PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Nonlinear relationship between pulse pressure and the risk of prediabetes: a secondary retrospective Chinese cohort study
AUTHORS	Cao, Changchun; Han, Yong; Hu, Haofei; He, Yongcheng; Luo, Jiao

VERSION 1 – REVIEW

REVIEWER	Fukuda, Yoshiharu Yamaguchi University, Community Health and Medicine
REVIEW RETURNED	06-Dec-2023

GENERAL COMMENTS	The pulse pressure is correlated with other parameters such as blood pressures, some of which are predictors of prediabetes. The authors should showed not only adjusted HRs of PP but also those of other important variables. These results will be informative to judge validity of analysis and conclusion of the present study.

REVIEWER	Ali, Hatem University Hospitals Birmingham NHS Foundation Trust
REVIEW RETURNED	22-Dec-2023

GENERAL COMMENTS	Study Design and Data Source: The study is a secondary retrospective cohort analysis, using data from the 'DATADRYAD' database. While using existing datasets can be efficient, it limits the control over data quality and variables included. The retrospective nature of the study may also introduce biases. Sample Selection and Exclusion Criteria: The study includes a large sample of 182,672 Chinese individuals, which is commendable for its size. However, the exclusion criteria, such as excluding individuals with diabetes at baseline or missing data, may have impacted the representativeness of the sample. Measurement and Definition of Prediabetes: The study defines prediabetes based on impaired fasting glucose levels only. This could potentially lead to underestimation of prediabetes incidence, as the study did not incorporate a 2-hour oral glucose tolerance test or glycosylated hemoglobin level measurements. Statistical Analysis: While the study uses robust statistical methods like Cox proportional hazards regression, the interpretation of results, especially regarding the nonlinear relationship, could be more clearly articulated. The study also conducts multiple imputations to handle missing data, which is a

	strength, but the assumptions behind these imputations should be scrutinized. Subgroup Analyses: The manuscript reports subgroup analyses, but there is a need for a more thorough discussion on how these subgroups were chosen and their relevance to the study's main findings. Generalizability: The study is based on a Chinese population, and while it offers valuable insights, the findings might not be directly generalizable to other populations due to genetic, lifestyle, and environmental differences. Limitations: The study acknowledges some limitations, like the lack of information on atherosclerosis, antihypertensive medications, and the presence of hypertension. It also doesn't account for changes in blood pressure over time. These factors could significantly impact the study outcomes and should be considered when interpreting the results. Potential for Confounding Factors: While the study controls for various confounders, the potential for residual confounding factors remains. The study could benefit from a more detailed discussion on how these factors were handled and their possible impact on the study's findings. In summary, while the study offers valuable insights into the relationship between pulse pressure and prediabetes risk, certain aspects like data source limitations, measurement methods, and generalizability need careful consideration. Further studies are recommended to build upon these findings and address the identified gaps.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Yoshiharu Fukuda, Yamaguchi University
Comments to the Author:
The pulse pressure is correlated with other parameters such as blood pressures, some of which are predictors of prediabetes. The authors should showed not only adjusted HRs of PP but also those of other important variables. These results will be informative to judge validity of analysis and conclusion of the present study.
Response: Thank you for your valuable feedback. We appreciate your attention to the correlation between PP and other important variables, including predictors of prediabetes.
In response to your suggestion, we included the adjusted HRs of other important variables in Table 2. This additional information provided a more comprehensive understanding of the relationship between these variables and the validity of our analysis and conclusions. We believe that incorporating these results enhanced the overall quality and significance of our study. Revisions are marked in red. Once again, we appreciate your insightful comments.

Reviewer: 2
Dr. Hatem Ali, University Hospitals Birmingham NHS Foundation Trust
Comments to the Author:
Study Design and Data Source: The study is a secondary retrospective cohort analysis, using data from the 'DATADRYAD' database. While using existing datasets can be efficient, it limits the control

over data quality and variables included. The retrospective nature of the study may also introduce biases.
Response: We are grateful for the insightful commentary you have provided on our research. Your critical appraisal concerning the methodological framework and the provenance of the data is highly valued.
In the original study, the data were collected under standardised conditions and followed according to uniform procedures by trained staff. Laboratory methods also were carefully standardised with rigorous internal and external quality controls. The acquisition of demographic parameters, such as stature, sphygmomanometric measurements, body mass, and chronological age, was carried out by trained staff in the original study. The original study was meticulously designed to guarantee the integrity of the data and the stringent control of the variables under consideration, as delineated previously. In addition, we thoroughly evaluated each variable of the raw data and did not find any obvious errors in these variables.
We acknowledge the retrospective design of our study as a potential source of bias. To account for the retrospective design, we have implemented several methodological strategies to minimize potential biases. These include a comprehensive adjustment for confounders that were available in the dataset, and sensitivity analyses to test the robustness of our results. We have also provided a transparent account of the data collection methods used in the original study from which the 'DATADRYAD' database was compiled, allowing for an informed assessment of potential biases.
As you say, because our study was a secondary analysis, we cannot guarantee data quality monitoring and variable control. In forthcoming research endeavors, we will endeavor to construct prospective cohort studies with enhanced data quality oversight and variable control, thereby mitigating bias. This limitation has been duly noted in the 'Discussion' section of our manuscript, highlighted for emphasis.
Your feedback is instrumental in our ongoing efforts to enhance the transparency and credibility of our research. We invite any additional recommendations or concerns you might have and extend our heartfelt gratitude for your constructive critique.

Sample Selection and Exclusion Criteria: The study includes a large sample of 182,672 Chinese individuals, which is commendable for its size. However, the exclusion criteria, such as excluding individuals with diabetes at baseline or missing data, may have impacted the representativeness of the sample.
Response: We extend our sincere gratitude for your recognition of the considerable magnitude of our sample in this study, which indeed fortifies the statistical validity and the generalizability of our conclusions pertaining to the association between pulse pressure and the risk of prediabetes. Additionally, we are appreciative of your astute scrutiny of our sample selection methodology and the criteria for exclusion.
In the foundational work by Chen et al., a diligent comparative evaluation was undertaken to gauge the congruence between the cohort that was incorporated into the study (211,833 individuals) and the segment that was not included (473,444 individuals). The findings from Chen et al. indicated that the demographic attributes such as age (42.1 years for included participants versus 41.9 years for excluded participants), body mass index (BMI) (23.2 kg/m² for included versus 23.3 kg/m² for excluded), and gender distribution (54.8% male for included versus 52.1% male for excluded) were remarkably similar across both groups. This suggests that the exclusion criteria, such as the omission of individuals with prevailing diabetes or incomplete data, may exert a minimal effect on the representativeness of the sample.
Within our own study, we further excluded 29,161 participants, predominantly those with prediabetes, culminating in a final sample size of 182,672 individuals. A comparative analysis of the baseline characteristics between the included participants and those excluded revealed that the latter group was, on average, older (46.8 years versus 40.8 years), had a higher BMI (24.3 kg/m² versus 23.0 kg/m²), and consisted of a greater proportion of males (62.5% versus 53.1%). Literature on the subject indicates that these characteristics are consistent with the demographic profile of a

prediabetic population. Given that the majority of the excluded 29,161 participants were prediabetic, it is reasonable that they exhibited these demographic trends.
It is imperative to acknowledge that a more inclusive approach to sample selection would have been beneficial, encompassing individuals with diabetes at baseline and those with missing data. Unfortunately, the "DATADRYAD" database, from which our data was sourced, did not offer information on the excluded cohorts. As you have astutely pointed out, these exclusion criteria may indeed have influenced the representativeness of our sample. Moving forward, we will endeavor to corroborate our findings through research conducted on a broader spectrum of populations, including those with baseline diabetes and incomplete datasets. In our revised manuscript, we have elaborated upon the Discussion section to reflect upon the limitations imposed by our exclusion criteria.
Once again, we express our heartfelt thanks for your invaluable critique.

Measurement and Definition of Prediabetes: The study defines prediabetes based on impaired fasting glucose levels only. This could potentially lead to underestimation of prediabetes incidence, as the study did not incorporate a 2-hour oral glucose tolerance test or glycosylated hemoglobin level measurements.
Response: Thanks for your excellent advice. As you considered, our study defines prediabetes based on impaired fasting glucose levels only. This could potentially lead to underestimation of prediabetes incidence. This is a secondary retrospective study, and the data was downloaded from the DATADRYAD database (www.datadryad.org). And the raw data did not provide information regarding 2-hour oral glucose tolerance test or glycosylated hemoglobin level measurements. In the future, we will consider designing our study to document more variables, including 2-hour oral glucose tolerance test or glycosylated hemoglobin level measurements. We've added this limitation to the "Discussion" section and marked it up in red. Thank you again for your kind suggestion.

Statistical Analysis: While the study uses robust statistical methods like Cox proportional hazards regression, the interpretation of results, especially regarding the nonlinear relationship, could be more clearly articulated. The study also conducts multiple imputations to handle missing data, which is a strength, but the assumptions behind these imputations should be scrutinized.
Response: Thank you for your insightful comments on the statistical analysis section of our study. We appreciate your recognition of the robust methods we employed, such as the Cox proportional hazards regression, and your constructive feedback on the interpretation of the nonlinear relationships and the use of multiple imputations for handling missing data.
Interpretation of the non-linear relationship
We used Cox proportional hazards regression with cubic spline functions and smooth curve fitting to explore the nonlinear relationship between PP and Pre-DM. We first utilized a recursive technique to locate the inflection point if a non-linear relationship was discovered. The recursive algorithm commences with an arbitrary initialization and subsequently undergoes a series of filtering and smoothing steps in order to identify the inflection point accurately. Following this, we construct a two-piece Cox proportional hazards regression model, separately analyzing the data on either side of the inflection point. Ultimately, the study determined the most appropriate model for PP's connection with Pre-DM through log-likelihood ratio analysis.
Multiple imputations
In response to your comment, we have conducted a thorough review of the assumptions for multiple imputation. We have ensured that the assumptions of missing at random (MAR) are reasonable for our dataset, and we have provided a justification for this based on the observed data patterns and the context of the study.
Furthermore, we have included a description of the imputation model used, detailing the variables included and the distributional assumptions made. To further substantiate the integrity of our multiple imputation approach, we conducted a comparative analysis of the baseline characteristics pre- and post-imputation. This comparative exercise revealed a remarkable congruence between the baseline characteristics before and after the application of multiple imputation (Supplemental Table 6), thereby

reinforcing the stability of our dataset and the negligible impact of the imputation on the foundational characteristics of our study sample.
We trust that these methodological enhancements and the supplementary analyses presented will address your concerns and underscore the robustness of our findings, despite the challenges posed by missing data.
We are grateful for the opportunity to fortify the methodological rigor of our work through your valuable feedback.

Subgroup Analyses: The manuscript reports subgroup analyses, but there is a need for a more thorough discussion on how these subgroups were chosen and their relevance to the study's main findings.
Response: Thank you for your thoughtful comments regarding our manuscript, particularly concerning the subgroup analyses. We understand the importance of providing a clear rationale for the selection of subgroups and their significance in relation to the main findings of our study on PP and the risk of prediabetes.
The subgroups chosen for analysis in our study were not arbitrary; they were selected based on a combination of clinical relevance, literature review, and the availability of data within our cohort. These subgroups included smoking status, age, BMI, family history of diabetes, gender, and alcohol consumption status. We believe that these factors are pertinent for several reasons:
1. Smoking Status: Smoking has been associated with vascular inflammation and insulin resistance, which can influence blood pressure and potentially modify the relationship between PP and prediabetes risk.
2. Age: Age is a well-established risk factor for both increased PP and the development of prediabetes. It is crucial to understand if age influences the association between PP and prediabetes risk.
3. BMI: Obesity is a known risk factor for diabetes and can also affect blood pressure. Subgroup analysis by BMI allows us to explore how adiposity may interact with PP in the context of prediabetes risk.
4. Family History of Diabetes: A family history of diabetes is a strong predictor of prediabetes. Analyzing this subgroup helps us to determine if genetic predisposition modifies the relationship between PP and the risk of prediabetes.
5. Gender: There are known differences in cardiovascular risk factors and the development of diabetes between genders. It is, therefore, essential to assess whether the association between PP and prediabetes differs between men and women.
6. Drinking Status: Alcohol intake can influence both blood pressure and glucose metabolism. We included this variable to investigate whether alcohol consumption affects the association between PP and prediabetes risk.
Prior to conducting the subgroup analyses, we performed interaction term analyses to ensure that the observed effects within subgroups were not due to chance and to assess the potential modification of the effect by these variables. Only subgroups with significant interaction terms were included in the final analyses, ensuring that our findings are robust and that the subgroups are relevant to the study's main findings.
Our analysis revealed that the relationship between PP and the emergence of Pre-DM was more pronounced in never-smokers, ever-smokers, females, and individuals with BMI< 25 kg/m2. In contrast, this association appeared attenuated in males, current smokers, and individuals with BMI≥25 kg/m2. Prior research has consistently identified obesity, smoking, and male as contributors to insulin resistance, which is a precursor to Pre-DM. We postulated that the attenuated association observed in these subgroups may be attributable to the overriding influence of these risk factors on the pathogenesis of Pre-DM. The direct impact of PP on prediabetes risk may be somewhat eclipsed by the more substantial effects of obesity, active smoking, and the male sex on insulin resistance and subsequent Pre-DM development. The revisions are marked in red.

We hope that these clarifications address your concerns and enhance the manuscript's contribution to the field. We are grateful for the chance to refine our work and look forward to any further suggestions you may have.

Generalizability: The study is based on a Chinese population, and while it offers valuable insights, the findings might not be directly generalizable to other populations due to genetic, lifestyle, and environmental differences.
Response: Thank you for your thoughtful commentary on the generalizability of our study's findings. We concur that the external validity of research findings is a critical aspect, especially when considering the influence of genetic, lifestyle, and environmental factors that can vary significantly across different populations.
Our study, which focuses on the association between PP and the risk of prediabetes in a Chinese population, indeed provides insights that are immediately relevant to this demographic. We recognize that the unique genetic makeup, dietary habits, and lifestyle practices inherent to the Chinese population may limit the direct applicability of our results to other ethnic or geographical groups.
In our manuscript, we have included a more detailed discussion of the potential limitations regarding generalizability. In the future, we will explore the relationship between PP and prediabetes risk in diverse populations. Comparative studies across different ethnic backgrounds could provide a more comprehensive understanding of the interplay between PP and glucose metabolism and could help to identify universal as well as population-specific risk factors.
We appreciate your attention to this matter and hope that our revisions have satisfactorily addressed your concerns.

Limitations: The study acknowledges some limitations, like the lack of information on atherosclerosis, antihypertensive medications, and the presence of hypertension. It also doesn't account for changes in blood pressure over time. These factors could significantly impact the study outcomes and should be considered when interpreting the results.
Response: Thank you very much for your input. We couldn't agree more with your comments. We strongly agree that atherosclerosis, antihypertensive medications, the presence of hypertension or changes in blood pressure over time may influence PP and prediabetes. When we explore the relationship between PP and prediabetes, we should adjust atherosclerosis, antihypertensive medications, and the presence of hypertension. In addition, we should utilize a GAM model to explore the impact of changes in PP on Pre-DM risk. As we were secondary analyzing, the data were downloaded from the DATADRYAD database (www.datadryad.org). The raw data did not provide information about atherosclerosis, antihypertensive medications, the presence of hypertension or changes in blood pressure over time. In the future, we will consider designing our own study and documenting more information, including atherosclerosis, antihypertensive medications, the presence of hypertension and changes in blood pressure over time. We've added this limitation in the Discussion section and marked it up in red.
In addition, to address this, we also explored the possibility of unmeasured confounders between PP and prediabetes risk by calculating the E-value. Unknown or unmeasured variables may have little impact on the association between PP and prediabetes, as the E-value (1.21) is greater than the relative risk of PP and unmeasured confounders (1.05). Therefore, we tend to think there is an independent relationship between PP and prediabetes. Because we are observational factors, we cannot get a causal relationship between PP and prediabetes. In addition, as you said, other factors (atherosclerosis, antihypertensive medications, the presence of hypertension or changes in blood pressure over time) have an impact on the relationship between PP and prediabetes. The causal association of PP with prediabetes will be explored in the future by designing RCT studies or Mendelian randomization studies.

Potential for Confounding Factors: While the study controls for various confounders, the potential for residual confounding factors remains. The study could benefit from a more detailed discussion on how these factors were handled and their possible impact on the study's findings.
Response: Thank you very much for your input. We couldn't agree more with your comments. As you said, as with all observational studies, there may be uncontrolled or unmeasured confounding factors, such as diet, exercise, atherosclerosis, the use of antihypertensive medications, and the presence of hypertension, despite controlling for known potential confounders like BMI, TC, LDL-C, AST, ALT, Scr, BUN, and FPG. To address this, we also explored the possibility of unmeasured confounders between PP and prediabetes risk by calculating the E-value. Unknown or unmeasured variables may have little impact on the association between PP and prediabetes, as the E-value (1.21) is greater than the relative risk of PP and unmeasured confounders (1.05). Therefore, we tend to think there is an independent relationship between PP and prediabetes. Because we are observational factors, we cannot get a causal relationship between PP and prediabetes. In addition, as you said, the potential for residual confounding factors have an impact on the relationship between PP and prediabetes. The causal association of PP with prediabetes will be explored in the future by designing RCT studies or Mendelian randomization studies. We added this limitation in the Discussion section and marked it up in red. Thanks again your excellent comment.

In summary, while the study offers valuable insights into the relationship between pulse pressure and prediabetes risk, certain aspects like data source limitations, measurement methods, and generalizability need careful consideration. Further studies are recommended to build upon these findings and address the identified gaps.
Response: Thank you for summarizing the strengths and areas for improvement in our study on the relationship between PP and the risk of prediabetes. We appreciate your recognition of the value our research adds to the current understanding of this association, and we fully agree with your recommendations for careful consideration of data source limitations, measurement methods, and generalizability.
In our revised manuscript, we have included a more detailed discussion of the data source limitations. We acknowledge that our findings are based on a specific cohort, which may have inherent characteristics that influence the observed relationship. We have also elaborated on the measurement methods used for assessing PP and prediabetes, noting any potential sources of error or bias that could affect the accuracy of our results.
Regarding generalizability, as previously discussed, we have now addressed the need for caution when extrapolating our findings to other populations, given the unique genetic and environmental factors of the Chinese population from which our sample was drawn.
Furthermore, we have explicitly stated the need for additional research to confirm and extend our findings. Prospective studies with more diverse populations and longitudinal designs are indeed necessary to validate the relationship between PP and prediabetes risk. Such studies should include comprehensive data on atherosclerosis, antihypertensive medication use, and hypertension status to better understand the complex interplay of these factors with pulse pressure and glucose metabolism. In the future, we will consider designing our own study and documenting more information, such as diet, exercise, atherosclerosis, antihypertensive medications, the presence of hypertension and changes in blood pressure over time, and then utilizing a GAM model to explore the impact of changes in PP on Pre-DM risk.
By addressing these gaps, we can enhance the reliability of the evidence base and inform more effective strategies for the prevention and management of prediabetes and its associated cardiovascular risks.
We are grateful for the opportunity to improve our manuscript and for your constructive feedback, which has undoubtedly strengthened the quality and impact of our study.

We tried our best to improve the manuscript and made some changes in the manuscript. These changes will not influence the content and framework of the paper.

We appreciate the Editors' and Reviewers' warm work earnestly and hope that the correction will meet with approval.
Once again, thank you very much for your comments and suggestions.

VERSION 2 – REVIEW

REVIEWER	Fukuda, Yoshiharu Yamaguchi University, Community Health and Medicine
REVIEW RETURNED	25-Feb-2024

GENERAL COMMENTS	The manuscript has been revised according to my comment. Finally, the authors should be careful about the number of digits after the decimal point in tables, since the number was too much.

REVIEWER	Ali, Hatem University Hospitals Birmingham NHS Foundation Trust
REVIEW RETURNED	26-Feb-2024

GENERAL COMMENTS	The study "Nonlinear relationship between pulse pressure and the risk of prediabetes: a secondary retrospective Chinese cohort study" provides valuable insights into cardiovascular and metabolic health. It aims to elucidate the complex relationship between pulse pressure and the incidence of prediabetes, a significant concern given the rising prevalence of both conditions globally. Objective and Significance The objective is well-defined and addresses an important gap in existing literature. Exploring a nonlinear relationship is particularly noteworthy, potentially offering novel insights that could influence risk management strategies for prediabetes and associated cardiovascular risks. Design and Methodology The manuscript employs a secondary retrospective cohort design, utilizing a large initial cohort of 685,277 individuals from the DATADRYAD database, which is methodologically sound for the research question. However, the exclusion of over 500,000 individuals to a final cohort of 182,672 subjects raises critical questions regarding selection bias and the impact on generalizability. Statistical Analysis The use of Cox proportional hazards regression models is appropriate, and the manuscript indeed includes confidence intervals and p-values, enhancing the clarity and reliability of the statistical analysis presented. These measures provide the necessary statistical rigor to support the study's findings. Results The identification of a nonlinear relationship between pulse pressure and prediabetes risk is a significant finding. The detailed presentation of hazard ratios, confidence intervals, and p-values for various models underscores the robustness of the study's results.

	Discussion and Conclusions The discussion provides a comprehensive context for the study's findings, comparing them with existing literature and suggesting plausible biological mechanisms. However, it could be strengthened by addressing the potential impact of the extensive exclusion criteria on the study's applicability and by discussing the limitations more critically. Strengths and Limitations The manuscript's transparency about its methodology and the detailed reporting of statistical analyses are notable strengths. Nevertheless, the extensive exclusion of participants and the retrospective nature of the study design are significant limitations that could affect the generalizability of the findings. A more thorough discussion on these aspects would provide readers with a more nuanced understanding of the study's applicability. Clinical Relevance and Generalizability The study offers important insights that could inform clinical practice, particularly in screening and risk management strategies for prediabetes. However, the selective cohort resulting from the extensive exclusion criteria may limit the generalizability of these findings to broader populations. Overall Quality The manuscript is well-written, with a logical structure that facilitates understanding of the complex analyses and their implications. Nonetheless, enhancing the discussion on methodological and analytical limitations and more critically appraising the impact of participant exclusion could further strengthen the manuscript. In conclusion, while the study provides valuable contributions to understanding the relationship between pulse pressure and prediabetes risk, considerations regarding the extensive exclusion criteria and the retrospective design's impact on generalizability should be carefully weighed. Future research could benefit from broader inclusion criteria to enhance the applicability of findings across more diverse populations.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

Dr. Yoshiharu Fukuda, Yamaguchi University

Comments to the Author:

The manuscript has been revised according to my comment. Finally, the authors should be careful about the number of digits after the decimal point in tables, since the number was too much.

Response: Thank you for your continued guidance and constructive feedback on our manuscript. We are grateful for the opportunity to refine our work further and appreciate your attention to detail regarding the presentation of our data. We recognize that too many decimal places can affect the readability and clarity of the data. Therefore, in response to your suggestion, we have limited the

number of decimal places to three for most data points, which we believe strikes the right balance between accuracy and clarity. Thank you again for your suggestion. And we marked it up in red.

Reviewer: 2

Dr. Hatem Ali, University Hospitals Birmingham NHS Foundation Trust

Comments to the Author:

The study "Nonlinear relationship between pulse pressure and the risk of prediabetes: a secondary retrospective Chinese cohort study" provides valuable insights into cardiovascular and metabolic health. It aims to elucidate the complex relationship between pulse pressure and the incidence of prediabetes, a significant concern given the rising prevalence of both conditions globally.

Objective and Significance

The objective is well-defined and addresses an important gap in existing literature. Exploring a nonlinear relationship is particularly noteworthy, potentially offering novel insights that could influence risk management strategies for prediabetes and associated cardiovascular risks.

Response: We sincerely appreciate your thoughtful and encouraging comments regarding the objective and significance of our study. Your recognition of the well-defined objective and its importance in addressing a gap in the existing literature is greatly valued. We look forward to the possibility of our study making a meaningful contribution to the field, and we are grateful for the opportunity to advance the discussion on this important topic. Thanks again for your good comments.

Design and Methodology

The manuscript employs a secondary retrospective cohort design, utilizing a large initial cohort of 685,277 individuals from the DATADRYAD database, which is methodologically sound for the research question. However, the exclusion of over 500,000 individuals to a final cohort of 182,672 subjects raises critical questions regarding selection bias and the impact on generalizability.

Response: Thank you for your insightful observations and for highlighting the critical issue of selection bias and its potential impact on the generalizability of our findings.

In the original study, Chen et al. gauged the unity between the cohort that was incorporated into the study (211,833 individuals) and the segment that was not included (473,444 individuals). The findings from Chen et al. indicated that the demographic attributes such as age (42.1 years for included participants versus 41.9 years for excluded participants), body mass index (BMI) (23.2 kg/m² for included versus 23.3 kg/m² for excluded), and gender distribution (54.8% male for included versus 52.1% male for excluded) were remarkably similar across both groups. This suggests that the exclusion criteria may exert a small impact on the sample's representativeness.

Within our study, we further excluded 29,161 participants, predominantly those with prediabetes, culminating in a final sample size of 182,672 individuals. A comparative analysis of the baseline characteristics between the included participants and those excluded revealed that the latter group was, on average, older (46.8 years versus 40.8 years), had a higher BMI (24.3 kg/m² versus 23.0 kg/m²), and consisted of a greater proportion of males (62.5% versus 53.1%). Literature on the subject indicates that these characteristics are consistent with the demographic profile of a

prediabetic population. Given that the majority of the excluded 29,161 participants were prediabetic, it is reasonable that they exhibited these demographic trends.

Unfortunately, the "DATADRYAD" database, from which our data was sourced, did not offer information on the excluded cohorts. As far as you are concerned, excluding over 500,000 individuals from a final cohort of 182,672 subjects could have selection bias and implications for generalisability. Moving forward, we will endeavor to corroborate our findings through research on a broader population spectrum. In our revised manuscript, we have elaborated upon the Discussion section to reflect upon the limitations imposed by our exclusion criteria. Once again, we express our heartfelt thanks for your invaluable critique.

Statistical Analysis

The use of Cox proportional hazards regression models is appropriate, and the manuscript indeed includes confidence intervals and p-values, enhancing the clarity and reliability of the statistical analysis presented. These measures provide the necessary statistical rigor to support the study's findings.

Response: We deeply appreciate your positive evaluation of the statistical analysis section of our manuscript. Your acknowledgment of these aspects as enhancing the clarity and reliability of our statistical analysis is highly valued. We look forward to the possibility of our study contributing valuable knowledge to prediabetes. Thank you once again for your constructive and encouraging feedback.

Results

The identification of a nonlinear relationship between pulse pressure and prediabetes risk is a significant finding. The detailed presentation of hazard ratios, confidence intervals, and p-values for various models underscores the robustness of the study's results.

Response: We are immensely grateful for your positive remarks regarding the Results section of our manuscript. The finding of a nonlinear relationship between pulse pressure and prediabetes risk is central to our study's contribution to the field. We believe highlighting the nonlinear relationship is crucial for developing more effective prevention and management strategies for at-risk individuals. We hope our work will inspire further investigation into the complex interplay between cardiovascular risk factors and prediabetes, ultimately leading to improved outcomes for those at risk. Thank you once again for your constructive and encouraging feedback.

Discussion and Conclusions

The discussion provides a comprehensive context for the study's findings, comparing them with existing literature and suggesting plausible biological mechanisms. However, it could be strengthened by addressing the potential impact of the extensive exclusion criteria on the study's applicability and by discussing the limitations more critically.

Response: Thank you for your insightful comments and the opportunity to address the concerns. It is important to clarify that our secondary analysis was constrained by the data provided in the original study, which did not provide data on the excluded populations.

Thank you for your insightful comments and the opportunity to address the concerns.

In the original study, Chen et al. gauged the unity between the cohort incorporated into the study (211,833 individuals) and the segment not included (473,444 individuals). The findings from Chen et al. indicated that the demographic attributes such as age (42.1 years for included participants versus 41.9 years for excluded participants), body mass index (BMI) (23.2 kg/m² for included versus 23.3 kg/m² for excluded), and gender distribution (54.8% male for included versus 52.1% male for excluded) were remarkably similar across both groups. This suggests that the exclusion criteria may exert a small impact on the sample's representativeness.

Within our study, we further excluded 29,161 participants, predominantly those with prediabetes, culminating in a final sample size of 182,672 individuals. A comparative analysis of the baseline characteristics between the included participants and those excluded revealed that the latter group was, on average, older (46.8 years versus 40.8 years), had a higher BMI (24.3 kg/m² versus 23.0 kg/m²), and consisted of a greater proportion of males (62.5% versus 53.1%). Literature on the subject indicates that these characteristics are consistent with the demographic profile of a prediabetic population. Given that the majority of the excluded 29,161 participants were prediabetic, it is reasonable that they exhibited these demographic trends.

Unfortunately, the "DATADRYAD" database, from which our data was sourced, did not offer information on the excluded cohorts. As you are concerned, excluding over 500,000 individuals from a final cohort of 182,672 subjects could have selection bias and implications for generalisability. Moving forward, we will endeavor to corroborate our findings through research on a broader population spectrum. In our revised manuscript, we have elaborated upon the Discussion section to reflect upon the limitations imposed by our exclusion criteria. Once again, we express our heartfelt thanks for your invaluable critique.

Strengths and Limitations

The manuscript's transparency about its methodology and the detailed reporting of statistical analyses are notable strengths. Nevertheless, the extensive exclusion of participants and the retrospective nature of the study design are significant limitations that could affect the generalizability of the findings. A more thorough discussion on these aspects would provide readers with a more nuanced understanding of the study's applicability.

Response: Thank you for your thoughtful and constructive feedback regarding our manuscript. We appreciate the opportunity to clarify and further discuss the strengths and limitations of our study, particularly in relation to the exclusion of participants and the retrospective nature of our study design.

In the original study, Chen et al. gauged the unity between the cohort that was incorporated into the study (211,833 individuals) and the segment that was not included (473,444 individuals). The findings from Chen et al. indicated that the demographic attributes such as age (42.1 years for included participants versus 41.9 years for excluded participants), body mass index (BMI) (23.2 kg/m² for included versus 23.3 kg/m² for excluded), and gender distribution (54.8% male for included versus 52.1% male for excluded) were remarkably similar across both groups. This suggests that the exclusion criteria may exert a small impact on the sample's representativeness.

Our study excluded 29,161 participants, predominantly those with prediabetes, culminating in a final sample size of 182,672 individuals. A comparative analysis of the baseline characteristics between the included participants and those excluded revealed that the latter group was, on average, older (46.8 years versus 40.8 years), had a higher BMI (24.3 kg/m² versus 23.0 kg/m²), and consisted of a greater proportion of males (62.5% versus 53.1%). Literature on the subject indicates that these characteristics are consistent with the demographic profile of a prediabetic population. Given that the

majority of the excluded 29,161 participants were prediabetic, it is reasonable that they exhibited these demographic trends.

Unfortunately, the "DATADRYAD" database, from which our data was sourced, did not offer information on the excluded cohorts. As you are concerned, excluding over 500,000 individuals from a final cohort of 182,672 subjects could have selection bias and implications for generalisability. Moving forward, we will endeavor to corroborate our findings through research on a broader population spectrum.

In addition, our study is a retrospective study, which is a limiting factor as it may introduce some biases that may affect the study results. We attempted to reduce these biases through rigorous statistical analyses and carefully interpreted our findings with these limitations. In the future, we will conduct prospective studies in a wide range of populations to help us validate this finding.

Thank you once again for your insightful comments. We are committed to improving our manuscript and contributing positively to the field of endocrinology.

Clinical Relevance and Generalizability

The study offers important insights that could inform clinical practice, particularly in screening and risk management strategies for prediabetes. However, the selective cohort resulting from the extensive exclusion criteria may limit the generalizability of these findings to broader populations.

Response: Thank you very much for your suggestion. As you are concerned, the selective cohort resulting from the extensive exclusion criteria may limit the generalizability of these findings to broader populations. In the future, we will conduct prospective studies in a wide range of populations to help us validate this finding. Thank you once again for your good suggestion.

Overall Quality

The manuscript is well-written, with a logical structure that facilitates understanding of the complex analyses and their implications. Nonetheless, enhancing the discussion on methodological and analytical limitations and more critically appraising the impact of participant exclusion could further strengthen the manuscript.

Response: Thank you very much for your insightful comments and the positive feedback on the structure and clarity of our manuscript. We appreciate your suggestion to enhance the discussion on methodological and analytical limitations, particularly regarding the impact of participant exclusion on our study's findings. In response to your valuable suggestion, we have revised our manuscript to include a more detailed discussion. We now explicitly acknowledge the limitation that the original studies did not provide data on excluded participants, which prevents us from assessing the potential biases introduced by such exclusions. In the future, we will conduct prospective studies in a wide range of populations to help us validate this finding. Revisions are marked in red. Thank you once again for your good suggestion.

In conclusion, while the study provides valuable contributions to understanding the relationship between pulse pressure and prediabetes risk, considerations regarding the extensive exclusion criteria and the retrospective design's impact on generalizability should be carefully weighed. Future

research could benefit from broader inclusion criteria to enhance the applicability of findings across more diverse populations.

Response: Thank you very much for your excellent comments. As far as you are concerned, broad exclusion criteria and retrospective designs can impact generalisability. In the future, we will conduct our prospective study and use broader inclusion criteria to improve the applicability of the findings to a more diverse population.

We tried our best to improve the manuscript and made some changes in the manuscript. These changes will not influence the content and framework of the paper.

We appreciate the Editors' and Reviewers’ warm work earnestly and hope the correction will be approved.

Once again, thank you very much for your comments and suggestions.