nature portfolio

Peer Review File

Disparities in high fasting plasma glucose-related cardiovascular disease burden in China

REVIEWER COMMENTS

Reviewer #1 (Remarks to the Author):

This study describes pooling of mean FPG data from three survey series conducted across Chinese provinces between 2010 and 2018.

Data on mean FPG were pooled in order to derive population attributable fractions of IHD and stroke deaths due to high FPG.

The methods of estimating mean FPG are reasonably well described in supplementary material, the bulk of methods to translate these exposure values into attributable fractions of CVD deaths is absent or poorly described.

1. for deaths, all I see mentioned is three sources of information on causes of death but no information on deriving population cause of death estimates from these incomplete data collection systems, nor any mention of what was done with ambiguous codes which in GBD are called 'garbage codes'

2. the Theoretical Minimum Risk Exposure Level was taken from GBD

3. I see no mention of how distributions of FPG were defined from the information on pooled mean FPG. To estimate PAFs, you would need to specify the full distribution.

4. Relative risks of IHD and stroke deaths look to have been taken from GBD2019 study without acknowledgement

Despite liberally adopting GBD2019 methods, you do not make any comparisons to GBD data.

Reviewer #2 (Remarks to the Author):

Cao at al use three poulation-based surveys to from Mainland China to estimate the burden of CVD attributable to high FPG. The authors used Bayesian spatial-temporal models to estimate the burden of CVD attributable to high FPG by age, sex, region and demographics. The statistical methods (the Bayedian model, posterior approximations, Years of life lost calculations, and the alternative decomposers considered) used by the authors are sound and clearly described in the methods section and in the supplementary material.

Reviewer #3 (Remarks to the Author):

The study estimated the cardiovascular disease (CVD) burden attributable to high fasting plasma glucose (FPG) in China from 2010 to 2018, analyzing data by age, sex, region, and socio-demographic index from approximately 800,000 individuals aged 25 and older, using three large population-based surveys. The authors found that CVD mortality rate attributable to high FPG increased by 3.99% from 2010 to 2018. Exposure to high FPG and population aging were the primary drivers of increases in FPG-related deaths due to CVD. The study is interesting, with solid data analyses. This reviewer has several minor comments.

1. Abstract: "The results showed that, in 2018, an estimated total of 512.29 thousand (95% uncertainty interval [UI] 488.60 to 538.65) adults aged 25 or older were attributable to high FPG in China." (Line 40-43). The authors should add "CVD-related deaths" to clarify the impact of high FPG.

2. Abstract: The authors concluded that “Nationally, compared to 2010, exposure to high FPG and population aging in 2018 were the primary drivers of 51 increased FPG-related deaths due to CVD” (Line 40-43). There was no result provided to support the impact of population aging.

3. The definition of high FPG should be substantiated with appropriate references and rationale, especially since the stated definition greater than or equal to 4.8-5.4 mmol/L (Line 66-70) lacks conventional support and seems unusual.

4. Clarification on the rationale behind the 25-year-old cutoff for combined analyses, given the varied age ranges of participants in the included three studies (CCDRFS age ≥18 years, CNNSs 6 years old and above, and CHS aged ≥ 35 years), would enhance understanding.

5. The determination of CVD should be described more specifically. Is it based on the ICD code or reported by the hospital? Why is heart failure not included for CVD?

6. Regarding the calculation of blood glucose levels, is the age-standardized FPG level adjusted for age as a covariate in the temporal-spatial hierarchical Bayesian model? And, age factors were not adjusted for when calculating blood glucose levels by age group.

7. “Moreover, we observed that the gap in CVD mortality attributable to high FPG between men and women had narrowed after the age of 50 in 2018, and even among those over 80, women have higher CVD mortality rate than men (Supplementary Table S5-S6)." (Line 112-115) Regarding this statement: It is difficult to discern the trend clearly through the tables. The reviewer suggests that the authors supplement the data by plotting the changes in CVD mortality counts and rates by age group for different sexes in 2018 using line graphs. This would provide a more intuitive representation.

8. "…..with elderly individuals (≥ 80 years old) accounting for 55% in 2010 and 44% in 2018 of CVD deaths attributable to high FPG (Supplementary Fig S2-S3)." (Line 121-123). Here, there might be a data error. According to Fig S2 and Fig S3, it should be 55% in 2018, and 44% in 2010. Your statement does not align with the data. Please confirm.

9. "Of note, for total CVD and its subtypes, men had a higher mortality burden than women in both 2010 and 2018 (Table 2)." (Line 131-132). In Table 2, there seems to be an error in the data for the ischemic stroke burden. The values for the Total row and the Female row are exactly the same, which is clearly not reasonable. Please address this discrepancy.

10. The Table legends for Tables S8-S11 are not clearly expressed and do not include the word 'death'.

Response Letter

Response to the reviewers' comments

Response to the 1st Reviewer

This study describes pooling of mean FPG data from three survey series conducted across Chinese provinces between 2010 and 2018.

Data on mean FPG were pooled in order to derive population attributable fractions of IHD and stroke deaths due to high FPG.

The methods of estimating mean FPG are reasonably well described in supplementary material, the bulk of methods to translate these exposure values into attributable fractions of CVD deaths is absent or poorly described.

Question 1:

For deaths, all I see mentioned is three sources of information on causes of death but no information on deriving population cause of death estimates from these incomplete data collection systems, nor any mention of what was done with ambiguous codes which in GBD are called 'garbage codes'.

Response:

Thanks for this helpful comment. As suggested, we have added more information on population cause of death estimates, and how 'garbage codes' was handled in method section of the revised Supplementary materials (Section 2, Pages 5-7)

Pages 5-7, Supplementary Section 2 is added:

Section 1. CVD mortality data

(1) the National Mortality Surveillance System (NMSS)

Cardiovascular disease (CVD) mortality data were derived from the National Mortality Surveillance System (NMSS), a system that collects death records from surveillance locations to understand death patterns in China. The National Mortality Surveillance System covers 605 surveillance points in 31 provincial-level administrative divisions in mainland China, accounting for 24.3% of the country's population with national and provincial representativeness.[1] Strict quality control measures were implemented

regularly in the National Mortality Surveillance System for both completeness and accuracy of cause of death identification by practitioners in the health facilities.

(2) Under-reporting survey

Underreporting field survey was conducted since 1990s for every three years periodically to ensure the utmost integrity and accuracy of cause-of-death data. The details of under-reporting field surveys have been reported previously.[2,3] Briefly, within each surveillance site, we designated one township (in rural areas) or street (in urban areas) with a crude death rate and economic level approximating the average, along with a population size at a moderate level, as potential survey locations. All residents within the chosen township/street were included and surveyed for demographic details, death-related information such as cause of death (COD), the highest level of hospital where the illness was diagnosed, and diagnostic criteria. To identify missed deaths, we initially cross-referenced death records between the field survey system and the routine online death cause surveillance system using an automated computer algorithm for verification. Any discrepancies were subject to further manual verification at the surveillance site level.

Missed death cases were subsequently identified following this comprehensive manual review process. Then, in this study, under-reporting rates (URR) annually were calculated for each age-sex stratum from 2010 to 2018 based on capture-mark-recapture method. Finally, we obtained underreporting-adjusted all-cause mortality rate by age-sex for all points by dividing reported number of deaths by (1-URR).

(3) Garbage code redistribution and CVD mortality estimation

In this study, garbage codes include those 1) not the primary COD, 2) intermediate COD, and 3) the actual COD is unknown. We grouped garbage code and assigned a target code for each group according to the characteristics of disease and rules for inferring cause of death. We redistributed garbage codes based on the proportion of the target

code, known coefficients from previous studies, or coefficients from the National Mortality Surveillance System.[4]

The proportion of cause of death for each outcome by province-age-sex was calculated by the number of CVD cases after redistribution divided by the total number of deaths. Mortality rate of CVD by each year, province, sex, and age group was then calculated by multiplying all-cause mortality rate by proportion of CVD in all deaths.

[References]

1 Wang, Y. et al. Under-5 mortality in 2851 Chinese counties, 1996-2012: a subnational assessment of achieving MDG 4 goals in China. *Lancet* **387**, 273-283 (2016).

2 Guo, K. et al. Propensity score weighting for addressing under-reporting in mortality surveillance: a proof-of-concept study using the nationally representative mortality data in China. *Popul Health Metr* **13**, 16 (2015).

3 Wang, W. et al. Mortality and years of life lost of cardiovascular diseases in China, 2005-2020: Empirical evidence from national mortality surveillance system. *Int J Cardiol* **340**, 105-112 (2021).

4 Qi, J. et al. National and subnational trends in cancer burden in China, 2005-20: an analysis of national mortality surveillance data. *Lancet Public Health* **8**, e943-e955 (2023).

Question2:

The Theoretical Minimum Risk Exposure Level was taken from GBD

Response:

We thank the reviewer's suggestion. We have refined the description of the TMREL as "…Consistent with the GBD 2019 study[1], TMREL is a level of FPG that minimises risk at the population level and captures the maximum attributable burden (4.8-5.4 mmol/L" in the revised manuscript (Lines 382-384, Page 15).

Additionally, we supplemented a section on theoretical minimum-risk exposure level in the revised Supplementary materials (Section 6, Pages 10-11). To make it clear to the readers, the changes we have made are listed as follows:

Section 6. The theoretical minimum-risk exposure level

The TMREL was established for high FPG as the lowest level of exposure within which its relationship with a disease outcome was not supported by the available evidence. In our study, the TMREL of high FPG was defined as a uniform distribution between 4.8-5.4 mmol/L across all age groups based on the GBD 2019 study.[1] Specifically, TMREL was calculated by taking the person-year weighted average of the levels of FPG that were associated with the lowest risk of mortality in the pooled analyses of prospective cohort studies.[2] Furthermore, further investigations based on cohorts or pooled cohort studies are needed to determine whether we need to consider the difference of the TMREL for FPG across different age groups.

[References]:

1. Murray, C. J. L. et al. Global burden of 87 risk factors in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. The *Lancet* **396**, 1223-1249 (2020).
2. Singh, G. M. et al. The age-specific quantitative effects of metabolic risk factors on cardiovascular diseases and diabetes: a pooled analysis. *PLoS One* 8, e65174 (2013).

Question3:

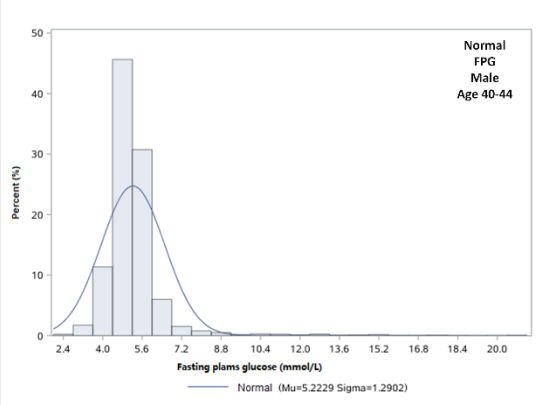
I see no mention of how distributions of FPG were defined from the information on pooled mean FPG. To estimate PAFs, you would need to specify the full distribution.

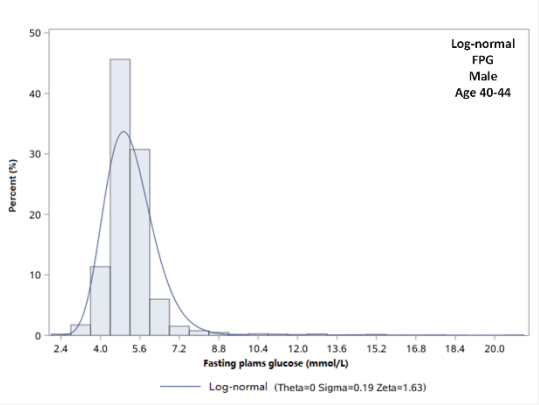
Response:

We are very grateful to the reviewer for raising this point. As suggested, we have supplemented the definition of FPG distribution in the revised Supplementary materials (Section 8, Page 11-12).

Section 8. Distribution of FPG in the population

We evaluated the fit of FPG exposure data from CHS to different distributions including normal and log-normal, and we found that normal fits the data best. Thus, the mean FPG, with a normal distribution, was used to calculate PAFs. Below is an example of the data and fitted probably distribution for male, age 40-44.





Question4:

Relative risks of IHD and stroke deaths look to have been taken from GBD2019 study without acknowledgement.

Response:

Thanks so much. As suggested, we have supplemented the acknowledgement to GBD 2019 in the Acknowledgement section of the revised manuscript (Lines 579-580, Page 23).

Question5:

Despite liberally adopting GBD2019 methods, you do not make any comparisons to GBD data.

Response:

We thank the reviewer for this constructive comment. We have added the comparisons between the findings in this current study and GBD data in the Discussion section of the revised manuscript (Lines 221-237, and 239-242, Page 10).

To make it clear, the changes we have made are listed as follows:

Manuscript Lines 221-237, and 239-242, Page 10:

Additionally, to our best knowledge, only one study deriving data from GBD 2019 have assessed the CVD burden (including ischemic heart disease，stroke，and peripheral arterial disease) attributable to high FPG in China from 1990 to 2019[1], suggesting that approximately 700.34 million CVD deaths were caused by high FPG in China in 2019, respectively. We observed that the estimated burden of CVD mortality attributable to high FPG in our study was slightly lower than the findings reported in GBD 2019. However, discrepancies in the definition of CVD and the research time window between our study and GBD 2019 render direct comparison challenging, hindering alignment of the findings on a comparable scale. Nevertheless, our study represented

the latest and most comprehensive information on CVD burden attributable to high FPG. Leveraging large-scale nationally representative cross-sectional surveys, this current research established a robust foundation for the precise assessment of FPG levels, facilitating comparability across China and its provinces from 2010 to 2018. The findings offered a comprehensive depiction of CVD burden attributable to high FPG across regions, age groups, and sex, thereby contributing to systematic and reliable evidence aimed at estimating the FPG-attributable burden for CVD and its types in China. (Lines 221-237, Page 10)

"…Previous study based on the global GBD 2019 showed that the burden of ischaemic heart disease attributable to high FPG was highest in the high-middle SDI[2], which was partially consistent with our findings." (Lines 239-242, Page 10)

[References]:

1. Liang Dong, Y. C., Lin Xiaoru, Zhao Yang, Ouyang Jiang, Lin Xiuquan. Burden of Cardiovascular Diseases Attributable to Diabetes among Chinese Adults from 1990 to 2019. *Chinese General Practice* **27**, 1380-1386, 1394 (2024).
2. Wang, W. et al. Global Burden of Disease Study 2019 suggests that metabolic risk factors are the leading drivers of the burden of ischemic heart disease. *Cell Metab* **33**, 1943-1956 e1942 (2021).

Response to the 2nd Reviewer

Cao at al use three poulation-based surveys to from Mainland China to estimate the burden of CVD attributable to high FPG. The authors used Bayesian spatial-temporal models to estimate the burden of CVD attributable to high FPG by age, sex, region and demographics. The statistical methods (the Bayedian model, posterior approximations, Years of life lost calculations, and the alternative decomposers considered) used by the authors are sound and clearly described in the methods section and in the supplementary material.

Response:

We appreciate the positive comments from the reviewer.

Response to the 3rd Reviewer

The study estimated the cardiovascular disease (CVD) burden attributable to high fasting plasma glucose (FPG) in China from 2010 to 2018, analyzing data by age, sex, region, and socio-demographic index from approximately 800,000 individuals aged 25 and older, using three large population-based surveys. The authors found that CVD mortality rate attributable to high FPG increased by 3.99% from 2010 to 2018. Exposure to high FPG and population aging were the primary drivers of increases in FPG-related deaths due to CVD.

The study is interesting, with solid data analyses. This reviewer has several minor comments.

Question 1:

1. Abstract: "The results showed that, in 2018, an estimated total of 512.29 thousand (95% uncertainty interval [UI] 488.60 to 538.65) adults aged 25 or older were attributable to high FPG in China." (Line 40-43). The authors should add "CVD-related deaths" to clarify the impact of high FPG.

Response:

We are very grateful to the reviewer for raising this point. We have modified this sentence into "In 2018, an estimated total of 512.29 thousand (95% uncertainty interval [UI] 488.60 to 538.65) CVD-related deaths were attributable to high FPG in China." in the abstract section of the revised manuscript (Lines 40-42, Page 3).

Question 2:

2. Abstract: The authors concluded that "Nationally, compared to 2010, exposure to high FPG and population aging in 2018 were the primary drivers of 51 increased FPG-related deaths due to CVD" (Line 40-43). There was no result provided to support the impact of population aging.

Response:

Thanks. In this study, decomposition analysis was used to quantify the drivers of change in the death numbers for CVD caused by high FPG based on methods developed by Das Gupta.[1] Briefly, we decomposed the change of CVD death attributable to high FGP from 2010 to 2018 into four explanatory components: change in population growth; change in population structure by sex; change in risk exposure to FPG; and change in risk-deleted mortality rates for CVD. The change in the population structure by age from 2010 to 2018 was used to indicate the impact of population aging, which was consistent with previous studies[2,3].

In Figure 3, we found that population aging accounted for approximately 62.7% increases in the number of death due to FPG-related CVD in China from 2010 to 2018.

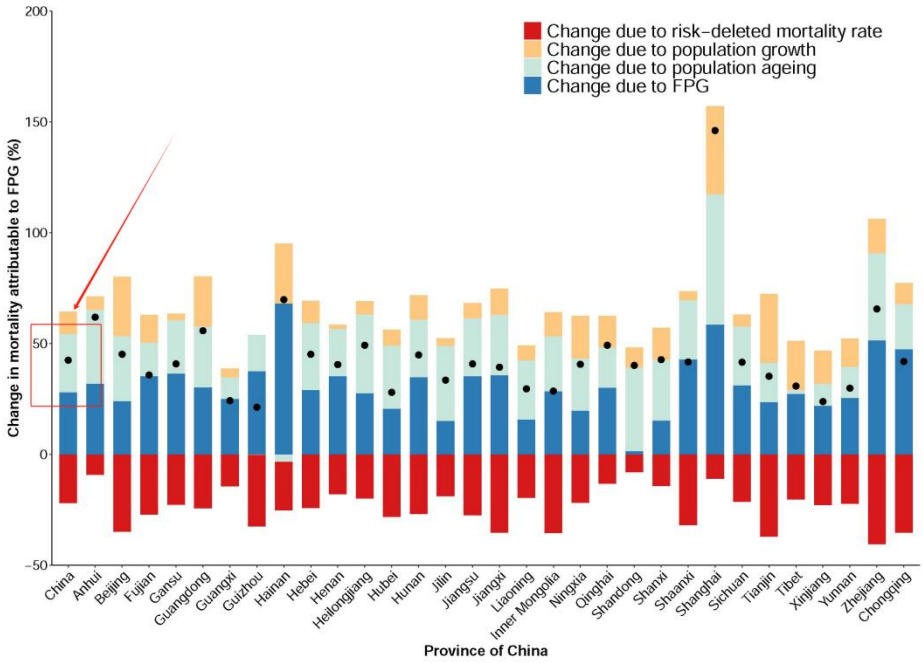


Figure 3. Changes in CVD deaths attributable to FPG from 2010 to 2018 by province in China.

[References]:

1. Das Gupta P. Standardization and decomposition of rates: A user's manual.
2. Collaborators, G. B. D. R. F. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet* **388**, 1659-1724 (2016).
3. Basu, S. et al. Population ageing and mortality during 1990–2017: A global decomposition analysis. *PLOS Medicine* **17** (2020).

Question 3:

3. The definition of high FPG should be substantiated with appropriate references and rationale, especially since the stated definition greater than or equal to 4.8-5.4 mmol/L (Line 66-70) lacks conventional support and seems unusual.

Response:

We appreciate the reviewer's helpful comments. As suggested, we have supplemented a reference for the definition of high FPG in the revised manuscript (Lines 382-384, Page 15). Additionally, in our study, the TMREL of high FPG was defined as a uniform distribution between 4.8-5.4 mmol/L across all age groups based on the recent study,[1] which is consistent with the GBD 2019 study.[2] we have added more detailed

information on the TMREL in the revised Supplementary materials. (Section 6, Pages 10-11)

Supplementary materials Section 6, Pages 10-11:

Section 6. The theoretical minimum-risk exposure level

The TMREL was established for high FPG as the lowest level of exposure within which its relationship with a disease outcome was not supported by the available evidence. In our study, the TMREL of high FPG was defined as a uniform distribution between 4.8-5.4 mmol/L across all age groups based on the GBD 2019 study.[1] Specifically, TMREL was calculated by taking the person-year weighted average of the levels of FPG that were associated with the lowest risk of mortality in the pooled analyses of prospective cohort studies.[2] Furthermore, further investigations based on cohorts or pooled cohort studies are needed to determine whether we need to consider the difference of the theoretical minimum-risk exposure level for FPG across different age groups and what impact this will have on the estimation of health burden.

[References]:

1. Murray, C. J. L. et al. Global burden of 87 risk factors in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. The *Lancet* **396**, 1223-1249 (2020).
2. Singh, G. M. et al. The age-specific quantitative effects of metabolic risk factors on cardiovascular diseases and diabetes: a pooled analysis. *PLoS One* **8**, e65174 (2013).

Question 4:

4. Clarification on the rationale behind the 25-year-old cutoff for combined analyses, given the varied age ranges of participants in the included three studies (CCDRFS age ≥18 years, CNNSs 6 years old and above, and CHS aged ≥ 35 years), would enhance understanding.

Response:

We highly appreciate your helpful comment. First, we obtained original mean FPG levels by age groups, sex, and regions from CCDRFS, CNNSs, and CHS, and the age ranges of these three surveys involved people with fasting glucose data were 18+, 6+, and 35+, respectively, which were the age range in which the three projects were originally designed. However, in this study, we used high FPG as a risk factor to calculate the CVD burden attributable to high FPG (only available for adults aged 25 years or older), which was also consistent with previous studies[1,2]. Therefore, we only used participants aged 25 years or older and a temporal-spatial hierarchical Bayesian model was applied to comprehensively estimate mean FPG levels by age group and sex for 31 provinces in mainland China from 2010 to 2018.[3,4]

Also, as suggested, we have added the rationale behind the 25-year-old cutoff for combined analyses in the revised manuscript (Lines 384-386, Page 15)

[References]:

1. Collaborators, G. B. D. D. i. t. A. Burden of diabetes and hyperglycaemia in adults in the Americas, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet Diabetes Endocrinol* **10**, 655-667 (2022).
2. Murray, C. J. L. et al. Global burden of 87 risk factors in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. The Lancet 396, 1223-1249 (2020).
3. Lim, S. S. et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *The Lancet* **380**, 2224-2260 (2012).
4. Finucane, M. M. et al. National, regional, and global trends in body-mass index since 1980: systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9·1 million participants. *The Lancet* **377**, 557-567 (2011).

Question 5:

5. The determination of CVD should be described more specifically. Is it based on the ICD code or reported by the hospital? Why is heart failure not included for CVD?

Response:

Thanks very much for raising this point. First, we used comparative risk assessment theory to quantify the CVD burden attributable to high FPG, and one of the important steps is to determine the risk-outcome pairs. In this study, risk-outcomes pairs were included based on the World Cancer Research Fund (WCRF) grades of convincing or probable evidence, which were consistent with the GBD 2019. Finally, Taking into account data availability, ischemic heart disease, ischemic stroke, and hemorrhagic stroke were included in our study. Moreover, there is insufficient convincing evidence to support the association between high FPG and heart failure; therefore, heart failure was not included, as well as GBD.

Additionally, the definition of CVD-related death was based on the International Classification of Diseases 10th Revision. Overall CVD mortality rates and mortality rates for its subgroups (ischaemic heart disease [I20-I22.9, I24.1-I24.9, I25.0-I25.1, I25.3-I25.9], ischaemic stroke [I63-I63.9, I65-I66.9, I67.2-I67.3, I67.5-I67.6, I69.3], hemorrhagic stroke [I60-I60.9, I69.0, I61-I62.9, I69.1-I69.2]) by each year, province, sex, and age group in mainland China between 2010 and 2018 were used to evaluate the CVD burden attributable to high FPG. We have added the determine of CVD and

the risk-outcome pairs in the section 5 of revised Supplementary materials (Section 5, Page 9-10).

To make it clear to the readers, the changes we have made are listed as follows:

Section 5. Determining the risk-outcome pairs and their relative risks

Risk-outcomes pairs were included based on the World Cancer Research Fund (WCRF) grades of convincing or probable evidence.[1-3] Within this paradigm, compelling evidence comprises biologically plausible relationships between exposure and disease elucidated through numerous epidemiological investigations across diverse populations. Substantive evidentiary inquiries necessitate inclusion of prospective observational studies and, where applicable, randomized controlled trials (RCTs) of adequate magnitude, duration, and caliber, demonstrating consistent effects. Probable evidence is similarly based on epidemiological studies with consistent associations between exposure and disease but for which shortcomings in the evidence exist, such as insufficient available trials (or prospective observational studies). In this study, following the criteria outlined by the World Cancer Research Fund, convincing evidence and probable evidence were included in the analysis. Taking into account data availability, finally, ischemic heart disease, ischemic stroke, and hemorrhagic stroke were included. Specifically, the definition of CVD-related death was based on the International Classification of Diseases 10th Revision.[4] Overall CVD mortality rates and mortality rates for its subgroups (ischaemic heart disease [I20-I22.9, I24.1-I24.9, I25.0-I25.1, I25.3-I25.9], ischaemic stroke [I63-I63.9, I65-I66.9, I67.2-I67.3, I67.5-I67.6, I69.3], hemorrhagic stroke [I60-I60.9, I69.0, I61-I62.9, I69.1-I69.2]) by each year, province, sex, and age group in mainland China between 2010 and 2018 were used to evaluate the CVD burden attributable to high FPG.

The RRs in FPG for each outcome was obtained from meta-analyses, and where available, pooled analyses of prospective observational studies,[2] which were consisted with GBD 2019. More information for RR estimation have been previously provided by the Global Health Data Exchange via a web tool.[3] Specifically, table S1 shows the

RRs used by this current study. Moreover, to reflect the uncertainty in estimated RRs, 1000 draws of RRs were produced for age-, sex-, province-, and year-specific FPG levels in the population to calculate the PAF and its 95% uncertainty interval (UI).

[References]:

1. Wiseman, M. The second World Cancer Research Fund/American Institute for Cancer Research expert report. Food, nutrition, physical activity, and the prevention of cancer: a global perspective. Proc Nutr Soc 67, 253-256 (2008).
2. Singh, G. M. et al. The age-specific quantitative effects of metabolic risk factors on cardiovascular diseases and diabetes: a pooled analysis. PLoS One 8, e65174 (2013).
3. Murray, C. J. L. et al. Global burden of 87 risk factors in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. The Lancet 396, 1223-1249 (2020).
4. Qi, J. et al. National and subnational trends in cancer burden in China, 2005-20: an analysis of national mortality surveillance data. Lancet Public Health 8, e943-e955 (2023).

Question 6:

6. Regarding the calculation of blood glucose levels, is the age-standardized FPG level adjusted for age as a covariate in the temporal-spatial hierarchical Bayesian model? And, age factors were not adjusted for when calculating blood glucose levels by age group.

Response:

Thanks very much. Indeed, the temporal-spatial hierarchical Bayesian model was used to obtain the mean FPG level. Specifically, we used a cubic spline to allow non-linear age relationship, with one knot at 50 years. The mid-age z_h of age group h was used to calculate the age model term γ_i:

$$\gamma(z_h) = \gamma_1 z_h + \gamma_2 z_h^2 + \gamma_3 z_h^3 + \gamma_4 (z_h - 50)^3,$$

Then, the direct standardization was applied to adjust demographic differences based on 2010 census. We have modified the description as “Age-standardised FPG

level, mortality rate and YLL rate for CVD attributable to high FPG were standardised to the population in 2010 census to adjust demographic differences using direct standardization" in the Method section of the revised manuscript (Lines 399-401, Page 16). Mover, we have added the standard population in 2010 census used in the study in Supplementary Table S3 (Page 16).

Table S1. The standard population used in the study.

Age group	Proportion
25-29	0.126992621
30-34	0.113309929
35-39	0.124927983
40-44	0.124348094
45-49	0.137093225
50-54	0.086122454
55-59	0.08600857
60-64	0.0687145
65-69	0.047476503
70-74	0.035744751
75-79	0.026394663
80-	0.022866709

Question 7:

7. "Moreover, we observed that the gap in CVD mortality attributable to high FPG between men and women had narrowed after the age of 50 in 2018, and even among those over 80, women have higher CVD mortality rate than men (Supplementary Table S5-S6)." (Line 112-115) Regarding this statement: It is difficult to discern the trend clearly through the tables. The reviewer suggests that the authors supplement the data by plotting the changes in CVD mortality counts and rates by age group for different sexes in 2018 using line graphs. This would provide a more intuitive representation.

Response:

We thank the reviewer for the helpful comment. As suggested, we have added Fig S2 to illustrate the percent change for CVD deaths and mortality rates attributable to high FPG between male and female across different age group in 2010 and 2018 in the revised Supplementary material (Fig S2, Page 58).

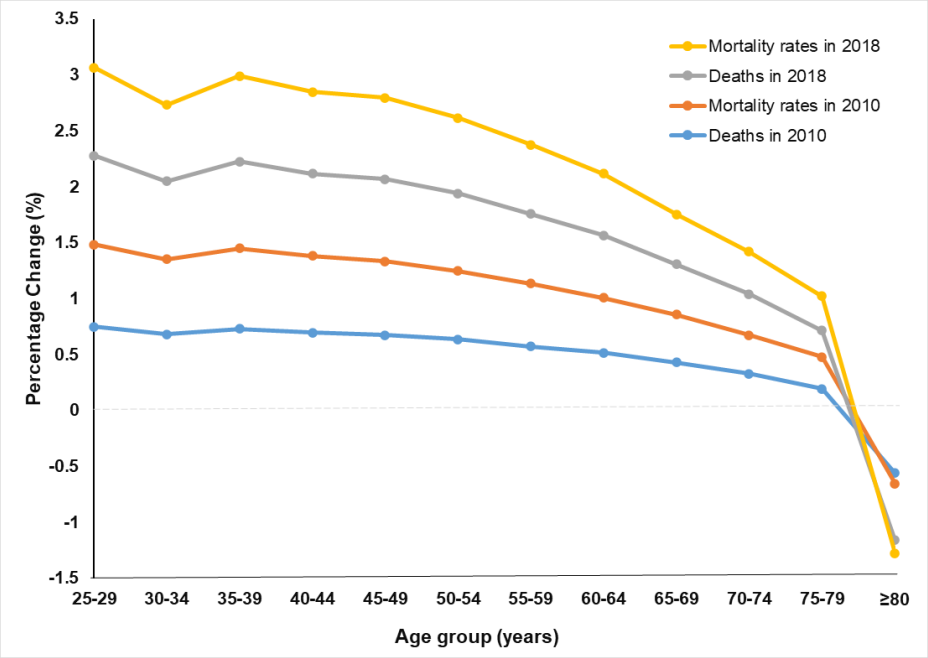


Fig S2. Percent change for CVD deaths and mortality rates attributable to high FPG between male and female across different age group in 2010 and 2018.

Question 8:

8. ".....with elderly individuals (≥ 80 years old) accounting for 55% in 2010 and 44% in 2018 of CVD deaths attributable to high FPG (Supplementary Fig S2-S3)." (Line 121-123). Here, there might be a data error. According to Fig S2 and Fig S3, it should be 55% in 2018, and 44% in 2010. Your statement does not align with the data. Please confirm.

Response:

We are very grateful to the reviewer for raising this important point. We have modified this sentence as ".....with elderly individuals (≥ 80 years old) accounting for 44% in 2010 and 55% in 2018 of CVD deaths attributable to high FPG" in the revised manuscript (Lines 117-120, Page 6).

Question 9:

9. "Of note, for total CVD and its subtypes, men had a higher mortality burden than women in both 2010 and 2018 (Table 2)." (Line 131-132). In Table 2, there seems to be an error in the data for the ischemic stroke burden. The values for the Total row and the Female row are exactly the same, which is clearly not reasonable. Please address this discrepancy.

Response:

We are very grateful to the reviewer for raising this point. We have checked again and modified Table 2 in the revised manuscript (Page 26).

To make it clear to the readers, the changes we have made are highlighted as follows:

Table 2. Number, rate, and age-standardised rate for CVD deaths attributable to high FBG by specific causes and sex in China, 2010-2018 (95%UI).

	2010			2018		
	Deaths (thousands)	Mortality rate per 100 000	Age-standardised mortality rate (95% UI), per 100 000	Deaths (thousands)	Mortality rate per 100 000	Age-standardised mortality rate (95% UI), per 100 000
CVD						
Total	362.50(346.46 to 379.37)	41.93(40.07 to 43.88)	41.93(40.07 to 43.88)	512.29(488.60 to 538.65)	54.47(51.95 to 57.27)	43.60(41.77 to 45.62)
Male	205.21(197.10 to 213.92)	46.94(45.09 to 48.94)	49.72(47.58 to 52.04)	281.54(267.89 to 295.05)	59.51(56.62 to 62.36)	51.66(49.24 to 54.05)
Female	157.38(144.08 to 171.52)	36.82(33.70 to 40.12)	33.98(31.38 to 36.74)	229.75(210.98 to 251.89)	49.16(45.14 to 53.90)	35.20(32.66 to 38.15)
Ischaemic heart disease						
Total	170.61(159.09 to 183.52)	19.73(18.40 to 21.23)	19.73(18.40 to 21.23)	254.13(235.63 to 274.51)	27.02(25.05 to 29.19)	21.44(20.01 to 22.98)
Male	92.88(87.16 to 98.47)	21.25(19.94 to 22.53)	22.66(21.14 to 24.21)	133.64(123.72 to 143.50)	28.25(26.15 to 30.33)	24.62(22.84 to 26.37)
Female	77.70(67.51 to 89.90)	18.18(15.79 to 21.03)	16.56(14.54 to 18.95)	120.56(104.93 to 137.43)	25.80(22.45 to 29.41)	18.05(15.94 to 20.32)
Ischaemic stroke						
Total	86.17(79.69 to 93.27)	9.97(9.22 to 10.79)	9.97(9.22 to 10.79)	139.95(128.14 to 152.81)	14.88(13.62 to 16.25)	11.66(10.75 to 12.66)
Male	48.09(44.13 to 52.48)	11.00(10.09 to 12.00)	11.77(10.73 to 12.95)	77.05(69.88 to 84.49)	16.29(14.77 to 17.86)	13.86(12.59 to 15.17)
Female	38.24 (32.66 to 44.31)	8.95(7.64 to 10.37)	8.22 (7.11 to 9.43)	62.93 (52.96 to 73.77)	13.46 (11.33 to 15.78)	9.49 (8.15 to 10.96)
Hemorrhagic stroke						
Total	105.51(101.24 to 110.14)	12.20(11.71 to 12.74)	12.20(11.71 to 12.74)	117.56(112.65 to 123.23)	12.50(11.98 to 13.10)	10.44(10.05 to 10.89)
Male	64.16(61.30 to 66.98)	14.68(14.02 to 15.32)	15.25(14.54 to 15.97)	70.82(67.49 to 74.42)	14.97(14.26 to 15.73)	13.19(12.59 to 13.83)
Female	41.41(38.15 to 44.93)	9.69(8.92 to 10.51)	9.18(8.52 to 9.90)	46.79(42.93 to 50.78)	10.01(9.19 to 10.87)	7.69(7.17 to 8.24)

CVD=cardiovascular disease, FPG=fasting plasma glucose, 95% UI=95% uncertainty intervals.

Question 10:

10. The Table legends for Tables S8-S11 are not clearly expressed and do not include the word 'death'.

Response:

We appreciate this helpful comment. As suggested, we have modified these table legends in the revised Supplementary material (Pages 37, 39, 41, and 43).

Supplementary material:

Page 37: Table S9. PAFs for total CVD death attributable to high FPG by sex and province, 2010-2018 (% (95% UI)) .

Page 39: Table S10. PAFs for ischaemic heart disease death attributable to high FPG by sex and province, 2010-2018 (% (95% UI)) .

Page 41: Table S11. PAFs for ischaemic stroke death attributable to high FPG by sex and province, 2010-2018 (% (95% UI)).

Page 43: PAFs for haemorrhagic stroke death attributable to high FPG by sex and province, 2010-2018 (% (95% UI)).

REVIEWER COMMENTS

Reviewer #1 (Remarks to the Author):

1. With regards to mortality estimation:

a. The DSP sites for cause of death data collection were set up many decades ago. While these may have been representative for province and national estimates at the time, this is likely to change over time in a country with large migration. When you claim that the data from DSPs are representative, I would expect information on the validity of such a claim. This could come from demographic analyses of censuses Without that I am not convinced you can make a statement about the DSP being representative.

b. You make general statement about garbage code redistributions but provide no useful detail on what you actually did. What garbage codes relevant to the CVD outcomes of interest were identified and how did you determine the proportions of those being redistributed? You only mention "previous studies, or coefficients from the National Mortality Surveillance System" and reference a paper on trends in cancer burden in China.

2. With regards to the modelling of exposure:

a. You explain how you estimated means from the three types of surveys but say nothing about how you estimated the standard deviation which you would have needed in order to define the normal distribution you state fit the data best. What criteria did you use to determine fit? Did you use information from all three survey series to back up this statement of 'best fit'?

3. With regards to RRs:

a. In the supplementary material you state "The RRs in FPG for each outcome was obtained from meta-analyses, and where available, pooled analyses of prospective observational studies,(11) which were consisted with GBD 2019. More information for RR estimation have been previously provided by the Global Health Data Exchange via a web tool." Reference 11 is a meta-analysis of metabolic risk factors on CVD and diabetes. How did you determine this paper was 'consistent' (I presume that is what you meant) with GBD2019? The next sentence suggests you took RR estimates from GHDx, which is a repository made available to show data inputs and results from GBD. The values of the RRs you present suggest to me that you used GBD2019 estimates and not the info from reference 11.

b. How did you stream out 1000 draws from the RR info you took from GBD? Did you similarly stream out 1000 draws of the distributions of FPG by age, sex, year and location?

4. With regards to TMREL:

a. Your writeup is similarly ambiguous about the use of the TMREL from GBD2019 and mentioning the meta-analysis from reference 11. You use one or the other. Which one was it?

Reviewer #3 (Remarks to the Author):

I have no further comments.

Response Letter

Response to the reviewers' comments

Response to the 1st Reviewer

Question 1: With regards to mortality estimation:

a. *The DSP sites for cause of death data collection were set up many decades ago. While these may have been representative for province and national estimates at the time, this is likely to change over time in a country with large migration. When you claim that the data from DSPs are representative, I would expect information on the validity of such a claim. This could come from demographic analyses of censuses Without that I am not convinced you can make a statement about the DSP being representative.*

Response: Thanks for this comment. The National Mortality Surveillance System (NMSS), established in 1978, has been continuously monitoring the mortality levels and patterns of disease among the Chinese population. In 2004, the system was expanded to 161 surveillance points and began to provide annual cause-of-death surveillance results in the form of datasets. Subsequently, in 2013, there was a significant expansion, with surveillance points increasing from 161 to 605, distributed across 31 provincial-level administrative regions in mainland China. These surveillance points collectively cover a population of 324 million, approximately 24.3% of the total national population. Previous literature extensively elucidated the selection process of surveillance points within the NMSS system across each province (Figure R1).[1] Briefly, a total of 605 surveillance points were strategically chosen using an iterative method involving multistage stratification that took into account the sociodemographic characteristics of the population. Each surveillance point covers a district (if in urban areas) or a county (if in rural areas).

After 2013, NMSS did not re-select surveillance points according to the latest economic development and population distribution. Nevertheless, NMSS covers an approximately population of 324 million individuals, accounting for 24% of the Chinese population, making it the most comprehensive source of mortality surveillance data in China to date. Some previous studies have analyzed mortality patterns across various diseases in China based on the NMSS.[2,3] In this current study, we also use these mortality data from the NMSS to estimate the CVD mortality burden attributable to high FPG in China.

Also, as suggested, we have refined and modified the claim about the NMSS in the revised manuscript (Lines 363-365, Page 15), and provided additional insights into the selection process of surveillance points in method section of the revised Supplementary materials (Section 2, Page 6).

To make it clear, the changes we have made are listed as follows:

Page 6, Supplementary Section 2 is modified:

"…, The NMSS, established in 1978, has been continuously monitoring the mortality levels and patterns of disease among the Chinese population. In 2004, the system was expanded to 161 surveillance points and began to provide annual cause-of-death surveillance results in the form of datasets. Subsequently, in 2013, there was a significant expansion, with surveillance points increasing from 161 to 605, distributed across 31 provincial-level administrative regions in mainland China. These surveillance points collectively cover a population of 300 million, approximately 24.3% of the total national population.…"

Lines 363-365, Page 15, Revised manuscript:

"Additionally, data on CVD mortality from 2010 to 2018 at the provincial level were derived from the National Mortality Surveillance System (NMSS), which covers 324 million people, accounting for 24·3% of the country's population."

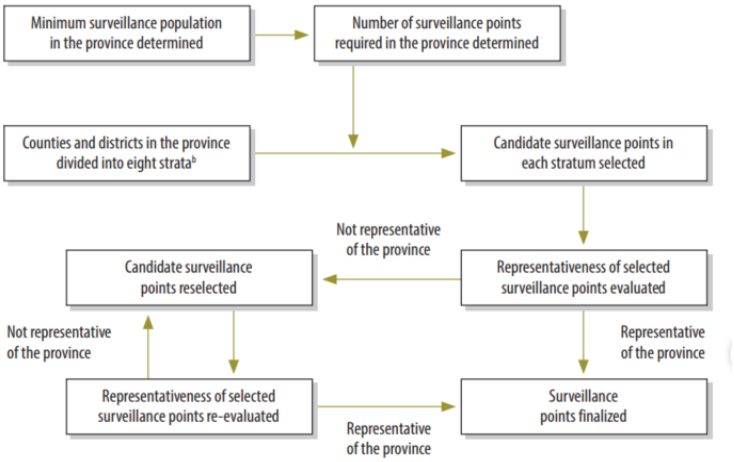


Figure R1: Selection of points in the national mortality surveillance system in each province, China.

[Reference]:

1. Liu, S. et al. An integrated national mortality surveillance system for death registration and mortality surveillance, China. *Bull World Health Organ* **94**, 46-57 (2016).
2. Wang, W. et al. Mortality and years of life lost of cardiovascular diseases in China, 2005-2020: Empirical evidence from national mortality surveillance system. Int J Cardiol 340, 105-112 (2021).
3. Qi, J. et al. National and subnational trends in cancer burden in China, 2005-20: an analysis of national mortality surveillance data. Lancet Public Health 8, e943-e955 (2023).

b. *You make general statement about garbage code redistributions but provide no useful detail on what you actually did. What garbage codes relevant to the CVD outcomes of interest were identified and how did you determine the proportions of those being redistributed? You only mention "previous studies, or coefficients from the National Mortality Surveillance System" and reference a paper on trends in cancer burden in China.*

Response: We highly appreciate your helpful comment. As suggested, we have further added information on garbage codes relevant to the CVD outcomes of interest and the proportion of redistribution in the revised manuscript (Lines 366-368, Page 15), and the method section of the revised Supplementary materials (Section 2, Pages 7-8).

To make it clear, the changes we have made are listed as follows:

Lines 366-368, Page 15, Revised manuscript:

"Underreporting surveys and garbage code redistribution were conducted to ensure the accuracy of CVD mortality estimates in NMSS. More details were provided in Supplementary Methods."

Pages 7-8, Supplementary Section 2 is added:

Section 1. CVD mortality data

(3) Garbage code redistribution and CVD mortality estimation

In this study, garbage codes include those 1) not the primary COD, 2) intermediate COD, and 3) having unknown actual COD. These codes were identified by consulting research from the Global Burden of Disease, Chinese death surveillance experts, and International Classification of Diseases code experts. They encompass not only uncategorized codes for symptoms, signs, and abnormal clinical and laboratory findings in the International Classification of Diseases-10th Revision (ICD-10), but also codes deemed insufficiently significant to yield practical implications for public health planning and the amelioration of health issues, such as I68.0- I68.8 (Cerebrovascular disorders in diseases classified elsewhere) in this study. Analysis of garbage codes serves as a metric for evaluating the quality of population surveillance data. Table S1 shows the garbage codes related to the CVD outcomes in this present study.

Garbage codes were grouped and assigned a target code for each group based on disease characteristics and established rules for inferring cause of death. The redistribution of garbage codes relied on the proportion of the target code, known coefficients from previous studies, or coefficients from the National Mortality Surveillance System.[1] This redistribution occurred through the following methods:

1) Redistribute garbage code based on the proportion of the target code

After stratifying data by sex and age, the summation of garbage codes within each group was calculated alongside the proportion of each target code in the total target code, determined by dividing its frequency by total deaths. The proportion of the target code in total deaths served as the coefficient. The following equation illustrates the calculation of frequency after redistribution:

Frequency after redistribution = Frequency before redistribution + total garbage code within each group * target code frequency before redistribution/total target code within each group

2) Redistribute garbage code based on known coefficients from previous studies

Garbage code pertaining to certain diseases is redistributed by leveraging established coefficients derived from prior research endeavors, such as those exemplified by the Global Burden of Disease research.

3) Redistribute garbage code based on coefficients from NMSS

Redistribution coefficients were determined based on pragmatic associations between garbage code and target code. Subsequently, the garbage code is redistributed in accordance with these coefficients.

Consistently, negative correlations between garbage code and target code were identified. This suggests that, while maintaining the total count constant, a higher prevalence of garbage code is linked to a decreased incidence of target code, and vice versa.

The proportion of cause of death for each outcome by province-age-sex was calculated by the number of CVD cases after redistribution divided by the total number of deaths. Mortality rate of CVD by each year, province, sex, and age group was then calculated by multiplying all-cause mortality rate by proportion of CVD in all deaths.

Table S1. List of garbage codes redistribution from NMSS cause list for CVD

Cause list	List of garbage codes (ICD-10)
Cardiovascular diseases	I10, I15, I15.0, I15.1, I15.2, I15.8, I15.9, I23, I23.0, I23.1, I23.2, I23.3, I23.4, I23.5, I23.6, I23.8, I24, I24.0, I25.2, I29, I32, I32.0, I32.1, I32.8, I39, I39.0, I39.1, I39.2, I39.3, I39.4, I39.8, I41, I41.0, I41.1, I41.2, I41.8, I41.9, I43, I43.0, I43.1, I43.2, I43.8, I52, I52.0, I52.1, I52.8, I64, I68, I68.0, I68.1, I68.2, I68.8, I79, I79.0, I79.1, I79.2, I79.8, I97, I97.0, I97.1, I97.2, I97.8, I97.9, I98, I98.0, I98.1, I98.2, I98.3, I98.8, I99

NMSS= National Mortality Surveillance System, CVD=cardiovascular disease

Question 2: With regards to the modelling of exposure:

a. You explain how you estimated means from the three types of surveys but say nothing about how you estimated the standard deviation which you would have needed in order to define the normal distribution you state fit the data best. What criteria did you use to determine fit? Did you use information from all three survey series to back up this statement of 'best fit'?

Response: We are very grateful to the reviewer for raising this point. As suggested, we have added more information on the estimation of standard deviation in Section 4 of the revised Supplementary materials (Section 4, Page 11).

Additionally, the distribution of FPG level was normal based on the individual data from CHS survey. Thanks for your kindly comment, we have modified the description of FPG distribution (Lines 395-396, Page 16) and modified the statement of distribution selection in Section 8 of the revised Supplementary materials (Page 13).

Moreover, we did not utilize all individual information from the three surveys to ascertain the optimal-fit distribution, owing to constraints in data availability. We have

added the limitation of distribution selection in the revised manuscript (Lines 335-337, Page 14).

To make it clear, the changes we have made are listed as follows:

Page 11, Supplementary Section 4 is supplemented:

The standard deviation of FPG distribution within a population was estimated at the county or district levels starting from age 25 using similar method. Then we calculated the standard deviation for each province using the following equation:

$$SD = \sqrt{\frac{1}{N}\sum_{k=1}^{K} N_k SD_k^2 + \frac{1}{N}\sum_{k=1}^{K} N_k(\eta_k - \eta)^2}$$

where K means different counties in a province, k=1, …, K; η means mean FPG level; N means the total sample size for every province; and N_k are the sample size for each county or district with each province.

Page 13, Supplementary Section 8 is modified:

"Based on the distribution of individual data from the CHS survey, the normal distribution of FPG was determined."

Lines 395-396, Page 16, Revised manuscript:

"…, assuming that the distribution of the FPG was normal:"

Lines 335-337, Page 14, Revised manuscript:

"Fifth, we did not utilize all individual information from the three surveys to ascertain the optimal-fit distribution of FPG, owing to constraints in data availability."

Question 3: With regards to RRs:

a. *In the supplementary material you state "The RRs in FPG for each outcome was obtained from meta-analyses, and where available, pooled analyses of prospective observational studies,(11) which were consisted with GBD 2019. More information for RR estimation have been previously provided by the Global Health Data Exchange via a web tool." Reference 11 is a meta-analysis of metabolic risk factors on CVD and diabetes. How did you determine this paper was 'consistent' (I presume that is what you meant) with GBD2019? The next sentence suggests you took RR estimates from GHDx, which is a repository made available to show data*

inputs and results from GBD. The values of the RRs you present suggest to me that you used GBD2019 estimates and not the info from reference 11.

Response: We are very grateful to you for raising this important point. As suggested, we have modified the description of RR estimation in the revised manuscript (Lines 386-387, Pages 15-16) and section 5 of the revised Supplementary materials (Page 12).

To make it clear, the changes we have made are listed as follows:

Lines 386-387, Pages 15-16, Revised manuscript:

"The age-specific relative risks (RRs) for each risk factor-disease pair were shown in Supplementary Table S2, which were obtained from GBD 2019."

Page 12, Supplementary Section 5 is added:

"The RRs in FPG for each outcome were consistent with GBD 2019, and methodological details of RR estimation are to be found in the Methods Appendix (Supplementary Appendix 1) of the 2019 GBD article: Global burden of 87 risk factors in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet 2020; 396: 1223–49."

b. *How did you stream out 1000 draws from the RR info you took from GBD? Did you similarly stream out 1000 draws of the distributions of FPG by age, sex, year and location?*

Response: Thanks very much. First, we obtained RRs and its 95%CI by age group from GBD 2019, as mentioned above. Then we created 1000 draws of RRs for the standard GBD age groups (5 years interval) using the *rand* function in SAS DATA step[1], which was updated to have better random properties and can generate data from a wide variety of statistical distributions. In this study, log(RR), namely, regression coefficient, was considered as normal distribution. Thus, 1000 draws of log(RRs) were obtained from a log-normal distribution with mean of log (RR) and standard deviation (SD) of the following equation:$SD = (Upper\ \ limit - Lower\ \ limit)/2 \times 1.96$. we have added more information in Section 5 of the revised Supplementary materials (Page 12).

For the FPG distribution by age, sex, year, and province, we didn't stream out 1000 draws. As suggested, we have added the limitation in the revised manuscript (Lines 334-335, Page 14). Furthermore, we will endeavor to further refine our calculation methodology to enhance the precision of attributable disease burden estimation.

To make it clear, the changes we have made are listed as follows:

Page 12, Supplementary Section 5 is added:

"Specifically, We created 1000 draws of RRs for the standard GBD age groups (5 years interval) using the *rand* function in SAS DATA step[1], which was updated to have better random properties and can generate data from a wide variety of statistical distributions.

1000 draws of log(RRs) were obtained from a log-normal distribution with mean of log (RR) and standard deviation (SD) of the following equation:$SD = (Upper\ \ limit - Lower\ \ limit)/2 \times 1.96$."

Lines 334-335, Page 14, Revised manuscript:

"Fourth, the reported UI in this study do not consider model misspecification bias and selection bias."

[Reference]:

1. Wicklin, R. Simulating data with SAS. (SAS Institute, 2013).

Question 4: With regards to TMREL:

a. Your writeup is similarly ambiguous about the use of the TMREL from GBD2019 and mentioning the meta-analysis from reference 11. You use one or the other. Which one was it?

Response: We highly appreciate your helpful comment. In our study, the TMREL of high FPG was defined as a uniform distribution between 4.8-5.4 mmol/L across all age groups, which was obtained from GBD 2019[1]. Following your suggestion, we further improved the description of this part in the Section 6 of the revised Supplementary materials (Page 12).

Page 12, Supplementary Section 6 is modified:

"…, In our study, the TMREL of high FPG was defined as a uniform distribution between 4.8-5.4 mmol/L across all age groups based on the GBD 2019 study,[1] and more details can be found in the Methods Appendix (Supplementary Appendix 1) of the 2019 GBD article: Global burden of 87 risk factors in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet 2020; 396: 1223–49."

[Reference]:

1. Murray, C. J. L. et al. Global burden of 87 risk factors in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. The Lancet 396, 1223-1249 (2020).

Reviewer #3 (Remarks to the Author):

I have no further comments.

Response: Thanks very much.

REVIEWER COMMENTS

Reviewer #1 (Remarks to the Author):

You have addressed most of my comments.

The only thing left is that you state you did not take uncertainty from your FPG distributions into account when computing uncertainty intervals for your main results. That seems an omission that you cannot just explain away as a limitation.

Response Letter

Response to the reviewers' comments

Reviewer #1 (Remarks to the Author):

You have addressed most of my comments.

1. *The only thing left is that you state you did not take uncertainty from your FPG distributions into account when computing uncertainty intervals for your main results. That seems an omission that you cannot just explain away as a limitation.*

Response: Thanks for your comment again. After careful deliberation and following the suggested recommendations, we have refined the calculation method for the FPG distribution. Subsequently, estimates of the FPG distributions were propagated through Monte Carlo samples to generate 1000 draws for each county or district, year, age, and sex. The revised methodology is detailed in Section 4 of the updated supplementary material (Pages 10-11). Furthermore, all results in both the revised manuscript and supplementary material have been updated, and it can also be seen that the findings of this study are robust.

To make it clear, the changes we have made are listed as follows:

Pages 10-11, Supplementary Section 4 is modified:

"…The estimates of the FPG distributions were then propagated through the Monte Carlo samples to obtain 1000 draws for each county or district, year, age, and sex…."

REVIEWERS' COMMENTS

Reviewer #1 (Remarks to the Author):

You have resolved my last issue.