Higher Long-term Visit-to-Visit Variability in Fasting Plasma Glucose Predicts New-Onset Heart Failure in the General Population

Yueying Wang

Tianjin Institute of Cardiology, Second Hospital of Tianjin Medical University

Wenwei Qi

Tianjin Institute of Cardiology, Second Hospital of Tianjin Medical University

Nan Zhang

Tianjin Institute of Cardiology, Second Hospital of Tianjin Medical University

Gary Tse

Tianjin Institute of Cardiology, Second Hospital of Tianjin Medical University

Guangping Li

Tianjin Institute of Cardiology, Second Hospital of Tianjin Medical University

Shouling Wu

Kailuan Hospital, North China University of Science and Technology

Tong Liu (✉ liutongdoc@126.com)

Tianjin Institute of Cardiology, Second Hospital of Tianjin Medical University

Research Article

Keywords: heart failure, fasting blood glucose variability

Posted Date: December 21st, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-1183160/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](#)

Abstract

Background: Previous studies suggested an adverse association between higher fasting blood glucose (FBG) and heart failure. However, FBG values fluctuate continuously over time, the association between FBG variability and the risk of heart failure is uncertain.

Aims: We investigated the relationship between visit-to-visit variability in FBG and the risk of new-onset heart failure.

Methods and Results: This was a population-based cohort study using the Kailuan dataset, which comprises of medical claims and a biennially health checkup information from a Chinese cohort. A total of 98 554 individuals (mean age: 53.63 years) who had at least two health checkups with FBG measurement between 2006 and 2012 without preexisting heart failure were included. FBG variability was calculated using the variability independent of the mean, coefficient of variation, standard deviation, and average successive variability (ARV). Participants were divided into quartiles of ARV. Cox regression was used to identify heart failure. Over a mean follow-up of 6.27 years, 1218 individuals developed heart failure. The incidence of heart failure was 1.97 per 1000 person-years. After adjusting for baseline FBG and other potential confounders, individuals in the highest quartile of the ARV of FBG had 32.6% higher risk of developing heart failure compared to those in the lowest quartile (hazard ratio, 1.326; 95% confidence interval, 1.120-1.570). This association remained significant in patients with or without prevalent hypertension. In subgroup analyses, individuals who were younger (<65 years), without diabetes mellitus or chronic kidney disease, and with a body mass index <25 kg/m² experienced a higher risk of heart failure.

Conclusions: Our data demonstrated that high FBG variability is independently associated with the development of new-onset heart failure. Future studies should explore whether measures to reduce variability can lead to improve clinical outcomes.

Trial registration: Chinese Clinical Trial Register, ChiCTR-TNRC-11001489. Registered on 24-08-2011.

Introduction

Diabetes mellitus is becoming increasingly prevalent worldwide, placing significant burdens on many healthcare systems. Glycemic impairment, including in the nondiabetic range, is an independent risk factor for heart failure.[1] Hitherto, previous studies investigating the hyperglycemia-related complications have mainly relied on punctual assessment of blood glucose, which may not capture the true levels over time. Sustained hyperglycemia is the predominant condition in patients with diabetes, especially at its advanced stages. However, recent studies have revealed that not only constant hyperglycemia, but also large glucose fluctuations, may influence cardiovascular risk in diabetic patients with even more deleterious effects than sustained hyperglycemia.[2, 3] Glycemic variability, an emerging marker of glycemic control, is a measurement that determines the fluctuations in glucose over a defined time interval. High glycemic variability appears to have more deleterious effects than sustained hyperglycemia in the pathogenesis of diabetic cardiovascular complications [4, 5], with potential implications for cardiovascular disease.[6] Previously published studies have found that visit-to-visit variability in fasting blood glucose (FBG) is an independent predictor of incidence of left ventricular adverse remodeling in type 2 diabetes mellitus patients with ST-segment elevation myocardial infarction.[7] However, the association of visit-to-visit FBG variability with new-onset heart failure in non-diabetic patients is unknown. Therefore, the purpose of our study was to prospectively investigate the association between visit-to-visit FBG variability and the risk of new-onset heart failure in the Kailuan study cohort.

Methods

Population

The participants were recruited from Kailuan study (registration number: ChiCTR-TNC-11001489), a prospective cohort study established at the Kailuan General Hospital and ten other affiliated hospitals, as described in detail elsewhere.[8] Among these subjects, who had at least two health examinations biennially, were included for the evaluation of FBG variability (n=100 305). Those subjects with pre-existing heart failure were excluded (n=477). Finally, the remaining 98 554 participants were included in the final analysis (**Figure 1**). All participants received interviews with pre-defined questionnaires, clinical examinations, and laboratory assessment. The study was performed according to the guidelines of the Declaration of Helsinki and was approved by the Ethics Committee of the Kailuan General Hospital (Approval Number: 2006-05). Written informed consent was obtained from all participants.

Data collection

Information on the demographic variables of age, sex, smoking status, alcohol drinking status, and use of antidiabetic medications was collected using standard questionnaires. Body weight and height were measured by trained nurses according to the standard protocols, allowing calculation of the body mass index (BMI) (weight in kilograms divided by height in meters squared). Blood samples for the measurement of FBG were drawn after an overnight fast. All blood measurements were performed using an automatic analyzer following standard operating procedures and were subjected to regular quality control. The baseline estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.[9] chronic kidney disease (CKD) was defined as an eGFR (calculated using the Modification of Diet in Renal Disease formula) under 60 mL/min at the baseline of health examination.[10]

Measures of fasting plasma glucose variability

FBG variability was determined as visit-to-visit intra-individual FBG variability during at least 4 years before the baseline. Visit-to-visit FBG variability was defined as variability in FBG recorded in at least 2 checkups. The alternative visit-to-visit of FBG metrics include:

(1) the coefficient of variation (CV)=(SD/x×100%),

$$(2) \text{ standard deviation} = \sqrt{\frac{1}{n-1} \sum_{i=1}^n (x_i - \bar{x})^2},$$

(3) the variability independent of the mean (VIM), which is calculated as $100 \times \text{SD} / \text{mean}^\beta$, where β is the regression coefficient based on natural logarithm of SD on natural logarithm of mean, and

$$(4) \text{ the average real variability (ARV)} = \frac{1}{N-1} \sum_{K=1}^{N-1} |Value_{K+1} - Value_K| \sum .$$

All the aforementioned measures of variability have been previously described.[11, 12] Given that there are no internationally agreed upon gold standard measures of FBG variability in general and of visit-to-visit in particular, we opted to include a wide range of measures, which would potentially capture different aspects of FBG variability.[13]

Follow-up and primary outcomes

The participants were followed from the baseline examination until December 31, 2016, or until the diagnosis of heart failure. The method for diagnosis of heart failure was described previously.[14] Incident heart failure was defined in accordance with the criteria of the European Society of Cardiology[15] on the basis of clinical symptoms, echocardiography, chest X-ray, and

electrocardiography. The diagnosis of heart failure was also confirmed based on an annual review of each patient's medical records by a team of experienced cardiologists.

Statistical analysis

Statistical analyses were performed using SAS software (SAS Institute, Inc., Cary, NC; version 9.4). Continuous variables with normal and skewed distributions were described as the mean $\pm$ standard deviation (SD) and the medians with interquartile ranges, respectively, whereas categorical variables were described as frequencies and percentages. Missing data for baseline covariates were dealt with using multiple imputation. χ^2 test for linear trend was used for categorical variables, and one-way analysis of variance for linear trend and Kruskal-Wallis test was performed for continuous variables with normal and skewed distributions, respectively. Visit-to-visit FBG variability was assessed by both quartiles and continuous variables. Univariate survival analysis was performed by the Kaplan-Meier method and the log-rank test.

Person-years were calculated from the date that the baseline interview was conducted to the date when the first occurrence of heart failure was detected, date of death, or date of participating in the last interview in this analysis, whichever came first.

The association of FBG variability with incidence of heart failure was determined by calculation of hazard ratios (HR) and 95% confidence intervals (CI) from Cox regression, after verification of the proportional hazard assumption with Schoenfeld residuals. All participants were divided into quartiles using ARV. Model 1 was adjusted for age and sex. Model 2 was further adjusted for history of diabetes mellitus, hypertension, whether to take hypotensive drugs and hypoglycemic drugs, baseline FBG, resting heart rate, LDL-C and HDL-C. Model 3 was further adjusted for SBP (systolic blood pressures), DBP (diastolic blood pressures), BMI, high-sensitivity C-reactive protein (Hs-CRP), smoking, alcohol abuse and physical activity.

Sensitivity analysis was conducted to test the robustness of our results, using three exclusion criteria. To assess the possibility that these inverse associations were driven by other risk factors of heart failure, we excluded participants who had a diagnosis of myocardial infarction and arrhythmia at baseline. In addition, we excluded individuals use of β -adrenergic blocking, angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), aldosterone antagonist to assess whether the main analysis could be affected by these agents which improve heart failure outcomes.

Also, subgroup analyses were conducted according to the following subgroups which were well-known risk factors for incident heart failure, as follows: age strata (<65 years and ≥ 65 years), sex, hypertension, diabetes mellitus, CKD ($\text{eGFR} \geq 60 \text{ mL/min/1.73m}^2$ and $\text{eGFR} < 60 \text{ mL/min/1.73m}^2$), and BMI ($< 25 \text{ kg/m}^2$ and $\geq 25 \text{ kg/m}^2$).

Results

Baseline characteristics

A total of 98 554 subjects (mean age, 53.63 ± 12.34 years; 78.83% male) were included in this study. Over a mean of 6.27 ± 0.91 years of follow-up, 1218 subjects were newly diagnosed with heart failure (1.97 per 1000 person-years).

Baseline characteristics of subjects according to quartiles of the ARV are presented in Table 1, and those according to VIM, CV, SD are presented in Table S2-S4. Subjects with the highest variability of ARV (ARV-Q4) were older, had higher proportion of male subjects, and had a higher number of comorbidities, higher proportion of current smokers, more subjects with low monthly income, higher body weight, BMI, SBP and DBP.

The baseline characteristics stratified by the outcome status of new onset heart failure are summarized in Table S1. Approximately 11.00% of participants with incident heart failure took hypoglycemic medications. Participants with incident heart failure were older, mostly male (85.39%), more obese, had higher rates of cardiovascular risk factors such as diabetes,

smoking, and worse renal function compared to those without incident heart failure ($p < 0.01$, respectively). The resting heart rate was significantly higher (76.75 ± 12.56 vs. 73.60 ± 10.46 , $p < 0.01$), and regular exercise was more frequently observed in participants with incident heart failure compared with those without it (73.56% vs. 70.08%, $p < 0.01$).

FBG variability and the risk of heart failure

As FBG variability increased from quartiles 2, 3 and 4, the incidence of heart failure increased from 1.41 to 1.55, 1.94, and 2.97 per 1000 person-years, respectively. The incidence rate of heart failure significantly increased with a higher variability of FBG. The associations between FBG variability and new-onset heart failure are shown in Table 2. The adjusted HR for the highest quartile of ARV was 1.326 (95% CI: 1.120-1.570) compared to the lowest quartile. Similarly, the highest VIM, CV, SD of FBG also showed a significant association with new-onset heart failure (Q4 versus Q1: HR, 1.285 [95% CI, 1.081-1.526]; HR, 1.245 [95% CI, 1.055-1.470]; HR, 1.315 [95% CI, 1.112-1.555], respectively). The cumulative incidence curves for new onset heart failure stratified by quartiles of FBG variability are shown in Figure 2. Individuals in the top quartile of variability of FBG experienced a higher risk than participants of the other quartiles over the 6.27 follow-up years for heart failure (log-rank test, $P < 0.001$).

Sensitivity analyses

The following sensitivity analyses were performed. In the first sensitivity analysis, we excluded all individuals with prevalent MI ($n = 471$). Among the remaining patients, Table 2 show the analysis resulted in adjusted HRs of 1.280 (95% CI, 1.070-1.531) were similar to those of the main analysis. Similarly, the highest VIM, CV, SD of FBG also showed a significant association with new-onset heart failure (Q4 versus Q1: HR, 1.246 [95% CI 1.037-1.497]; HR, 1.204 [95% CI 1.009-1.437]; HR, 1.676 [95% CI 1.429-1.965], respectively) among individuals free of myocardial infarction over the entire observation period.

Second, we excluded individuals diagnosed with arrhythmias (eg. atrial fibrillation, atrial flutter, atrial premature beat, ventricular ectopic beats, and/or atrioventricular block) at baseline ($n = 1331$). In second sensitivity analysis using a higher ARV and SD of FBG measures to estimate variability, the association between visit-to-visit variability in FBG with the risk of incident heart failure was consistent with that observed in the primary analysis. Higher CV and VIM was not significantly associated with incident heart failure.

The last sensitivity analysis demonstrated similar to those of the main analysis when individuals use of β -adrenergic blockers, ACEI, ARB and aldosterone antagonists were removed ($n = 1340$).

Subgroup analyses

Subgroup analysis for age demonstrated that the association of FBG ARV with heart failure was stronger among those < 65 years compared with those ≥ 65 years [age < 65 years: HR 1.356 (95% CI 1.074-1.712); age ≥ 65 years: HR 1.276 (95% CI 0.998-1.633), interaction p -value 0.0471] (Table S5). There was no interaction by sex, hypertension, diabetes, BMI or eGFR on the association of FBG ARV with incident heart failure (Figure 3). Moreover, ARV of FBG was associated with the risk of heart failure across both patients with or without prevalent hypertension. In subgroup analysis, the impact of high FBG variability on heart failure development was stronger in high-risk subjects, who were younger (< 65 years), without diabetes mellitus or chronic kidney disease, and with a BMI < 25 kg/m². Stratified analysis of subjects according to VIM, CV, SD are presented in Table S6-S8, the results were similar those using ARV.

Discussion

In this study, we examined the influence of FBG variability on new onset heart failure. The primary findings from this large, prospective, population-based cohort study showed that higher visit-to-visit variability of FBG was associated with an increased risk for heart failure events over 6.27 years of follow-up. The positive association of FBG variability and heart failure was significant and greater in magnitude among people without diabetes compared with those with diabetes. The direction and the magnitude of these associations were roughly consistent across measures of variability. These findings were obtained after adjustment for traditional risk factors for heart failure, including a prior history of diabetes mellitus, hypertension, high BMI, resting heart rate and FBG levels. Our findings add to the growing body of evidence on the risk of cardiovascular disease with higher visit-to-visit variability in FBG and highlight the importance of glycemic fluctuations.

FBG variability has emerged as a measure that can accurately capture the pathological processes that mediate different complications. However, there remains an extensive debate about FBG variability as a risk factor for cardiovascular disease. Our study expands on the findings from previous studies which have also shown an association of FBG variability with new onset of cardiovascular disease.[3, 6, 16, 17] However, these previous studies have been limited by their small size, [16, 17] the restriction to individuals with diabetes only[17], main outcomes not including heart failure,[3, 6] a variable interval between visits at which glycemia was assessed (ranging from days to months),[18] and the methodologies used to estimate variability.[19] All these factors not only would influence variability in FBG but also could impact the strength of the association with outcomes.

The exact mechanisms linking increased FBG variability to an increased risk of adverse outcomes are unknown, but there are several hypotheses[20-23]. Glucose oscillation enhanced human tubule-interstitial cell growth and collagen synthesis and accelerated apoptosis in human endothelial cells more than exposure to a constantly high glucose concentration. [24] Oxidative stress was shown to be the key player in mediating endothelial damage and dysfunction.[25] Several other studies have since confirmed that oscillating glucose concentrations, via increased oxidative stress, can adversely affect the cells of different organs.[26] These pathophysiological changes may trigger cardiovascular disease.

We did not identify any association between FBG variability and increased risk of heart failure in women. A possible explanation for the sex-specific observations may be the higher estrogen level in this subgroup.[27, 28] Studies have suggested that higher estrogen levels can up-regulate the expression of anti-oxidant genes [29, 30] and inhibit the expression of pro-inflammatory genes.[31] Therefore, because of estrogen protection, women may be more adaptable to FBG variability than men, which may reduce the risk of cardiovascular disease mediated by increased FBG variability.

The lack of association of FBG variability with outcomes among those with diabetes may be due to a number of factors, including the use of diabetes medications in this subgroup that may have blunted glycemic variability, as well as the possible underestimation of the number of diabetes cases, as we did not have data on HbA1c or 2-h post load glucose, especially as 2-h post load glucose variability may be strongly associated with outcomes.[32] It is also possible that long-term glycemic variability matters more among those without diabetes, and among those with diabetes short-term variability is a predictor of outcomes. Among those with diabetes, the lack of association of FBG variability with heart failure is apparently consistent with results of previous studies.[16]

Strengths and limitations

The strengths of the present study include its prospective design and large sample size, and that the association between visit-to-visit FBG variability and risk of heart failure was determined for the first time. However, several limitations should be noted. Firstly, the observational study design limited the ability to establish causal pathways. Secondly, we did not have data on glycemic markers other than FBG, such as HbA1c or 2-hour post-prandial glucose, and long-term variability in HbA1c or in 2-hour post-prandial glucose may provide additional value for risk stratification. Thirdly, although we adjusted antidiabetic drugs, we could not fully eliminate some unmeasured confounding factors, which may blunt the FBG variability, such as diet management. Fourthly, FBG values were only measured for two or three times and the median follow-up time was

approximately 6 years, which is relatively short. Finally, all the participants in our study were Chinese, which may limit the generalizability of the results of our investigation to other ethnic groups.

Conclusions

Our findings demonstrate that higher visit-to-visit variability in FBG is associated with an increased risk of new onset heart failure, especially among people without diabetes. Future studies are needed to further elucidate the mechanisms underlying a high level of FBG variability and whether measures that reduce this variability can lead to improve clinical outcomes.

Abbreviations

HR: hazard ratios; SD: standard deviation; 95% CI: 95% confidence interval; BMI: body mass index; MI: myocardial infarction; SBP: systolic blood pressures; DBP: diastolic blood pressures; FBG: fasting blood glucose; LDL-C: low-density lipoprotein cholesterol; CKD: chronic kidney disease; eGFR, estimated glomerular filtration rate; RHR, resting heart rate; TC, total cholesterol; TG, triglyceride; Hs-CRP, High-sensitivity C-reactive protein; CV, coefficient of variance; VIM, variability independent of mean; SD, the standard deviation; ARV: average successive variability

Declarations

Acknowledgments

We thank all study participants, their relatives, the members of the survey teams at the 11 regional hospitals of the Kailuan Medical Group for contributing to the dataset.

Authors'contributions

TL, SLW, YYW and WWQ conceived and designed the study. YYW, WWQ and NZ analyzed, interpreted the data and drafted the first version of the manuscript. All authors have interpreted the data, critically revised, provided intellectual contributions and approved the final version of the manuscript. TL is the guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Funding

This work was supported by the grants from Tianjin Natural Science Foundation (20JCZDJC00340, 20JCZXJC00130 to TL).

Availability of data and materials

The data that support the findings of this study are available from Kailuan General Hospital, but restrictions apply to the availability of these data, and so are not publicly available. Data can be accessed via application to Kailuan General Hospital.

Ethics approval and consent to participate

Granted by the Ethics Committee of the Kailuan General Hospital (Approval Number: 2006-05). There were no patients and/or public involved around the clinical research question or conception and design of the study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests

References

1. Danaei G, Finucane MM, Lu Y, Singh GM, Cowan MJ, Paciorek CJ, Lin JK, Farzadfar F, Khang YH, Stevens GA *et al*: National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2·7 million participants. *Lancet* 2011, 378(9785):31-40.
2. Di Flaviani A, Picconi F, Di Stefano P, Giordani I, Malandrucchio I, Maggio P, Palazzo P, Sgreccia F, Peraldo C, Farina F *et al*: Impact of glycemic and blood pressure variability on surrogate measures of cardiovascular outcomes in type 2 diabetic patients. *Diabetes Care*. 2011, 34(7):1605-1609.
3. Wang A, Liu X, Xu J, Han X, Su Z, Chen S, Zhang N, Wu S, Wang Y, Wang Y: Visit-to-Visit Variability of Fasting Plasma Glucose and the Risk of Cardiovascular Disease and All-Cause Mortality in the General Population. *J Am Heart Assoc* 2017, 6(12).
4. Nusca A, Tuccinardi D, Albano M, Cavallaro C, Ricottini E, Manfrini S, Pozzilli P, Di Sciascio G: Glycemic variability in the development of cardiovascular complications in diabetes. *Diabetes Metab Res Rev* 2018, 34(8): e3047.
5. Lee S, Zhou J, Wong WT, Liu T, Wu W, Wong I, Zhang Q, Tse G: Glycemic and lipid variability for predicting complications and mortality in diabetes mellitus using machine learning. *BMC Endocr Disord* 2021, 21(1):94.
6. Bi J, Song L, Wang L, Wu M, Chen S, Wang Y, Wu S, Tian Y: Visit-to-visit fasting blood glucose variability and lifetime risk of cardiovascular disease: a prospective study. *Cardiovasc Diabetol*. 2021, 20(1):207.
7. Yang CD, Shen Y, Ding FH, Yang ZK, Hu J, Shen WF, Zhang RY, Lu L, Wang XQ: Visit-to-visit fasting plasma glucose variability is associated with left ventricular adverse remodeling in diabetic patients with STEMI. *Cardiovasc Diabetol*. 2020, 19(1):131.
8. Wu S, Huang Z, Yang X, Zhou Y, Wang A, Chen L, Zhao H, Ruan C, Wu Y, Xin A *et al*: Prevalence of ideal cardiovascular health and its relationship with the 4-year cardiovascular events in a northern Chinese industrial city. *Circ Cardiovasc Qual Outcomes*. 2012, 5(4):487-493.
9. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AR, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T *et al*: A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009, 150(9):604-612.
10. Inker LA, Astor BC, Fox CH, Isakova T, Lash JP, Peralta CA, Kurella TM, Feldman HI: KDOQI US commentary on the 2012 KDIGO clinical practice guideline for the evaluation and management of CKD. *Am J Kidney Dis*. 2014, 63(5):713-735.
11. Muntner P, Whittle J, Lynch AJ, Colantonio LD, Simpson LM, Einhorn PT, Levitan EB, Whelton PK, Cushman WC, Louis GT *et al*: Visit-to-Visit Variability of Blood Pressure and Coronary Heart Disease, Stroke, Heart Failure, and Mortality: A Cohort Study. *Ann Intern Med*. 2015, 163(5):329-338.
12. Bangalore S, Fayyad R, Laskey R, DeMicco DA, Messerli FH, Waters DD: Body-Weight Fluctuations and Outcomes in Coronary Disease. *N Engl J Med*. 2017, 376(14):1332-1340.
13. Monnier L, Colette C, Owens DR: The application of simple metrics in the assessment of glycaemic variability. *Diabetes Metab*. 2018, 44(4):313-319.
14. Wu Z, Jin C, Vaidya A, Jin W, Huang Z, Wu S, Gao X: Longitudinal Patterns of Blood Pressure, Incident Cardiovascular Events, and All-Cause Mortality in Normotensive Diabetic People. *Hypertension*. 2016, 68(1):71-77.
15. Swedberg K, Cleland J, Dargie H, Drexler H, Follath F, Komajda M, Tavazzi L, Smiseth OA, Gavazzi A, Haverich A *et al*: Guidelines for the diagnosis and treatment of chronic heart failure: executive summary (update 2005): The Task Force

- for the Diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology. *Eur Heart J*. 2005, 26(11):1115-1140.
16. Echouffo-Tcheugui JB, Zhao S, Brock G, Matsouaka RA, Kline D, Joseph JJ: Visit-to-Visit Glycemic Variability and Risks of Cardiovascular Events and All-Cause Mortality: The ALLHAT Study. *Diabetes Care*. 2019, 42(3):486-493.
 17. Segar MW, Patel KV, Vaduganathan M, Caughey MC, Butler J, Fonarow GC, Grodin JL, McGuire DK, Pandey A: Association of Long-term Change and Variability in Glycemia with Risk of Incident Heart Failure Among Patients With Type 2 Diabetes: A Secondary Analysis of the ACCORD Trial. *Diabetes Care*. 2020, 43(8):1920-1928.
 18. Zinman B, Marso SP, Poulter NR, Emerson SS, Pieber TR, Pratley RE, Lange M, Brown-Frandsen K, Moses A, Ocampo FA et al: Day-to-day fasting glycaemic variability in DEVOTE: associations with severe hypoglycaemia and cardiovascular outcomes (DEVOTE 2). *Diabetologia*. 2018, 61(1):48-57.
 19. Nalysnyk L, Hernandez-Medina M, Krishnarajah G: Glycaemic variability and complications in patients with diabetes mellitus: evidence from a systematic review of the literature. *Diabetes Obes Metab*. 2010, 12(4):288-298.
 20. Lee S, Liu T, Zhou J, Zhang Q, Wong WT, Tse G: Predictions of diabetes complications and mortality using hba1c variability: a 10-year observational cohort study. *Acta Diabetol*. 2021, 58(2):171-180.
 21. Sheng CS, Tian J, Miao Y, Cheng Y, Yang Y, Reaven PD, Bloomgarden ZT, Ning G: Prognostic Significance of Long-term HbA(1c) Variability for All-Cause Mortality in the ACCORD Trial. *Diabetes Care*. 2020, 43(6):1185-1190.
 22. Scott ES, Januszewski AS, O'Connell R, Fulcher G, Scott R, Kesaniemi A, Wu L, Colagiuri S, Keech A, Jenkins AJ: Long-Term Glycemic Variability and Vascular Complications in Type 2 Diabetes: Post Hoc Analysis of the FIELD Study. *J Clin Endocrinol Metab*. 2020, 105(10).
 23. Rama CS, A VR, Thomas A, Lim LL, Ratnasingam J, Tan A, S LGD: Role of Composite Glycemic Indices: A Comparison of the Comprehensive Glucose Pentagon Across Diabetes Types and HbA1c Levels. *Diabetes Technol Ther* 2020, 22(2):103-111.
 24. Ceriello A, Monnier L, Owens D: Glycaemic variability in diabetes: clinical and therapeutic implications. *Lancet Diabetes Endocrinol*. 2019, 7(3):221-230.
 25. Quagliaro L, Piconi L, Assaloni R, Martinelli L, Motz E, Ceriello A: Intermittent high glucose enhances apoptosis related to oxidative stress in human umbilical vein endothelial cells: the role of protein kinase C and NAD(P)H-oxidase activation. *Diabetes*. 2003, 52(11):2795-2804.
 26. Frontoni S, Di Bartolo P, Avogaro A, Bosi E, Paolisso G, Ceriello A: Glucose variability: An emerging target for the treatment of diabetes mellitus. *Diabetes Res Clin Pract*. 2013, 102(2):86-95.
 27. Kander MC, Cui Y, Liu Z: Gender difference in oxidative stress: a new look at the mechanisms for cardiovascular diseases. *J Cell Mol Med*. 2017, 21(5):1024-1032.
 28. Knowlton AA, Lee AR: Estrogen and the cardiovascular system. *Pharmacol Ther*. 2012, 135(1):54-70.
 29. Viña J, Borrás C, Gambini J, Sastre J, Pallardó FV: Why females live longer than males? Importance of the upregulation of longevity-associated genes by oestrogenic compounds. *Febs Lett*. 2005, 579(12):2541-2545.
 30. Tarry-Adkins JL, Ozanne SE, Norden A, Cherif H, Hales CN: Lower antioxidant capacity and elevated p53 and p21 may be a link between gender disparity in renal telomere shortening, albuminuria, and longevity. *Am J Physiol Renal Physiol* 2006, 290(2): F509-F516.
 31. Hamilton KL, Lin L, Wang Y, Knowlton AA: Effect of ovariectomy on cardiac gene expression: inflammation and changes in SOCS gene expression. *Physiol Genomics*. 2008, 32(2):254-263.
 32. Ceriello A, Kilpatrick ES: Glycemic variability: both sides of the story. *Diabetes Care*. 2013, 36 Suppl 2(Suppl 2): S272-S275.

Tables

Table 1

Variables	Total N=98554	Quartile 1 N=24807	Quartile 2 N=24289	Quartile 3 N=24968	Quartile 4 N=24490	P value
Age, y	53.63±12.34	51.97±12.43	52.55±12.40	54.01±12.30	55.97±11.81	<0.01
Male sex, n (%)	77688 (78.83)	19037 (76.74)	18766 (77.26)	19858 (79.53)	20027 (81.78)	<0.01
Comorbidities						
Hypertension, n (%)	15490 (15.72)	3218 (12.97)	3406 (14.02)	3923 (15.71)	4943 (20.18)	<0.01
Diabetes mellitus, n (%)	4388 (4.45)	315 (1.27)	355 (1.46)	590 (2.36)	3128 (12.77)	<0.01
Dyslipidemia, n (%)	4648 (4.72)	959 (3.87)	1072 (4.41)	1167 (4.67)	1450 (5.92)	<0.01
CKD, eGFR <60 mL/min, n (%)	8359 (8.48)	1869 (7.53)	1898 (7.81)	2030 (8.13)	2562 (10.46)	<0.01
Medications						
Antihypertensive agents, n (%)	14392 (14.60)	2941 (11.86)	3124 (12.86)	3661 (14.66)	4666 (19.05)	<0.01
Glucose-lowering agents, n (%)	3805 (3.86)	261 (1.05)	303 (1.25)	502 (2.01)	2739 (11.18)	<0.01
Lipid-lowers agents, n (%)	969 (0.98)	161 (0.65)	196 (0.81)	234 (0.94)	378 (1.54)	<0.01
Lifestyle						
Current smoker, n (%)	33595 (34.09)	8275 (33.36)	8133 (33.48)	8657 (34.67)	8530 (34.83)	<0.01
Current alcohol use, n (%)	34799 (35.31)	8803 (35.49)	8482 (34.92)	8930 (35.77)	8584 (35.05)	0.18
Regular exercise, n (%)	69113 (70.13)	17584 (70.88)	16933 (69.71)	17406 (69.71)	17190 (70.19)	<0.01
Low-income level, n (%)	51514 (52.27)	13208 (53.24)	12444 (51.23)	12694 (50.84)	13168 (53.77)	<0.01
Health examination						
Body weight, kg	71.13±11.28	70.49±11.29	70.88±11.31	71.12±11.20	72.04±11.29	<0.01
BMI, kg/m ²	25.08±3.40	24.84±3.35	24.99±3.37	25.06±3.37	25.44±3.46	<0.01
RHR, bpm	73.64±10.49	72.90±9.98	73.00±10.04	73.46±10.45	75.19±11.28	<0.01
SBP, mmHg	132.01±20.13	129.60±19.88	130.20±19.59	132.42±19.96	135.81±20.49	<0.01
DBP, mmHg	84.71±11.16	83.84±11.07	84.16±11.01	84.91±11.23	85.94±11.23	<0.01
FPG, mmol/L	5.69±1.85	5.22±0.72	5.30±0.78	5.48±0.99	6.77±3.18	<0.01
TC, mmol/L	5.01±1.38	4.93±1.09	4.97±1.42	5.02±1.55	5.11±1.39	<0.01

*TG, mmol/L	1.29 (0.92,1.92)	1.23 (0.87,1.80)	1.25 (0.90,1.85)	1.29 (0.92,1.90)	1.40 (1.00,2.11)	<0.01
LDL-C, mmol/L	2.62±1.07	2.60±0.89	2.62±1.08	2.61±1.20	2.64±1.09	<0.01
HDL-C, mmol/L	1.54±0.53	1.53±0.51	1.54±0.51	1.55±0.51	1.54±0.58	<0.01
Scr, µmol/L	82.56±28.18	81.75±23.59	81.99±26.73	82.44±27.71	84.07±33.73	<0.01
eGFR, mL/min	88.79±20.75	89.99±21.10	89.61±20.11	88.65±19.84	86.89±21.76	<0.01
*Hs-CRP	1.20 (0.54,2.77)	1.10 (0.50,2.60)	1.10 (0.50,2.60)	1.18 (0.54,2.72)	1.30 (0.60,3.10)	<0.01
The number of FBP measurements						<0.01
2	41965 (42.58)	12004 (48.39)	8582 (35.33)	9550 (38.25)	11829 (48.30)	
3	56589 (57.42)	12803 (51.61)	15707 (64.67)	15418 (61.75)	12661 (51.70)	
FBP Variability						
*SD	0.43 (0.24,0.71)	0.14 (0.08,0.20)	0.33 (0.27,0.40)	0.53 (0.45,0.63)	1.03 (0.80,1.54)	<0.01
*VIM	0.43 (0.24,0.71)	0.14 (0.08,0.20)	0.33 (0.27,0.40)	0.53 (0.45,0.63)	1.03 (0.80,1.54)	<0.01
*CV	8.14 (4.56,13.20)	2.70 (1.50,3.82)	6.34 (5.17,7.77)	10.14(8.48,12.13)	18.05(14.33,24.08)	<0.01
<p>Note: Q1, the average real variability of FPG < 0.30; Q2, 0.30 ≤ the average real variability of FPG < 0.54; Q3, 0.54 ≤ the average real variability of FPG < 0.94; Q4, the average real variability of FPG ≥ 0.94.</p> <p>Low-income level: income≥800 Renminbi/month.</p> <p>Continuous variables are presented as mean±SD, and categorical variables are presented as percentage.</p> <p>Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; Scr, serum creatinine levels; BMI, body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; RHR, resting heart rate; TC, total cholesterol; TG, triglyceride; Hs-CRP, High-sensitivity C-reactive protein; CV, coefficient of variance; VIM, variability independent of mean; SD, the standard deviation.</p> <p>*Triglyceride levels, Hs-CRP levels, the SD of fasting plasma glucose levels, the variability independent of the mean and the average real variability are presented as median (interquartile range).</p>						

Table 2

Event Numbers, Incidence Rates and Hazard Ratios for New-onset Heart Failure by Quartiles of Variability of Fasting Plasma Glucose Levels

HR (95% CI) for Quartiles of Variability of Fasting Plasma Glucose

Variable	Quartile 1	Quartile 2	Quartile 3	Quartile 4
FPG-ARV				
Heart failure, case, n (%)	220 (0.89)	234 (0.96)	302 (1.21)	462 (1.89)
IR*	1.41	1.55	1.94	2.97
Cox regression models				
Model 1	1(reference)	1.062(0.883-1.276)	1.216(1.022-1.447)	1.688(1.437-1.982)
P value	<0.0001†	0.5236	0.0271	<0.0001
Model 2	1(reference)	1.050(0.873-1.262)	1.168(0.981-1.390)	1.370(1.157-1.621)
P value	0.0007†	0.6047	0.081	0.0003
Model 3	1(reference)	1.048(0.872-1.260)	1.151(0.967-1.370)	1.326(1.120-1.570)
P value	0.0038†	0.6195	0.113	0.0011
Sensitivity analysis ^a	1(reference)	1.051(0.866-1.276)	1.118(0.929-1.344)	1.280(1.070-1.531)
	0.0319†	0.6146	0.2369	0.0071
Sensitivity analysis ^b	1(reference)	1.080(0.841-1.387)	1.165(0.916-1.48)	1.326(1.045-1.684)
	0.1017†	0.5449	0.2132	0.0204
Sensitivity analysis ^c	1(reference)	1.043(0.864-1.259)	1.112(0.93-1.33)	1.299(1.092-1.544)
	0.0115†	0.6611	0.2456	0.0031
FPG-STD				
Heart failure, case, n (%)	224 (0.90)	239 (0.96)	287 (1.18)	468 (1.90)
IR*	1.42	1.55	1.89	3.01
Cox regression models				
Model 1	1(reference)	1.049(0.874-1.258)	1.176(0.988-1.401)	1.676(1.429-1.965)
P value	<0.0001†	0.61	0.0687	<0.0001
Model 2	1(reference)	1.038(0.865-1.246)	1.134(0.952-1.351)	1.361(1.152-1.609)
P value	0.0007†	0.6883	0.1600	0.0003
Model 3	1(reference)	1.037(0.864-1.244)	1.121(0.941-1.336)	1.315(1.112-1.555)
P value	0.0042†	0.6963	0.1995	0.0014
Sensitivity analysis ^a	1(reference)	1.035(0.854-1.255)	1.093(0.908-1.316)	1.276(1.068-1.526)
	0.0254†	0.7225	0.3483	0.0074
Sensitivity analysis ^b	1(reference)	1.077(0.836-1.388)	1.148(0.899-1.466)	1.315(1.034-1.672)
	0.1189†	0.5659	0.2689	0.0256
Sensitivity analysis ^c	1(reference)	1.031(0.856-1.242)	1.071(0.894-1.283)	1.292(1.088-1.534)
	0.0086†	0.7461	0.457	0.0034
FPG-VIM				

Heart failure, case, n (%)	224 (0.90)	239 (0.97)	338 (1.24)	417 (1.93)
IR*	1.42	1.55	1.98	3.05
Cox regression models				
Model 1	1(reference)	1.049(0.874-1.259)	1.230(1.038-1.456)	1.680(1.428-1.977)
P value	<0.0001†	0.6556	0.0165	<0.0001
Model 2	1(reference)	1.039(0.866-1.246)	1.184(1.0001-1.402)	1.332(1.122-1.582)
P value	0.0032†	0.6829	0.0501	0.0011
Model 3	1(reference)	1.038(0.865-1.245)	1.169(0.987-1.385)	1.285(1.081-1.526)
P value	0.0151†	0.6912	0.0704	0.0044
Sensitivity analysis ^a	1(reference)	1.036(0.855-1.256)	1.139(0.952-1.364)	1.246(1.037-1.497)
	0.0733†	0.7197	0.1554	0.0187
Sensitivity analysis ^b	1(reference)	1.078(0.836-1.388)	1.218(0.961-1.543)	1.249(0.974-1.601)
	0.2361†	0.5629	0.1022	0.0793
Sensitivity analysis ^c	1(reference)	1.032(0.857-1.243)	1.123(0.944-1.336)	1.261(1.057-1.504)
	0.0407†	0.7398	0.1909	0.0100

FPG-CV

Heart failure, case, n (%)	229 (0.93)	255 (1.04)	311 (1.26)	423 (1.72)
IR*	1.47	1.67	2.03	2.72
Cox regression models				
Model 1	1(reference)	1.101(0.921-1.316)	1.239(1.045-1.470)	1.503(1.280-1.766)
P value	<0.0001†	0.2911	0.0137	<0.0001
Model 2	1(reference)	1.084(0.907-1.296)	1.195(1.007-1.418)	1.274(1.080-1.504)
P value	0.0227†	0.3733	0.0413	0.0041
Model 3	1(reference)	1.088(0.910-1.300)	1.184(0.998-1.405)	1.245(1.055-1.470)
P value	0.0524†	0.3565	0.0525	0.0095
Sensitivity analysis ^a	1(reference)	1.087(0.900-1.313)	1.165(0.972-1.397)	1.204(1.009-1.437)
	0.1847†	0.3854	0.0982	0.0396
Sensitivity analysis ^b	1(reference)	1.230(0.959-1.579)	1.339(1.052-1.704)	1.231(0.966-1.570)
	0.1277†	0.1035	0.0176	0.0935
Sensitivity analysis ^c	1(reference)	1.069(0.89-1.283)	1.15(0.965-1.371)	1.212(1.023-1.437)
	0.1308†	0.4758	0.1183	0.0265

*IR (incidence rate) presented as per 1000 person-years

†P for trend

Model 1, adjusted for age and sex

Model 2, Model 1 + RHR, LDL-C, HDL-C, baseline FPG, hypotensive drugs, hypoglycemic drugs, hypertension and diabetes mellitus

Model 3, Model 2 + SBP, DBP, BMI, Hs-CRP, smoking status, drinking status, and physical exercise

^a Sensitivity analysis was excluded the participants with myocardial infarction event at baseline, and adjusted for variables in model 3

^b Sensitivity analysis was excluded the participants with arrhythmia (eg, atrial fibrillation, atrial flutter, atrial premature beat, ventricular ectopic beats, and/or atrioventricular block) at baseline, and adjusted for variables in model 3

^c Sensitivity analysis was excluded the participants use of β -adrenergic blocking, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and diuretics at baseline, and adjusted for variables in model 3

Abbreviations: CI, confidence interval; HR, hazard ratio; RHR, resting heart rate; DBP, diastolic blood pressure; SBP, systolic blood pressure; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; BMI, body mass index; Hs-CRP, High-sensitivity C-reactive protein; FPG, fasting plasma glucose.

Figures

Figure 1

Selection of the study population.

Figure 2

A, Kaplan-Meier estimates of heart failure grouped by quartiles of the variability independent of the mean of fasting plasma glucose levels. B, Kaplan-Meier estimates of heart failure grouped by quartiles of standard deviation of fasting plasma glucose levels. C, Kaplan-Meier estimates of heart failure grouped by quartiles of the coefficient of variability of fasting plasma glucose levels. D, Kaplan-Meier estimates of heart failure grouped by quartiles of the average real variability of fasting plasma glucose levels.

Figure 3

Hazard ratio for incident heart failure in different subgroups in overall population. Stratified analysis by age, gender, hypertension, diabetes mellitus, chronic kidney disease and body mass index was performed. HR significantly differed between older (≥ 65 years) and younger (< 65 years) participants (interaction p-value < 0.05). In this analysis, HR was adjusted for age, gender, systolic and diastolic blood pressure, resting heart rate, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, baseline fasting plasma glucose levels, high-sensitivity C-reactive protein, body mass index, history of diabetes mellitus, history of hypertension, antihypertensive medications use, antidiabetic medications use, current smoking, alcohol intake, and physical exercise. Boxes indicate the hazard ratio, limit lines indicate the 95% confidence interval, and the

vertical line (at hazard ratio 1) indicates no difference in the hazard ratios between heart failure and no heart failure. Note: CI, confidence interval; HR, hazard ratio; **Bold** values were the *P* values for interaction.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [4Supplementmaterials.pdf](#)