PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Exposure to early-life adversity and long-term trajectories of multimorbidity among older adults in China: analysis of longitudinal data from the China Health and Retirement Longitudinal Study
AUTHORS	Liu, Huiying; Zhang, Mi; Zhang, Xinyan; Zhao, Xinyi

VERSION 1 – REVIEW

REVIEWER	Foley, Louise National University of Ireland Galway, School of Psychology
REVIEW RETURNED	18-Sep-2023

GENERAL COMMENTS	This observational study provides evidence for the association between type and number of early life adversities and development of multimorbidity in older adulthood. The identification of multimorbidity trajectories provides insight into the varied experiences of older adults. The study is well justified and clearly reported. I have some minor suggestions for the authors to consider: Introduction 1. The authors refer to a “powerful influence on brain architecture” when referring to the impacts of early life adversities. This statement is overly vague and should be explained further – have any specific pathways linking ELA and multimorbidity been identified? Methods 2. How did the authors select the 14 conditions that were considered when defining multimorbidity? If an existing list/index was used this should be cited. 3. The authors measured several covariates that potentially impact on both ELA and multimorbidity. How were these variables selected? If existing literature was drawn on this could be referenced here for context. Results 4. It is reported that participants across trajectory groups differed in demographic, socio-economic and health behaviour variables. The tables indicate these variables were adjusted for. This should also be reported in the analysis section in the methods. Discussion 5. Implications and recommendations are first mentioned in the conclusion paragraph. I’d suggest dedicating a new section to this, highlighting potential policy, practice and research implications. The study provides evidence for the potential impact of preventing ELA which could reduce the burden of multimorbidity in later life – implications for individuals, society and healthcare systems are

	wide reaching. Reflecting and commenting on the system-level impacts would add value to the discussion. 6. The authors suggest at one point that ELA experiences explain heterogeneity in multimorbidity trajectories in later life. This could be further contextualised given other variables that are likely to influence the outcome beyond ELA alone. Supplementary material 7. A STROBE checklist (or equivalent) should be included.

REVIEWER	Abdel-Qader, Derar H. University of Petra
REVIEW RETURNED	09-Nov-2023

GENERAL COMMENTS	Introduction: The introduction provides a thorough background on the prevalence and impact of multimorbidity among older adults, particularly in China. It sets the stage well by emphasizing the significance of understanding the long-term trajectories of multimorbidity. The introduction successfully identifies a gap in the literature regarding the effects of early-life adversity (ELA) on these trajectories. However, the introduction could be enhanced by briefly discussing the implications of these findings for public health policies and practices. Moreover, while the life-course perspective is well-articulated, a brief mention of opposing or alternative viewpoints could offer a more balanced approach. Sampling Methodology: The study's sampling approach utilizes data from the China Health and Retirement Longitudinal Survey (CHARLS), which is robust and nationally representative. However, the exclusion of individuals over 85 years old may result in an underestimation of multimorbidity prevalence and trajectories in the oldest segments of the population. Given that multimorbidity is likely to increase with age, it would be beneficial for future research to explore ways to include this demographic to provide a more comprehensive view of multimorbidity across the full age spectrum. Sample Size: The final analytical sample size of 9,112 respondents is commendable as it likely provides sufficient power to detect statistically significant differences in multimorbidity trajectories. However, the report could be strengthened by including power calculations that justify the sample size and by discussing how the sample size allows for subgroup analyses, especially when examining the impacts of different types of ELA. Statistical Analysis: The choice of group-based trajectory modeling (GBTM) is appropriate for the identification of distinct multimorbidity trajectories. The multinomial logistic regression models used to examine the relationship between ELA and multimorbidity trajectories are also suitable for the data and research question. Nonetheless, the methodology would benefit from: 1. Justification of the Model Choice: While GBTM is an established method, it assumes that the population is composed of distinct groups following different trajectories. The rationale for choosing GBTM over other potential approaches, such as latent class

	growth analysis or growth mixture modeling, which might account for within-group variability, should be discussed. 2. Addressing Model Assumptions: The study should discuss how the assumptions of GBTM were tested and met, as well as any sensitivity analyses conducted to ensure that results were robust to violations of these assumptions. 3. Handling of Missing Data: It is unclear how missing data was handled in the analyses. Given that longitudinal studies often face issues with attrition and missingness, it is critical to address how such data was treated—whether through multiple imputation, complete case analysis, or another method—and how this might affect the findings. 4. Consideration of Confounding Variables: While the study includes numerous covariates, there could be unmeasured confounding factors that influence both ELA and multimorbidity. A discussion regarding potential residual confounding would be informative. 5. Model Fit and Selection: The report could expand on the model selection process, including the consideration of model fit indices such as the Bayesian Information Criterion (BIC) and the interpretability of the models. A more detailed discussion on the thresholds for BIC differences that guided model selection would be useful. 6. Validation of Results: The methods section would be strengthened by including information on whether the results were validated in an independent dataset or through cross-validation techniques within the sample. Results: The results section is well-organized and presents the identified multimorbidity trajectories and their association with ELA effectively. The use of descriptive statistics and regression models to elucidate these relationships is methodologically sound. However, there is a lack of discussion on the clinical relevance of the different trajectories and how these findings could inform interventions to prevent or manage multimorbidity. Also, the results would benefit from a more detailed examination of potential confounders and interactions between different types of ELA. Conclusion: The conclusion succinctly summarizes the study's findings and emphasizes the importance of a supportive early-life environment. It appropriately suggests implications for practice, such as the need for practitioners to consider upstream factors. However, it would be beneficial to discuss the potential for these findings to inform broader societal interventions, such as poverty reduction programs or early childhood supports, which could mitigate the long-term effects of ELA on health. Language: The manuscript is well-written and clear. The language is mostly academic and appropriate for a scientific journal. However, there are a few instances where the language could be tightened to maintain a formal tone consistently. Avoiding passive voice and

	ensuring precision in language would further strengthen the manuscript.

REVIEWER	Gumedze, Freedom University of Cape Town, Statistical Sciences
REVIEW RETURNED	23-Nov-2023

GENERAL COMMENTS	The paper set out to identify long-term heterogeneous trajectories of multimorbidity among Chinese older adults starting in late adulthood and followed up to 35 years and to examine the relationship between exposure to ELA (including specific types of adversity and accumulation of different adversities) and these long-term multimorbidity trajectories using population-based longitudinal data. The paper has clear aims and objectives. The study is well executed and the results are correctly interpreted. The statistical methods, being group-based trajectory models and multinomial logistic regression models, to analyse the data are clearly described. The paper is well written. The authors have clearly acknowledged the limitation of their study. However, the analysis of the data and the presentation of the results could be improved. I recommend a minor revision of the manuscript. Below are some specific comments: 1. Page 12, lines 40-46: The authors report that they used the BIC to choose the better-fit model yet in Table 2, the model the 4 groups is chosen but the corresponding BIC is not the smallest. Can the authors clarify this. Table 3: The results for models 1 and 2 should be presented in separate tables. Presentation the results of the two models in one table can be read to imply that Model had the covariates Parental illness....ELA 5-7 which is not true. Table 3, Table 2 and Figure 2: What model was used to determine the group membership? Did the fitted model include linear plus quadratic and or cubic number of age/time effects? Table 2: In models 1 and 2 is group membership the response variable? If yes, would the results of the models 1 and 2 be different if the number of groups was larger or smaller than 4? Table 2: Remove the "*" symbols which indicate the size of the p-values. The reader can decide on the statistical/clinical significance of estimated effects based on the p-values or confidence.

VERSION 1 – AUTHOR RESPONSE

SPECIFIC COMMENT:
Introduction
Comment 1
The authors refer to a “powerful influence on brain architecture” when referring to the impacts of early life adversities. This statement is overly vague and should be explained further-have any specific

pathways linking ELA and multimorbidity been identified?

Response:
Thanks for your comment. In the revised manuscript, we have replaced the term “powerful” and provided more specificity to previously ambiguous statements. Meanwhile, we have elucidated two pathways linking ELA and multimorbidity. Relevant revisions have been made to the Introduction Section (Page 6 Line 103 to Page 6 Line 114) as well as the following:
“The life-course perspective provides two important theoretical models explaining the mechanisms underlying the association between ELA and health development [19]. The critical period model asserts that exposure to ELA has long-lasting influence on individuals’ developmental trajectories of health. This influence could vary across different types of ELA experiences, and operate by shaping the structural aspects of individuals’ brain architecture and behavioral development [20][21]. Existing studies supporting this model have demonstrated that exposure to specific types of ELA (e.g., domestic violence and food deprivation) could increase the risk of multimorbidity in various older populations through the dysregulation of centrally mediated stress-response processes [22][23]and the promotion of detrimental behaviors or poor social ties [24][25].”

Methods
Comment 1
How did the authors select the 14 conditions that were considered when defining multimorbidity? If an existing list/index was used this should be cited.

Response:
Yes, the selection of the 14 chronic conditions was used from an existing list. This list is adapted from the China Health and Retirement Longitudinal Study (CHARLS) team, whom has established the effectiveness and reliability of this particular set of chronic conditions for measuring multimorbidity (Zhao et al., 2022). Meanwhile, the utilization and performance of this list in the Chinese older population have been previously documented (Fan et al., 2021; Liu et al., 2022; Li, 2023). In each CHARLS survey, respondent was asked about whether he/she was diagnosed with any of the listed 14 chronic conditions (the original question is DA007 in CHARLS survey). The respondent who answered in the affirmative was then asked to report the year when the condition was first diagnosed (the original question is DA009 in CHARLS survey). Based on this information, we created 14 binary variables indicating the presence of each chronic condition, and then defined multimorbidity as the coexistence of two or more chronic conditions.

Following your suggestion, we have added a reference when introducing the 14 chronic conditions. Please refer to the corresponding revisions located in the Methods Section (Page 10 Line 181) as well as the following:
“We obtained information about each respondent’s history of chronic conditions from the 2011-2018 CHARLS survey…... the following 14 chronic conditions…... [29].”
[29] Zhao Y, Strauss J, Chen X, Wang Y, Gong J, Meng Q, Wang G, Wang H. China Health and Retirement Longitudinal Study Wave 4 user’s guide. National School of Development, Peking University; 2020.
The original questions in CHARLS were copied below:
DA007 Have you been diagnosed with [conditions listed below, read one by one] by a doctor?
DA007_1. Hypertension
DA007_2. Dyslipidemia (elevation of low density lipoprotein, triglycerides (TGs),and total cholesterol, or a low high density lipoprotein level)
DA007_3. Diabetes or high blood sugar
……
DA007_13. Arthritis or rheumatism
DA007_14. Asthma

DA009 When was the condition first diagnosed or known by yourself?
DA009_1 Diagnosed Year_ condition 1
DA009_2 Diagnosed Year_ condition 2
DA009_3 Diagnosed Year_ condition 3
……
DA009_13 Diagnosed Year_ condition 13
DA009_14 Diagnosed Year_ condition 14

Comment 2
The authors measured several covariates that potentially impact on both ELA and multimorbidity. How were these variables selected? If existing literature was drawn on this could be referenced here for context.

Response:
Thank you for your suggestion. In this study, the selection of covariates was driven by a comprehensive examination of existing literature, and the chosen variables were supported by documented associations with both ELA and multimorbidity in relevant studies. In this revised manuscript, we have rewritten the paragraph describing the covariates, with three supporting references being added. Please refer to the corresponding revisions located in the Methods Section (Page 11 Line 209 to Page 11 Line 218) as well as the following:
"We controlled for a number of confounding factors identified in previous studies that may contribute to the association between ELA and multimorbidity [10][33][34]. These factors include (1) demographic characteristics: gender, residence area (urban versus rural), and marital status (married versus other status including unmarried/divorced/separated/widowed); (2) socioeconomic characteristics: educational attainment (below high school versus high school and above), whether receiving Dibao assistance, and types of medical insurance (none, urban employee, urban and rural resident, and others); and (3) health behavior factors: smoking, drinking, and physical activity (no-, light-, moderate- and vigorous-intensity physical activity)."

Results
Comment 1
It is reported that participants across trajectory groups differed in demographic, socio-economic and health behaviour variables. The tables indicate these variables were adjusted for. This should also be reported in the analysis section in the methods.

Response:
Thank you for your comment. In the revised manuscript, we have reported our adjustment for these variables in the analysis section in the methods. Please refer to the corresponding revisions located in the Methods Section (Page 13 Line 266 to Page 14 Line 269) as well as the following:
"Multivariate logistic models were used to assess the association between ELA and trajectory group memberships after controlling for various confounding factors including demographic features, socioeconomic factors, and health behavior factors."

Discussion
Comment 1
Implications and recommendations are first mentioned in the conclusion paragraph. I'd suggest dedicating a new section to this, highlighting potential policy, practice and research implications. The study provides evidence for the potential impact of preventing ELA which could reduce the burden of multimorbidity in later life – implications for individuals, society and healthcare systems are wide reaching. Reflecting and commenting on the system-level impacts would add value to the discussion.
Response:
Thank you for your valuable suggestions. We have added a section "Conclusion and Implications" to

highlight potential policy, practice and research implications. Please see the corresponding revisions located in the Conclusion and Implication Section (Page 22 Line 463 to Page 23 Line 485) as well as the following:
“Conclusion and Implication
In conclusion, our study indicated that the development of multimorbidity shows considerable heterogeneity within the older Chinese population with respect to the onset and increased rate of conditions, and such heterogeneity can be explained by ELA experiences. The findings highlight the critical role of childhood in an individual’s physical and psychological development, as childhood adversity can even influence the trajectory of multimorbidity in old age. Our findings could have the following implications. First, poverty alleviation programs or rural revitalization programs should pay specific attention to poor children and endeavor to provide them with better living conditions, thereby reducing the burden of multimorbidity in later life. Second, expanding existing child health services to include child support interventions that advance nurturing care is essential for a multisectoral effort to support families and benefit children [56]. For example, services that improve the nutritional status of infant and young children, as well as social work practice that identifies and intervenes in children’s unfavorable developmental environments (e.g., family violence and parental quarrels) may be helpful. Third, clinicians should develop early preventive interventions for susceptible middle-aged and older adults (such as those with ELA experience, female gender, lower education, etc.) so as to alleviate the rapid increases in chronic diseases in later adulthood. The integral treatment or management of multimorbidity to mitigate the deleterious health consequences of ELA. Moreover, future studies that identify mechanisms linking ELA with multimorbidity is needed to inform health management strategies and social policies that support long-term health in middle-aged and older adults.”

Comment 2
The authors suggest at one point that ELA experiences explain heterogeneity in multimorbidity trajectories in later life. This could be further contextualised given other variables that are likely to influence the outcome beyond ELA alone.

Response:
Yes, the result from our study suggests that the influence of ELA on the multimorbidity trajectories was significant after adjusting for demographic features, socioeconomic factors, and health behavior factors. In the revised manuscript, we have added several sentences to better interpret this result by further contextualizing it with the fact that these covariates are likely to influence the outcome beyond ELA alone. Please see the corresponding revisions located in the Discussion Section (Page 20 Line 421 to Page 21 Line 436, Page 22 Line 450 to Page 22 Line 454) as well as the following:
“Notably, the influence of ELA on the multimorbidity trajectories observed above remained significant even after adjusting for demographic features, socioeconomic factors, and health behavior factors. Consistent with the existing literature linking a range of individual difference factors with later-life health development [10] [33], our result revealed that factors such as gender, marital status, educational attainment, Dibao assistance, smoking or not smoking, and physical activity exerted independent effect on multimorbidity trajectories. In specific, being female, married, having high school and above educational attainment, receiving Dibao assistance, smoking, and engaging in moderate physical activity intensity were significantly associated with a higher risk of developing more severe multimorbidity trajectories. Our study contributed to the literature by providing new evidence that ELA served as an explanatory factor influencing long-term trajectories of multimorbidity. Future research could build upon out study by further examiningthe impact of ELA on multimorbidity trajectories in interaction with various confounders (e.g., gender and marital status).”

“Additionally, the issue of omitted variables may persist in our study, and future research was encouraged to employ more comprehensive datasets to investigate the relationship between potentially influential confounders (e.g., genetic inheritance and resilience) with multimorbidity trajectories.”

Supplementary material
Comment 1
A STROBE checklist (or equivalent) should be included.

Response:
Thanks for your comment. In the revised manuscript, we have added the STROBE checklist (Supplementary Table2). Please see the Methods Section (Page 14 Line 279 to Page 14 Line 280) as well as the following:
“We followed the STROBE checklist for reporting observational studies (see Supplementary Table2).”

PART 3. Response to Comments from Reviewer 2
Introduction
Comment 1
The introduction provides a thorough background on the prevalence and impact of multimorbidity among older adults, particularly in China. It sets the stage well by emphasizing the significance of understanding the long-term trajectories of multimorbidity. The introduction successfully identifies a gap in the literature regarding the effects of early-life adversity (ELA) on these trajectories. However, the introduction could be enhanced by briefly discussing the implications of these findings for public health policies and practices. Moreover, while the life-course perspective is well-articulated, a brief mention of opposing or alternative viewpoints could offer a more balanced approach.

Response：
Thank you for your suggestion. In this revised manuscript, we have added a discussion of the implications of our study for public health policies and practices. Moreover, we briefly mentioned the cumulative disadvantage (CDA) framework and considered it as alternative viewpoints.
Concerning a brief discussion of the implications：
In the revised manuscript, we have added one sentence to discuss the implications. Relevant revisions have been made to the Introduction Section (Page 8 Line 146 to Page 8 Line 147) as well as the following:
“Clarifying the impact of ELA experiences on later-life health will provide a basis for health care providers to develop comprehensive lifecycle health interventions.”
Concerning a brief mention of alternative viewpoints：
We acknowledge the importance of presenting alternative viewpoints. In addition to adopting the life-course perspective in our study, we have now added a brief discussion of the cumulative disadvantage (CDA) framework. To our knowledge, there is currently no research integrating life-course perspective and the Cumulative Disadvantage (CDA) framework to investigate the relationship between ELA and multimorbidity trajectories, particularly by linking the two aspects of ELA experiences (types and accumulation) with long-term distinct trajectories of multimorbidity. In the revised manuscript, we have added a paragraph describing the CDA framework and integrating both the life-course theory and the CDA framework, providing us with a theoretical perspective. Relevant revisions have been made to the Introduction Section (Page 7 Line 123 to Page 7 Line 132, Page 7 Line 134 to Page 7 Line 136) as well as the following:
“In addition to the life-course perspective, the cumulative disadvantage (CDA) framework also provides important viewpoints for understanding the impact of ELA on later-life health disparities highlighting the mechanism of path dependence. It posits that initial disparities can be linked to later-life health outcomes indirectly through influencing adulthood exposure to environmental risks and health opportunities [27]. Empirical studies have revealed that disadvantaged early environment (e.g., lower educational attainment) may lead to poorer socioeconomic status in adulthood (e.g., placement in the occupational hierarchy), subsequently exerting significant effects on later-life health through the influence of lifestyle choices or access to medical services [28].”

“To our knowledge, no existing studies have incorporated the life-course theory and the CDA framework for understanding the impact of ELA experiences on health development in later life……”

Methods

Comment 1

The study's sampling approach utilizes data from the China Health and Retirement Longitudinal Survey (CHARLS), which is robust and nationally representative. However, the exclusion of individuals over 85 years old may result in an underestimation of multimorbidity prevalence and trajectories in the oldest segments of the population. Given that multimorbidity is likely to increase with age, it would be beneficial for future research to explore ways to include this demographic to provide a more comprehensive view of multimorbidity across the full age spectrum.

Response：

Thank you for your suggestion. In this study, we excluded individuals over 85 years old because the oldest-old group was not well represented in the CHARLS. The proportion of respondents aged over 85 in the 2018 CHARLS survey was 1.6%. After a careful consideration and following relevant literature, we have added a limitation in the discussion section to acknowledge the limitation of our sample population, namely the exclusion of individuals aged 85 and above. Please see the Discussion Section (Page 22 Line 454 to Page 22 Line 461) as well as the following:

“Nevertheless, this study also has some limitations. First…..Third, our sample excluded individuals over 85 years old, which may have incurred some sample selection bias. Our research findings should thus be interpreted with caution regarding the possible underestimation of multimorbidity prevalence and trajectories in the oldest segments of the population. Considering this limitation, future research could focus on developing inclusive sampling strategies to ensure a more comprehensive representation of individuals aged 85 and above. This approach would contribute to a more comprehensive view of multimorbidity across the full age spectrum.”

Comment 2

The final analytical sample size of 9,112 respondents is commendable as it likely provides sufficient power to detect statistically significant differences in multimorbidity trajectories. However, the report could be strengthened by including power calculations that justify the sample size and by discussing how the sample size allows for subgroup analyses, especially when examining the impacts of different types of ELA.

Response：

Thank you for your suggestion. In this revised manuscript, we have added one sentence to justify the sample size. Moreover, we have discussed how the sample size allows for subgroup analyses, especially when examining the impacts of different types of ELA.

Concerning a discussion to justify the sample size:

In the revised manuscript, we have discussed the justification of the sample size. Relevant revisions have been made to the Methods Section (Page 9 Line 166 to Page 9 Line 170) as well as the following:

“To validate that the sample size in this study enabled subgrouping analyses, a power analysis using Stata 17 determined that, given an α level of 0.05 and a power of 0.8, the sample size required to achieve the detection of significant relationships between study variables would be approximately 863 respondents.”

Concerning a discussion to how the sample size allows for subgroup analyses:

In our GBTM subgrouping results, the group with the smallest number accounted for 16.2% of the total sample, which met the GBTM subgrouping requirements (smallest group ≥ 5%). In the revised manuscript, we have added two sentences to discuss how the sample size allows for subgroup analyses. Relevant revisions have been made to the Methods Section (Page 12 Line 241 to Page 12 Line 245) as well as the following:

“GBTM assumes that the sample size of each subgroup should not be less than 5% of the total sample size. In this study, the smallest subgroup constituted 16.2% of the total sample (the sample sizes of the four groups were 1743, 2119, 3779, and 1471, respectively), exceeding the model requirements significantly.”

Statistical Analysis
The choice of group-based trajectory modeling (GBTM) is appropriate for the identification of distinct multimorbidity trajectories. The multinomial logistic regression models used to examine the relationship between ELA and multimorbidity trajectories are also suitable for the data and research question. Nonetheless, the methodology would benefit from:
Comment 1
Justification of the Model Choice: While GBTM is an established method, it assumes that the population is composed of distinct groups following different trajectories. The rationale for choosing GBTM over other potential approaches, such as latent class growth analysis or growth mixture modeling, which might account for within-group variability, should be discussed.

Response：
Thank you for your feedback. In this revised manuscript, we have expanded our discussion to provide a more comprehensive justification for choosing GBTM over other potential approaches, such as latent class growth analysis (LCGA) or growth mixture modeling (GMM).
(1) Reasons for choosing GBTM: The choice of GBTM in our study for measuring multimorbidity trajectories was grounded in empirical evidence from existing literature, where GBTM has been widely utilized to identify heterogeneous groups within populations exhibiting diverse trajectories of multimorbidity (Newman et al., 2023; Ji et al., 2023; Murray et al., 2020). The GBTM approach allows for identifying distinct groups of individuals with similar trajectories of the outcome of interest over time (Nagin et al., 2018). Applied to our study, it enables the assignment of individuals into distinct groups based on the similarity of multimorbidity trajectories as they age (Hanson et al., 2015), in specific, each individual was assigned to a single group in which they have the highest posterior probability of membership.
(2) Reasons for not choosing LCGA: LCGA assumes that the entire population follows a small number of distinct trajectory patterns (Jung & Wickrama, 2008), which may oversimplify the inherent diversity in multimorbidity trajectories and overlook individual-level variations within identified classes (Muthén & Muthén, 2000). Instead, GBTM can capture the nuanced individual differences, which is more suitable for our study.
(3) Reasons for not choosing GMM: GMM typically emphasizes the distribution of latent classes at a specific point in time, which may not be informative enough for capturing the dynamic progression of multimorbidity over the study period (Muthén & Shedden, 1999; Nylund et al., 2007). Instead, GBTM focused on the change in patterns over time, which is better aligned with our goal of understanding the temporal evolution of multimorbidity within the population.
In summary, while LCGA and GMM are valuable methods, each with its strengths, we ultimately chose the GBTM to fulfill our research goal of capturing individual-specific trajectories, identifying distinct trajectory groups, and accommodating within-group variability. In this revision, we have added detailed explanations for choosing GBTM. Please see the Methods Section (Page 11 Line 221 to Page 12 Line 228) as well as the following:
“The group-based trajectory modeling (GBTM) approach was used to model progression in the number of chronic conditions over time (i.e., from late adulthood to old age) [35][36][37]. The GBTM approach is designed to identify distinctive groups of individuals sharing a similar trajectory using finite mixtures of suitably defined probability distributions [35]. Applied to this study, this approach enables the assignment of individuals into distinct trajectories based on the similarity of multimorbidity trajectories as they age. In specific, each individual was assigned to a single group in which they have the highest posterior probability of membership [6].”

Comment 2
Addressing Model Assumptions: The study should discuss how the assumptions of GBTM were tested and met, as well as any sensitivity analyses conducted to ensure that results were robust to violations of these assumptions.

Response：
Thank you for your suggestion. The assumptions of GBTM and how these assumptions were met in our study are presented in the following table:
GBTM Assumptions How the assumptions were tested/met
in our study
(1) Data distribution：continuous distribution with finite starting and ending points The chronic conditions data ranged from 0 to 14. GBTM provided a censored normal model for trajectory fitting for this type of data.
(2) Differences in trajectory groups: GBTM believes that group heterogeneity is due to differences in trajectory development rather than differences due to other variables. We compared the model with random effects such as gender and rural/urban residence to the model without random effects, and the results were not significantly different.
(3) The longitudinal feature of the data：all of the trajectories are steadily increasing or declining. The number of chronic conditions in individuals increased over time.
(4) Sub-group sample size: the sample size of each subgroup should not be less than 5% of the total sample size. The lowest sample size group was 16.2% of the total sample, which was far more than the requirement of the model.
In the revised manuscript, we have added several sentences to discuss how this study tested and met the four assumptions of GBTM. Please see the Methods Section (Page 12 Line 230 to Page 12 Line 245) as well as the following:
“We examined a series of foundational assumptions of GBTM. First, GBTM assumes that the data follow continuous distribution with finite starting and ending points ((in this study, the chronic conditions data are continuous, ranging from 0 to 14). Given the slight skewness in the data, we examined the applicability of the censored normal(cnorm) model and the zero-inflated Poisson(zip) model. The results indicated a better fit for the cnorm model. Second, GBTM assumes that heterogeneity between groups arises from differences in trajectory development rather than other variables. We compared the model with random effects, including gender, to the model without random effects, and the results did not show significant differences. Third, GBTM posits that all trajectories exhibit steady changes (in this study, the number of chronic conditions in individuals increased over time). Fourth, GBTM assumes that the sample size of each subgroup should not be less than 5% of the total sample size. In this study, the smallest subgroup constituted 16.2% of the total sample (the sample sizes of the four groups were 1743, 2119, 3779, and 1471, respectively), exceeding the model requirements significantly.”
Besides, we performed a series of sensitivity analyses to ensure that results were robust. Please see the Methods Section (Page 14 Line 271 to Page 14 Line 277) as well as the following:
“We performed a series of sensitivity analyses: (1) We reran the GBTM analyses using 12 chronic conditions (excluding memory-related and emotional/psychiatric problems given their low prevalence in the study population). (2) We also reran the main analyses using a different set of ELA indicators (including two additional indicators that have been suggested as having a potential influence on health in later life) and using different categorizations for the accumulation of ELA. (3) All the analyses were stratified by gender and urban-rural residence.”

Comment 3
Handling of Missing Data: It is unclear how missing data was handled in the analyses. Given that longitudinal studies often face issues with attrition and missingness, it is critical to address how such data was treated—whether through multiple imputation, complete case analysis, or another method—and how this might affect the findings.

Response：
Thanks for your comment. In this study, the majority of participants had complete data on all the items of chronic conditions and ELA information. Missing data was minimal and occurred due to no-response or incomplete responses to the chronic conditions and ELA questions, which were treated as missing at random. In our study, there were 9,863 individuals aged 60-85 in CHARLS 2018 survey. Among them, 30 individuals (accounting for 0.3% of the total) had missing data on chronic conditions. A generally accepted guideline for managing missing data is that when the missing data is below 10%, all records with missing data can be deleted without a significant loss of statistical power in the modeling results based on such dataset; if missing data is more than 10%, then an imputation strategy can be used since deleting would result in a significant loss of statistical power (Bennett, 2001; Little & Rubin, 2019). Given the very low number of missing values, we deleted 30 individuals who had any missing chronic condition data, resulting in a sample size reduced from 9,863 to 9,833. After a further exclusion of participants with missing data on ELA, our final sample size was 9112. This sample reduction process has been presented in Figure 1.

In this manuscript, we have added a more detailed discussion on the rationale behind the handling of missing data and its potential implications on the finding in the Analytical Strategy Section. Please refer to the Methods Section (Page 13 Line 248 to Page 13 Line 250) as well as the following:
“A small amount of missingness occurred due to no-response or incomplete responses to the chronic conditions and ELA information; these missing data were treated as missing at random.”

Comment 4
Consideration of Confounding Variables: While the study includes numerous covariates, there could be unmeasured confounding factors that influence both ELA and multimorbidity. A discussion regarding potential residual confounding would be informative.

Response：
Thank you for your suggestion. We acknowledge that there may be potential unmeasured confounding factors in our study that could impact both ELA and multimorbidity. In this revision, we have discussed possible residual confounding in the discussion section. And, we have revised the limitations section and emphasized the caution with which we interpret the study results. This will help ensure that readers have a comprehensive and accurate understanding of the conclusions drawn from our research. Relevant revisions have been made to the Discussion Section (Page 22 Line 450 to Page 22 Line 454) as well as the following:
“Additionally, the issue of omitted variables may persist in our study, and future research was encouraged to employ more comprehensive datasets to investigate the relationship between potentially influential confounders (e.g., genetic inheritance and resilience) with multimorbidity trajectories.”

Comment 5
Model Fit and Selection: The report could expand on the model selection process, including the consideration of model fit indices such as the Bayesian Information Criterion (BIC) and the interpretability of the models. A more detailed discussion on the thresholds for BIC differences that guided model selection would be useful.

Response：
Thank you for your valuable feedback. We appreciate your suggestion to provide a more detailed discussion of the model selection process, particularly focusing on the Bayesian Information Criterion (BIC) and the interpretability of the models. We have made the necessary revisions to enhance the clarity and completeness of our manuscript. Please refer to the Methods Section (Page 13 Line 250 to Page 13 Line 263) as well as the following:

“For model selection, we used the following model-fit indices and statistical criteria in combination with conceptual considerations of group distinctiveness and interpretability: (a) the Bayesian Information Criteria (BIC) values. The BIC is the most widely used criteria for model selection, with a BIC closer to 0 indicating better model fit. (b) relative entropy estimates the accuracy (convergence) of classification of individuals into the different latent classes. Entropy values close to 1 indicate lower classification uncertainty. (c) the average posterior probability of group assignment that measures the probability of a group individual belonging to this specific trajectory group was set at greater than 0.7; and (d) according to the posterior probability of the group member, a minimum membership of 5% is required in each trajectory group [40]. These criteria were applied iteratively, and the final model was chosen based on a comprehensive evaluation of statistical fit and conceptual coherence, striking a balance between model complexity and interpretability.”

Comment 6
Validation of Results: The methods section would be strengthened by including information on whether the results were validated in an independent dataset or through cross-validation techniques within the sample.

Response：
Thank you for your suggestion. In the revision, information about the validation of results have been added to the Methods Section and the Sensitivity Analyses Section (please see the following and the revised manuscript Page 14 Line 271 to Page 14 Line 277, Page 17 Line 342 to Page 17 Line 347).
“We performed a series of sensitivity analyses: (1) We reran the GBTM analyses using 12 chronic conditions (excluding memory-related and emotional/psychiatric problems given their low prevalence in the study population). (2) We also reran the main analyses using a different set of ELA indicators (including two additional indicators that have been suggested as having a potential influence on health in later life) and using different categorizations for the accumulation of ELA. (3) All the analyses were stratified by gender and urban-rural residence.”
“The results remained generally consistent when restricting the GBTM analyses to only 12 chronic conditions, when using a different set of ELA indicators or different categorization for the accumulation of ELA, and when stratifying by gender and urban-rural residence (please see Supplemental Table3 and Supplemental Table5-9 for details).”

Results
Comment 1
The results section is well-organized and presents the identified multimorbidity trajectories and their association with ELA effectively. The use of descriptive statistics and regression models to elucidate these relationships is methodologically sound. However, there is a lack of discussion on the clinical relevance of the different trajectories and how these findings could inform interventions to prevent or manage multimorbidity. Also, the results would benefit from a more detailed examination of potential confounders and interactions between different types of ELA.

Response：
Thank you for your comment. Following your suggestion, we have made revisions to the interpretation of findings and implication discussions.
(1) On the one hand, we have added more interpretation about our results of the association of ELA and multimorbidity trajectory in the Discussion Section. Please refer to Page 18 Line 367 to Page 18 Line 372, Page 19 Line 384 to Page 19 Line 391, Page 19 Line 391 to Page 19 Line 398, Page 20 Line 412 to Page 20 Line 421, and Page 20 Line 422 to Page 21 Line 436 as well as the following:
“A similar trajectory of health development in later life has been consistently reported in previous studies among older Chinese populations across a variety of health outcomes, including frailty and functional disability [42][43]. This might because that increasing life expectancy and decreasing incidence of infectious diseases have led to an increase in chronic disease in old age [44].”

“Specifically, our finding was consistent with previous studies linking childhood food insufficiency with a higher risk of chronic conditions in middle and old age [45][25][46]. This might due to the fact that individuals shape physiological characteristics in early life that make them be capable of maintaining homeostasis in metabolism when challenged by a metabolic load [47][25]. Food insufficiency in childhood may lead to malnutrition, which may impair the development of metabolic capacity and increase the susceptibility to chronic diseases in the long term [47].”
“Additionally, our finding of the harmful effects of parental quarrel/divorce on long-term multimorbidity trajectories extended the literature on the importance of early-life dysfunctional family relationships for physical and mental health in adulthood [48][49]. One possible explanation might be that parental quarrel/divorce would cause psychological stress in childhood [48], which causes behavioral proclivities (such as unhealthy lifestyle choices) and hormonal dysregulation (such as altered endocrine patterns) over the life span [50], and thereby giving rising to increased risks of chronic diseases [44].”
“Initial disadvantages may cause individuals to be exposed to subsequent risk factors, such as interrupted education in adolescence, employment disadvantages and unhealthy lifestyles in adulthood, leading to greater disparities in health status in old age [53] [54]. On the one hand, early life adversity such as poverty and food insufficiency may cause excessive wear and tear in the body. As people age, they are at increasing risks of chronic diseases such as arthritis. On the other hand, since China’s reform and opening up in the late 1970s, with socioeconomic development, individuals who have experienced childhood adversity may have more compensatory energy intake [55], leading to hypertension, diabetes, and other cardiometabolic diseases.”
“Notably, the influence of ELA on the multimorbidity trajectories observed above remained significant even after adjusting for demographic features, socioeconomic factors, and health behavior factors. Consistent with the existing literature linking a range of individual difference factors with later-life health development [10] [33], our result revealed that factors such as gender, marital status, educational attainment, Dibao assistance, smoking or not smoking, and physical activity exerted independent effect on multimorbidity trajectories. In specific, being female, married, having high school and above educational attainment, receiving Dibao assistance, smoking, and engaging in moderate physical activity intensity were significantly associated with a higher risk of developing more severe multimorbidity trajectories. Our study contributed to the literature by providing new evidence that ELA served as an explanatory factor influencing long-term trajectories of multimorbidity. Future research could build upon out study by further examiningthe impact of ELA on multimorbidity trajectories in interaction with various confounders (e.g., gender and marital status).”

(2) On the other hand, we have made corresponding societal and clinical implications in the “conclusion and implications” section. Please refer to Page 22 Line 463 to Page 23 Line 485 as well as the following:
“Conclusion and Implication
In conclusion, our study indicated that the development of multimorbidity shows considerable heterogeneity within the older Chinese population with respect to the onset and increased rate of conditions, and such heterogeneity can be explained by ELA experiences. The findings highlight the critical role of childhood in an individual’s physical and psychological development, as childhood adversity can even influence the trajectory of multimorbidity in old age. Our findings could have the following implications. First, poverty alleviation programs or rural revitalization programs should pay specific attention to poor children and endeavor to provide them with better living conditions, thereby reducing the burden of multimorbidity in later life. Second, expanding existing child health services to include child support interventions that advance nurturing care is essential for a multisectoral effort to support families and benefit children [56]. For example, services that improve the nutritional status of infant and young children, as well as social work practice that identifies and intervenes in children’s unfavorable developmental environments (e.g., family violence and parental quarrels) may be helpful. Third, clinicians should develop early preventive interventions for susceptible middle-aged and older adults (such as those with ELA experience, female gender, lower education, etc.) so as to alleviate

the rapid increases in chronic diseases in later adulthood. The integral treatment or management of multimorbidity to mitigate the deleterious health consequences of ELA. Moreover, future studies that identify mechanisms linking ELA with multimorbidity is needed to inform health management strategies and social policies that support long-term health in middle-aged and older adults."

Conclusion

Comment 1

The conclusion succinctly summarizes the study's findings and emphasizes the importance of a supportive early-life environment. It appropriately suggests implications for practice, such as the need for practitioners to consider upstream factors. However, it would be beneficial to discuss the potential for these findings to inform broader societal interventions, such as poverty reduction programs or early childhood supports, which could mitigate the long-term effects of ELA on health.

Response：

Thank you for your valuable comment. We have added more content about the implications to broader societal intervention. First, poverty alleviation programs or rural revitalization programs should pay specific attention to poor children and endeavor to provide them with better living conditions, thereby reducing the burden of multimorbidity in later life. Second, expanding existing child health services to include child support interventions that advance nurturing care is essential for a multisectoral effort to support families and benefit children (Daelmans et al., 2017). For example, services that improve the nutritional status of infant and young children, as well as social work practice that identifies and intervenes in children's unfavorable developmental environments (e.g., family violence and parental quarrels) may be helpful. Please refer to the Conclusion and Implication Section (Page 22 Line 463 to Page 23 Line 485) as well as the following:

"Our findings could have the following implications. First, poverty alleviation programs or rural revitalization programs should pay specific attention to poor children and endeavor to provide them with better living conditions, thereby reducing the burden of multimorbidity in later life. Second, expanding existing child health services to include child support interventions that advance nurturing care is essential for a multisectoral effort to support families and benefit children [56]. For example, services that improve the nutritional status of infant and young children, as well as social work practice that identifies and intervenes in children's unfavorable developmental environments (e.g., family violence and parental quarrels) may be helpful. Third, clinicians should develop early preventive interventions for susceptible middle-aged and older adults (such as those with ELA experience, female gender, lower education, etc.) so as to alleviate the rapid increases in chronic diseases in later adulthood. The integral treatment or management of multimorbidity to mitigate the deleterious health consequences of ELA. Moreover, future studies that identify mechanisms linking ELA with multimorbidity is needed to inform health management strategies and social policies that support long-term health in middle-aged and older adults."

Language

Comment 1

The manuscript is well-written and clear. The language is mostly academic and appropriate for a scientific journal. However, there are a few instances where the language could be tightened to maintain a formal tone consistently. Avoiding passive voice and ensuring precision in language would further strengthen the manuscript.

Response：

Thank you for your feedback. We have thoroughly reviewed the entire manuscript, meticulously revising each sentence to enhance clarity and ensure a consistently formal tone. Here are a few examples of the modifications made:

Original: "It is estimated that over half of Chinese older adults are living with two or more chronic conditions [3] ……"

Revised: “More than half of Chinese older adults are estimated to have two or more chronic conditions [3] ……”

Original: “Among various life-course models, the critical period model asserts that ELA experiences can get ‘under the skin’ by exerting a powerful influence on individuals’ brain architecture and behavioral development.……”
Revised: “Among various life-course models, the critical period model asserts the significant impact of ELA experiences on individuals' health outcomes later in life……”

Original: “Data used in the present study were derived from the four waves (2011-2018) of the China Health and Retirement Longitudinal Study (CHARLS) and the 2014 Life History Survey.”
Revised: “The present study utilized data from the four waves (2011-2018) of the China Health and Retirement Longitudinal Study (CHARLS) and the 2014 Life History Survey.”

PART 4. Response to Comments from Reviewer 3
GENERAL COMMENT:
The paper set out to identify long-term heterogeneous trajectories of multimorbidity among Chinese older adults starting in late adulthood and followed up to 35 years and to examine the relationship between exposure to ELA (including specific types of adversity and accumulation of different adversities) and these long-term multimorbidity trajectories using population-based longitudinal data. The paper has clear aims and objectives. The study is well executed and the results are correctly interpreted. The statistical methods, being group-based trajectory models and multinomial logistic regression models, to analyse the data are clearly described. The paper is well written. The authors have clearly acknowledged the limitation of their study. However, the analysis of the data and the presentation of the results could be improved.

GENERAL RESPONSE:
Thank you for your encouragement and careful review of our paper. We have revised our manuscript according to your comments and suggestions. All the changes we made were highlighted in blue throughout the manuscript, tables, and figure. Please see below a point-by-point response to your comments and suggestions.

SPECIFIC COMMENT:
Results
Comment 1
Page 12, lines 40-46: The authors report that they used the BIC to choose the better-fit model yet in Table 2, the model the 4 groups is chosen but the corresponding BIC is not the smallest. Can the authors clarify this.

Response：
Thank you for your comment. In this study, our model selection process involved not only the Bayesian Information Criterion (BIC) but also the consideration of entropy as a complementary criterion for determining the optimal number of trajectory groups. While the BIC value is a primary indicator of model fit, entropy adds an additional information by measuring the clarity and distinctiveness of group assignments.

In our study, on the one hand, we observed that the BIC value for Group 4 was approaching zero, indicating a competitive fit. After Group 4, there was a reduced rate of BIC reduction, indicating that further increases in model complexity no longer yielded significant benefits. On the other hand, entropy for Group 4 was at a "turning point," and its corresponding value was close to 1 (the highest among Groups 1-6), indicating high certainty in the group assignments. Based on considerations of changes in BIC and entropy, a logit model with four trajectory groups was the most suitable fit for the

data.

Following your suggestion, we have provided a more detailed explanation of the rationale for our model selection in the revised manuscript. Please refer to the Results Section (Page 15 Line 301 to Page 15 Line 308) as well as the following:
"Comparatively, the BIC and entropy indicated that Group 4 and Group 6 were more suitable than the other groups. The optimal BIC was found in Group 6 (closest to 0), and Group 4 exhibited the highest entropy (closest to 1, at 0.976). Meanwhile, we observed a diminished rate of BIC reduction after Group 4, suggesting that further increasing model complexity no longer yields significant benefits [40]. Based on considerations of changes in BIC and entropy, a logit model with four trajectory groups was the most suitable fit for the data."

Comment 2
Table 3: The results for models 1 and 2 should be presented in separate tables. Presentation the results of the two models in one table can be read to imply that Model had the covariates Parental illness.... ELA 5-7 which is not true.

Response：
Thank you for pointing this out. In this revision, we have modified the presentation of Table 3 to accurately display the model results. Please see the revised Table 3 and Table 4 for more details.

Comment 3
Table 3, Table 2 and Figure 2: What model was used to determine the group membership? Did the fitted model include linear plus quadratic and or cubic number of age/time effects?

Response：
We used cnorm model in the Group Based Trajectory Model(GBTM) to determine the group membership and to fit developmental trajectories, which is a finite mixture model and also a semiparametric model for longitudinal data. The fitted model includes linear plus quadratic number of age/time effects. Specifically, the fit to each set of trajectories starts with a cubic fit, and if that trajectory is not fitted well, it is reduced to a squared fit until it is adjusted to the most appropriate fit. Suppose {Yi = yi1, yi2, yi3, ..., y1T} represents the longitudinal sequence of measurements on an individual i over T periods, and P(Yi) denotes the probability of Yi. The group-based trajectory model assumes that the population is composed of a mixture of J underlying trajectory groups such that ; where Pj（Yi） is the probability of Yi given membership in group j, and πj is the probability of group j. The basic model also assumes that conditional on membership in group j, the random variables, yit, t = 1, 2, ..., T , are independent. The group membership probabilities, πj, j= 1, ..., J, are not estimated directly but instead are estimated by a multinomial logit function, Estimation of πj in this fashion ensures that each such probability properly falls between 0 and 1 (Jones & Nagin, 2007).

Comment 4
Table 2: In models 1 and 2 is group membership the response variable? If yes, would the results of the models 1 and 2 be different if the number of groups was larger or smaller than 4?

Response：
Yes, group membership is response variable. In this study, the data analysis process consists of two main steps. Step 1: Determined how many multimorbidity trajectory groups exist among older adults. In this step, we used GBTM to fit the multimorbidity trajectories from Group 1 to Group 6. We finally found Group 4 provided the best fit (please see Table 2 for more details). Step 2: Analyzed the relationship between ELA and four trajectory groups. In this step, four trajectory groups were included as fixed dependent variables in Model 1 and Model 2, and the number of groups smaller or larger than 4 was no longer considered in the analysis.

Comment 5
Table 2: Remove the "*" symbols which indicate the size of the p-values. The reader can decide on the statistical/clinical significance of estimated effects based on the p-values or confidence.

Response：
Thank you for your suggestion. The "*" symbols which indicate the size of the p-values has been removed in the revised Table 3.

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VERSION 2 – REVIEW

REVIEWER	Foley, Louise National University of Ireland Galway, School of Psychology
REVIEW RETURNED	30-Jan-2024

GENERAL COMMENTS	Thanks to the authors for responding to my comments on the paper. I have no further comments on this version.

REVIEWER	Gumedze, Freedom University of Cape Town, Statistical Sciences
REVIEW RETURNED	01-Feb-2024

GENERAL COMMENTS	I have carefully read the revised version of the manuscript. The authors have adequately addressed all the concerns raised in the original manuscript submission. I recommend that the revised manuscript be published in BMJ Open.