response to this comment, we have revised the manuscript by adding a new paragraph to the Limitations section. This paragraph explicitly addresses the structural uncertainty inherent in all long-term forecasting. It clarifies that our 2050 projections are scenario-based extrapolations conditional on the continuation of past trends, not deterministic predictions. We state that the model, as a static framework, cannot simulate the impact of future non-linear shifts, such as accelerating obesity, changes in hypertension policies, or differential adoption of new pharmacotherapies, and that these factors could substantially alter the projected burden. This addition provides the necessary context, ensuring our forecasts are correctly interpreted as a quantitative baseline for comparison against future outcomes shaped by interventions or disruptions.
Page 21:
Fifth, the projections from the BAPC model offer baseline forecasts based on historical trends. As a static framework, the model cannot simulate the effect of future interventions, policy changes, or clinical advances. Consequently, our estimates do not include their potential mitigation, and sensitivity analyses of hypothetical strategies were not performed, as this study aimed to establish a data-informed reference scenario. These projections should therefore be interpreted as a benchmark for guiding public health planning, not as a definitive outcome.

Major Comment 4: The Discussion attributes male predominance in HF burden to detailed molecular mechanisms (e.g., GRK2 signaling, estrogen pathways, GPR30). While these mechanisms are biologically plausible, this mechanistic depth is disproportionate for an ecological, population-level modeling study and risks overstating biological certainty. The discussion would be strengthened by emphasizing behavioral risk factors, metabolic burden, and sex-specific healthcare utilization patterns, rather than speculative molecular pathways.
Response: We thank the reviewer for this insightful and constructive critique. We concur that the level of molecular mechanistic detail in our original discussion was not well-aligned with the ecological, population-level nature of our study derived from the GBD dataset. While references to pathways like GRK2 signaling or GPR30 are biologically plausible and supported by experimental literature, their inclusion in this context risked implying a degree of biological certainty that our modeling data cannot substantiate. The reviewer's suggestion to refocus the discussion on factors more directly inferable from population-level trends—namely, differential behavioral risk exposures, metabolic burden, and potential sex-specific patterns in healthcare

access and utilization—is both methodologically appropriate and would strengthen the public health relevance of our interpretation.
Actions taken: We have substantially revised the relevant section of the Discussion to address this point. The detailed molecular mechanisms have been removed. The revised text now foregrounds the pronounced disparities in modifiable cardiometabolic risk factor profiles (e.g., smoking, hypertension, obesity patterns) and discusses the potential role of sex differences in healthcare-seeking behavior and diagnostic timeliness as contributing factors to the observed burden gap. Any mention of hormonal modulation is now framed at a systemic level, briefly noting it as one potential contributing biological influence among others, with the primary emphasis firmly placed on the behavioral and healthcare system factors that are more directly relevant to population-level intervention planning.
Page 19:
Males exhibitied a systematically higher burden of HF than females across all geographic regions and age subgroups during 1990-2021. This disparity can be attributed to a confluence of divergent behavioral and metabolic risk profiles, potential biological contributors, and sex-specific patterns in healthcare utilization. Men have historically demonstrated a higher prevalence of modifiable risk factors, including smoking, diabetes, and central obesity. Additionally, biological differences may play a role; premenopausal females benefit from relative cardioprotection linked to estrogen, which is associated with favorable vascular physiology and a lower incidence of heart failure compared to age-matched males.

Minor Comment : The manuscript contains frequent grammatical errors and non-native phrasing that substantially affect clarity and professionalism. Representative examples include:
“HF burden sustainly rised” (should be “HF burden increased steadily”),
“performanced increases” (should be “demonstrated increases”),
“which below the global average” (should be “which is below the global average”).
Response: We sincerely thank the reviewer for their meticulous attention to language and clarity. We acknowledge and apologize for the grammatical errors and non-native phrasing present in the original submission, which understandably detracted from the professionalism and readability of the manuscript.
Actions taken: We have undertaken a comprehensive line-by-line revision of the entire manuscript to correct grammatical errors, improve syntax, and ensure idiomatic English expression. All specific examples highlighted by the reviewer (e.g., “HF burden increased steadily,” “demonstrated increases,” “which is below the global average”) and similar instances throughout the text have been corrected. We are confident that these efforts have substantially enhanced the clarity, fluency, and overall quality of the presentation.

1. Revised Manuscript.docx PDF HTML