Research Square

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Frailty modifies the association between long-term fasting glucose variability and incident type 2 diabetes in older adults

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Abstract

Background: Type 2 diabetes (T2D) is a major contributor to morbidity in older adults, yet accurate identification of high-risk individuals remains difficult. Although long-term fasting plasma glucose (FPG) variability predicts incident T2D, whether frailty modifies this association is unclear. We examined this in a large elderly cohort.

Methods: We conducted a population-based retrospective cohort study including 71,849 Chinese adults aged ≥65 years without diabetes at baseline. Frailty was assessed using an electronic Frailty Index (eFI) derived from routinely collected electronic health records. Long-term FPG variability was quantified using the standard deviation (SD), coefficient of variation (CV), and variability independent of the mean (VIM) from three serial health examinations. Incident T2D was identified through electronic health records during follow-up. Cox proportional hazards models were used to examine associations and test interactions between frailty and glucose variability.

Results: During a median follow-up of 3.15 years, 4,635 participants developed T2D. Higher long-term FPG variability was independently associated with increased T2D risk. Frailty significantly modified this association. Each standard deviation increase in FPG-SD was associated with a 24% higher risk of incident T2D among non-frail participants (HR 1.24, 95% CI 1.21–1.27), compared with a 13% higher risk among frail participants (HR 1.13, 95% CI 1.02–1.25). Similar interaction patterns were observed for FPG-CV and FPG-VIM.

Conclusions:

Frailty substantially influences the predictive value of long-term glucose variability for incident T2D in older adults. These findings suggest that frailty should be incorporated into glycaemic risk stratification and support a more individualized approach to diabetes prevention in ageing populations.

Background

Population ageing has led to a rapid increase in the burden of type 2 diabetes (T2D) worldwide. Older adults account for a disproportionate share of diabetes-related morbidity, disability, cardiovascular complications, and healthcare utilization[1]. Although lifestyle interventions can effectively delay or prevent the onset of T2D, their implementation at the population level requires accurate identification of older individuals at high risk. Improving diabetes risk stratification in older adults has therefore become an important priority for geriatric medicine.

Long-term fasting plasma glucose (FPG) variability has recently emerged as an independent predictor of incident T2D beyond conventional glycaemic measures, including mean FPG and glycated haemoglobin[2]. Unlike single glucose measurements, long-term glycaemic variability reflects chronic instability of glucose homeostasis and may capture early metabolic dysregulation before overt diabetes develops[3]. Previous large population-based studies have consistently demonstrated that greater visit-

to-visit FPG variability is associated with an increased risk of incident T2D, suggesting that glucose variability may represent a useful marker for early diabetes risk assessment[4, 5]. However, these studies have generally assumed that the predictive value of glucose variability is homogeneous across older populations, despite the marked heterogeneity in biological ageing and physiological reserve among older adults.

Frailty has emerged as one of the most important indicators of biological ageing and has become central to individualized care in older adults[6]. Characterized by reduced physiological reserve and impaired homeostatic capacity across multiple organ systems, frailty profoundly influences metabolic regulation, body composition, inflammatory responses, and resilience to physiological stress[7]. Increasing evidence suggests that frailty is associated with altered glucose metabolism and an elevated risk of diabetes and other cardiometabolic diseases[8, 9]. More importantly, because frailty reflects substantial changes in underlying physiology, biomarkers that accurately predict disease risk in robust older adults may not retain the same predictive value in frail individuals[10]. Therefore, frailty should not simply be regarded as another risk factor for diabetes, but rather as a potential modifier of how metabolic biomarkers are interpreted in clinical practice.

Recent advances in electronic health records (EHRs) have enabled large-scale assessment of both longitudinal glycaemic trajectories and frailty in routine clinical care[11, 12]. The electronic Frailty Index (eFI), developed using routinely collected EHR data based on the cumulative deficit model, has demonstrated good validity for identifying frailty in population-based studies while requiring no additional clinical assessment[13, 14]. Combining EHR-derived frailty with longitudinal glucose variability therefore provides an opportunity to develop more individualized and scalable approaches for diabetes risk stratification in older adults[15, 16].

Despite the growing clinical importance of both glycaemic variability and frailty, whether frailty modifies the association between long-term glucose variability and incident T2D remains unknown. Addressing this question is clinically relevant because it may improve interpretation of glucose variability and facilitate more personalized diabetes prevention strategies in ageing populations. Therefore, using a large population-based cohort of 71,849 Chinese older adults with longitudinal EHR data, we investigated the association between long-term FPG variability and incident T2D and examined whether this association differed according to frailty status assessed by the electronic Frailty Index.

Methods

Study population

This is a population-based cohort study utilizing electronic health record (EHR) linked data. A total number of 152,965 individuals were recruited from community health centers in Chongqing and Kunshan, China, between May 2019 and August 2021. The community health centers will conduct free annual health examinations for the local older population. The results of health examinations were

uploaded to the EHR system. All participants signed informed consent to contribute their EHR for investigations aiming to improve the health of the older people. The study protocol was approved by the institutional review board of the Fifth People's Hospital of Chongqing and the First People's Hospital of Kunshan.

We collected EHR data of the recruited population from 2014 to 2021 based on the regional health information system which covered all aspects of the public health and medical care services managed by the local health commission. The EHR data was anonymized based on the Chinese confidentiality guidelines. The health examination database of the EHR data recorded comprehensive data on lifestyle and laboratory measurements. The medical treatment database of the EHR data recorded the results of diagnosis, medication, and admission. Individuals were excluded from the analysis if their EHR data had any missing of the following: at least one missing variable, fewer than three health examinations, a T2D diagnosis before the third examination, age below 65 at the third examination, or a missing eFI during the third examination. Finally, 71,849 individuals were used in the statistical analysis (Fig. 1).

Assessment of glucose variability

Glucose variability was evaluated using fasting glucose measurements from three serial health examinations. Three commonly used metrics of glucose variability including coefficient of variation (CV), standard of deviation (SD), and variability independent of the mean (VIM) were calculated. VIM was defined as $100*\mathrm{SD}/\mathrm{mean}^{\beta}$, where β is the regression coefficient, based on the ln of the SD over the ln of the mean.

Assessment of frailty

The eFI was calculated based on the cumulative deficit model. Briefly, the selection of variables adhered to the core criteria: (a) biological relevance, (b) age-related, (c) avoidance of early saturation, and (d) coverage of a range of systems. Following these criteria and building upon the Frailty Index (FI) developed by Fan J et al. for the Chinese population, a total of 26 items were selected for the eFI construction in this study. These items comprised various diseases, signs, symptoms, and abnormal test results. Consistent with the original deficit accumulation model, we calculated the eFI by dividing the sum of deficit items by the total number of items. A higher eFI score indicates a more severe frailty status. To validate the eFI, the association between eFI and an established clinical frailty parameter, the FRAIL scale, was calculated. Spearman's correlation coefficient was calculated between continuous eFI and FRAIL scale scores. By previous reports, the frailty status was categorized into two groups: frailty (eFI ≥ 0.25), and non-frailty (eFI < 0.25)[8].

T2D definitions

The diagnosis of type 2 diabetes was defined based on the ICD-10 codes (E11–E14) or fasting glucose levels $\geq$ 7 mmol/L (126 mg/dL).

Statistical analysis

Baseline characteristics of individuals were presented as the mean (SD) for quantitative parameters and percentage for categorical variables. The individuals were stratified into four groups according to the quartiles of FPG variability. The baseline characteristics between different quartiles were compared using ANOVA or χ^2 test. The cumulative incidence of T2D events across quartiles of FPG variability was calculated, and the log-rank test was performed to test the differences between quartiles.

The Cox proportional hazard model was used to estimate the hazard ratio (HR) and 95% CI of FPG variability on T2D. The association between FPG variability and T2D incidence was examined by multivariate Cox regression. The likelihood ratio test for trends was used to demonstrate the relationship between quartiles of FPG variability and the risk of T2D. Effect modification was concluded when the slope of the interaction term of FPG variability and eFI was significant in the Cox models. The proportional hazard assumption in the Cox model was assessed with the Schoenfeld residuals test. All statistical analyses were performed using R software version 4.2.1. The statistical significance level was set at a 2-tailed $P < 0.05$.

Results

Baseline characteristics

Table 1 shows the baseline characteristics of the 71,849 participants according to the quartiles of FPG-SD. The mean age of the participants was 72.23 years. Age, mean FPG, and triglyceride were positively associated with FPG-SD. A higher prevalence of hypertension and frailty was also observed with increasing FPG-SD. Moreover, higher quartiles of FPG-SD tended to have poor health habits including smoking and lack of exercise. Similar associations existed in FPG-CV and FPG-VIM (Supplementary Tables 1 and 2).

Table 1
Baseline characteristics of subjects according to the quartiles of FPG-SD

Age, years	**Q1 (n = 17,870)**	**Q2 (n = 18,346)**	**Q3 (n = 18,073)**	**Q4 (n = 17,560)**	***P* value**
	71.93 (5.59)	**71.95 (5.72)**	**72.24 (5.86)**	**72.81 (6.15)**	**< 0.001**
Women (%)	8173 (45.8)	8387 (45.8)	8425 (46.7)	8309 (47.4)	0.005
BMI, mean (SD)	23.49 (2.89)	23.50 (2.90)	23.49 (2.91)	23.53 (2.95)	0.455
Waist, mean (SD)	81.06 (7.97)	81.16 (7.98)	81.21 (7.91)	81.24 (8.03)	0.133
Mean FG, mean (SD)	5.33 (0.48)	5.34 (0.49)	5.34 (0.52)	5.49 (0.69)	< 0.001
FPG variability					
SD (mmol/L)	0.13 (0.05)	0.27 (0.04)	0.43 (0.05)	0.77 (0.26)	< 0.001
CV (%)	2.38 (0.98)	5.11 (0.90)	8.07 (1.26)	14.09 (4.32)	< 0.001
VIM (%)	1.36 (0.57)	2.91 (0.57)	4.59 (0.82)	7.93 (2.49)	< 0.001
Current smoking	2221 (12.4)	2415 (13.2)	2592 (14.3)	2512 (14.3)	< 0.001
Regularly exercise	1201 (6.7)	1088 (5.9)	1057 (5.8)	991 (5.6)	< 0.001
TC, mean (SD)	4.91 (2.15)	4.93 (2.23)	4.87 (2.15)	4.82 (2.28)	< 0.001
TG, mean (SD)	1.49 (0.96)	1.50 (0.99)	1.50 (0.95)	1.54 (1.01)	< 0.001
HDL, mean (SD)	1.50 (0.57)	1.49 (0.51)	1.49 (0.53)	1.48 (0.60)	0.002
LDL, mean (SD)	2.79 (1.01)	2.82 (0.90)	2.80 (1.02)	2.82 (1.07)	0.001
Hypertension, %	9,023 (50.5)	9,730 (53.0)	9,939 (55.0)	9,833 (56.0)	< 0.001
Frail participants, %	566 (3.2)	582 (3.2)	634 (3.5)	669 (3.8)	0.002

Association between FPG variability and incident T2D

During a median follow-up period of 3.15 (interquartile range 1.44–4.61) years, there were 4,635 individuals diagnosed with T2D. As illustrated in Fig. 2, elevated FPG variability was significantly associated with higher T2D incidence without or with ($P < 0.001$ and $P < 0.001$) adjustment for known

risk factors of T2D. Individuals in the top quartile of FPG-SD had a higher risk of T2D (HR: 3.45, 95% CI: 3.16–3.77) compared to the lowest quartile in the basic model (Table 2). After adjusting for known established T2D risk factors, higher T2D incidence (HR: 2.19, 95% CI: 2.00–2.40) was also observed in the top quartile of FPG-SD compared to the lowest quartile (Table 2). Similar associations were observed in the FPG-CV and FPG-VIM. Cumulative incidence curves demonstrated that higher T2D incidence in the higher FPG variability quartile groups, compared with the lower FPG variability groups (Fig. 2).

Table 2
The associations between FPG variability and incident T2D

	Participants/events (n)	Median follow-up duration (person-years)	Incidence rate (per 1,000 person-years)	Basic model		Full model	
				HR (95% CI)	P value	HR (95% CI)	P value
FPG-SD							
Q1	17,870/640	55,862	11.46	1		1	
Q2	18,346/803	56,747	14.15	1.23 (1.11–1.37)	< 0.001	1.17 (1.05–1.30)	0.003
Q3	18,073/1,022	59,666	17.13	1.54 (1.39–1.70)	< 0.001	1.39 (1.26–1.54)	< 0.001
Q4	17, 560/2,170	55,037	39.43	3.45 (3.16–3.77)	< 0.001	2.19 (2.00-2.40)	< 0.001
P for trend					< 0.001		< 0.001
FPG-CV							
Q1	18,109/721	54,228	13.30	1		1	
Q2	18,085/901	55,989	16.09	1.24 (1.13–1.37)	< 0.001	1.22 (1.10–1.34)	< 0.001
Q3	18,049/1,137	58,7251	19.52	1.54 (1.40–1.69)	< 0.001	1.52 (1.38–1.67)	< 0.001
Q4	17,606/1,876	57, 786	32.46	2.59 (2.38–2.82)	< 0.001	2.17 (1.99–2.37)	< 0.001
P for trend					< 0.001		< 0.001
FPG-VIM							
Q1	18,107/757	53,180	14.23	1		1	
Q2	18,080/926	55,924	16.56	1.21 (1.10–1.33)	< 0.001	1.21 (1.10–1.34)	< 0.001
Q3	18,037/1,173	58,114	20.18	1.51 (1.38–1.66)	< 0.001	1.54 (1.40–1.68)	< 0.001

	Participants/events (n)	Median follow-up duration (person-years)	Incidence rate (per 1,000 person-years)	Basic model		Full model	
				HR (95% CI)	P value	HR (95% CI)	P value
Q4	17,625/1,779	58,428	30.45	2.31 (2.12–2.52)	< 0.001	2.19 (2.01–2.39)	< 0.001
P for trend					< 0.001		< 0.001
Full model was adjusted for age, sex, BMI, alcohol, smoking, exercise, hypertension, waist, low-density lipoprotein, high-density lipoprotein, total cholesterol, triglyceride, mean FPG							

Association of FPG variability with T2D risk in non-frail and frail groups

All participants were categorized into two groups non-frailty (eFI $<$ 0.25) and frailty (eFI $\geq$ 0.25) according to their eFI. The associations of the continuous standard values of FPG-SD variability with incident T2D in the frail and non-frail groups were analyzed. As illustrated in Table 3, we observed a significant interaction between the eFI and FPG-SD variability on the T2D risk in the models without or with adjusting for other risk factors (*P* for interaction < 0.001, *P* for interaction = 0.047), suggesting that frailty had a significant influence on the association of FPG-SD variability with incident T2D. Each standard deviation increment in FPG-SD variability was associated with 24% (95% CI: 21%-27%) higher T2D risk after adjusting the confounders in the non-frail groups. However, each standard deviation increment in FPG-SD variability was associated with 13% (95% CI: 2%-25%) higher T2D risk after adjusting the confounders in the frail groups. Similarly, the same results were observed in the FPG-CV and FPG-VIM. The negative interaction suggests that the association of FPG variability with incident T2D was stronger in non-frail individuals than in frail individuals.

Table 3
HR and 95% CI for every 1 SD increase of FPG variability in non-frail and frail groups.

	Basic model		**Full model**	
	HR (95% CI)	***P* value**	**HR (95% CI)**	***P* value**
Non-frail group				
FPG-SD	1.67 (1.63–1.70)	< 0.001	1.24 (1.21–1.27)	< 0.001
Frail group				
FPG-SD	1.41 (1.29–2.54)	< 0.001	1.13 (1.02–1.25)	0.023
P for interaction		< 0.001		0.047
Non-frail group				
FPG-CV	1.42 (1.40–1.45)	< 0.001	1.30 (1.27–1.33)	< 0.001
Frail group				
FPG-CV	1.25 (1.12–1.39)	< 0.001	1.14 (1.02–1.28)	0.017
P for interaction		0.017		0.014
Non-frail group				
FPG-VIM	1.36 (1.33–1.39)	< 0.001	1.35 (1.32–1.39)	< 0.001
Frail group				
FPG-VIM	1.20 (1.06–2.35)	0.003	1.16 (1.03–1.32)	0.017
P for interaction		0.046		0.011
Full model was adjusted for age, sex, BMI, alcohol, smoking, exercise, hypertension, waist, low-density lipoprotein, high-density lipoprotein, total cholesterol, triglyceride, mean FPG				

Discussion

In this large population-based cohort of more than 70,000 older adults, we demonstrated that greater long-term fasting plasma glucose variability was independently associated with an increased risk of incident T2D. More importantly, we found that frailty significantly modified this association, with glucose variability showing substantially stronger predictive value among non-frail older adults than among frail individuals. These findings were consistently observed across three complementary measures of glycaemic variability, suggesting that frailty influences the clinical interpretation of glucose variability rather than representing merely another risk factor for diabetes. To our knowledge, this is the first large-scale study demonstrating that frailty modifies the association between long-term glucose variability and future T2D.

Our findings extend previous evidence regarding glycaemic variability and diabetes risk. Previous studies have consistently reported that greater visit-to-visit glucose variability predicts future T2D independently of average glucose levels. However, these studies largely treated older adults as a homogeneous population and assumed that glucose variability has comparable predictive value across different ageing phenotypes. Older adults exhibit substantial heterogeneity in physiological reserve, metabolic regulation and functional status, with frailty representing one of the most clinically relevant manifestations of biological ageing. Our results suggest that identical levels of glucose variability may indicate different levels of diabetes susceptibility depending on frailty status. Therefore, incorporating frailty into diabetes risk assessment may improve the interpretation of glycaemic variability and facilitate more individualized prevention strategies in older adults.

Several biological mechanisms may explain why frailty attenuates the association between glucose variability and incident T2D[17, 18]. Long-term glucose variability has been linked to oxidative stress, chronic inflammation, endothelial dysfunction and impaired β-cell function, all of which contribute to insulin resistance and diabetes development[19, 20]. In contrast, frailty is characterized by profound alterations in body composition, nutritional status, hormonal regulation and energy metabolism[21, 22]. Weight loss and reduced adiposity, common features of frailty, may partially alleviate insulin resistance despite declining physiological reserve[23, 24]. Consequently, glucose variability may be less reflective of progressive metabolic dysfunction among frail older adults than among robust individuals[25, 26]. Alternatively, frailty itself encompasses multiple competing pathological processes, including sarcopenia, chronic inflammation and multimorbidity, which may reduce the relative contribution of glucose variability to diabetes risk[27]. Future studies integrating longitudinal metabolic phenotyping and biomarkers of biological ageing are needed to clarify these mechanisms.

An important strength of this study lies in its translational potential. Both long-term glucose variability and frailty were derived from routinely collected electronic health records, making this approach readily scalable without requiring specialized laboratory testing or additional clinical assessments[28]. As healthcare systems increasingly adopt electronic frailty assessment in routine geriatric practice, integrating frailty with longitudinal glycaemic information may provide a practical strategy for precision diabetes prevention. Rather than applying identical risk thresholds to all older adults, our findings support a frailty-informed interpretation of glucose variability, thereby contributing to more personalized risk stratification in ageing populations.

This study has several strengths. It included a large population-based cohort with more than 70,000 older adults and over 4,600 incident T2D events, providing substantial statistical power. The consistency of findings across three complementary measures of glucose variability supports the robustness of our results. Furthermore, frailty was assessed using a validated electronic Frailty Index derived from routinely collected healthcare data, enhancing the clinical applicability of our findings. Several limitations should also be acknowledged. First, the observational design precludes causal inference despite comprehensive adjustment for potential confounders. Second, participants were exclusively older

Chinese adults, and external validation in other ethnic populations is warranted. Third, although the electronic Frailty Index has been extensively validated, other frailty models such as the frailty phenotype may capture different dimensions of frailty. Finally, mechanistic pathways underlying the interaction between frailty and glucose variability require further investigation.

Conclusion

In conclusion, frailty significantly modifies the association between long-term glucose variability and incident T2D among older adults. Our findings suggest that frailty should be considered when interpreting glucose variability for diabetes risk assessment and support the integration of routinely collected frailty information into individualized diabetes prevention strategies for ageing populations.

Declarations

Clinical trial number: Not applicable.

Ethics approval and consent to participate:This study was formally registered in an official regulatory registry (Registration No.: IEC-SOP-007-A07-V4.0; registration date: August 11, 2023). Ethical approval was granted by the Independent Ethics Committee of the First People's Hospital of Kunshan. All participants gave their written informed consent to take part in this study, and signed informed-consent documents were completed by every participant.All procedures performed in this study involving human participants were in accordance with the ethical standards of the committee and with the 1964 Declaration of Helsinki and its subsequent amendments.

Consent for publication:Not applicable.

Availability of data and materials:The datasets generated and/or analysed during the current study are not publicly available due [REASON WHY DATA ARE NOT PUBLIC] but are available from the corresponding author on reasonable request.

Competing interests: None declared.

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Authors' contributions:

PY: experimental design, article writing, statistical analysis of data;

ZL, SJ: Statistical analysis of data, mapping;

ZJL ,LYJ:Conduct research, collect data, and organize data;

ZKX: Research guidance, paper review, financial support.

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Figures

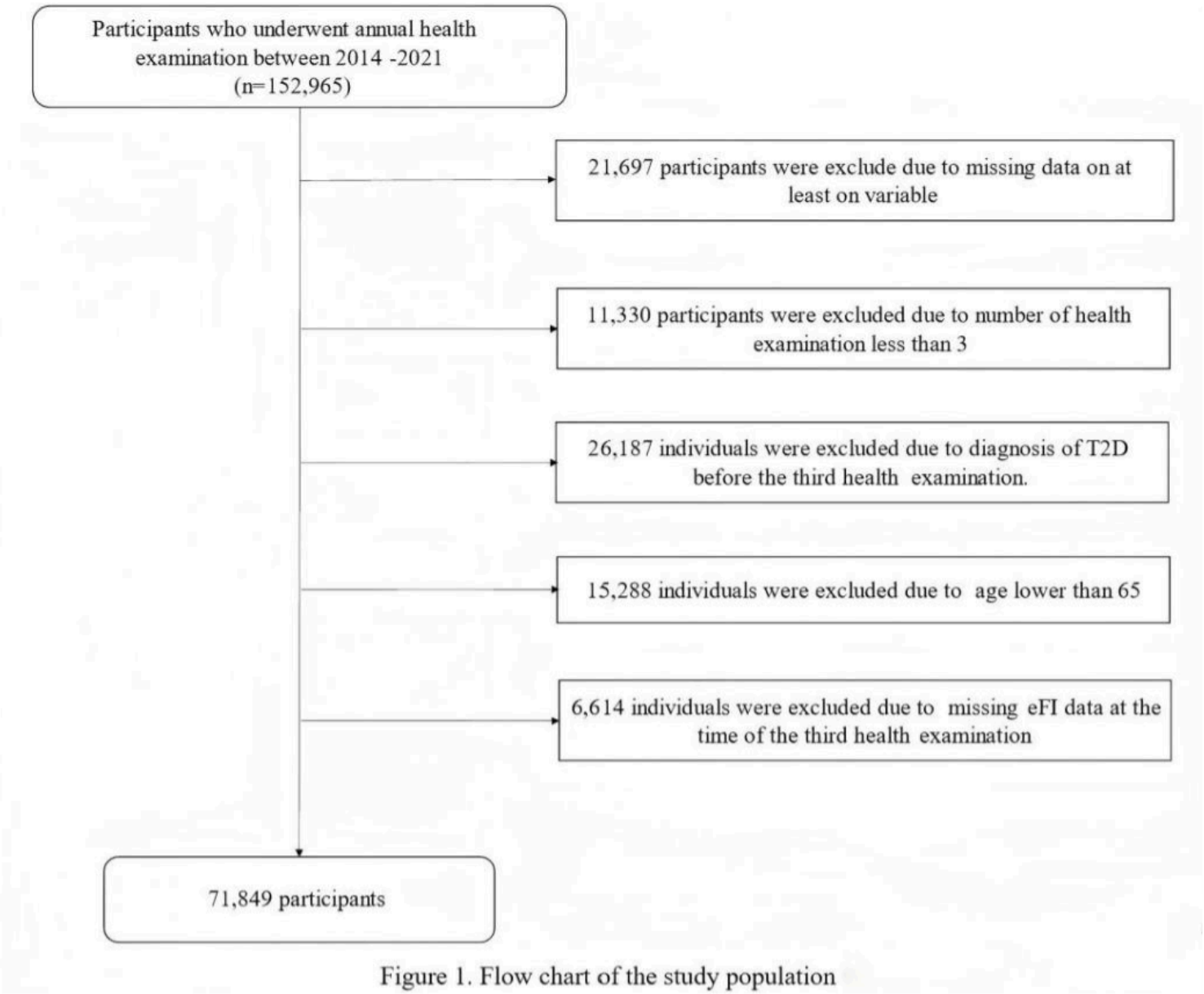


Figure 1. Flow chart of the study population

Figure 1

See image above for figure legend.

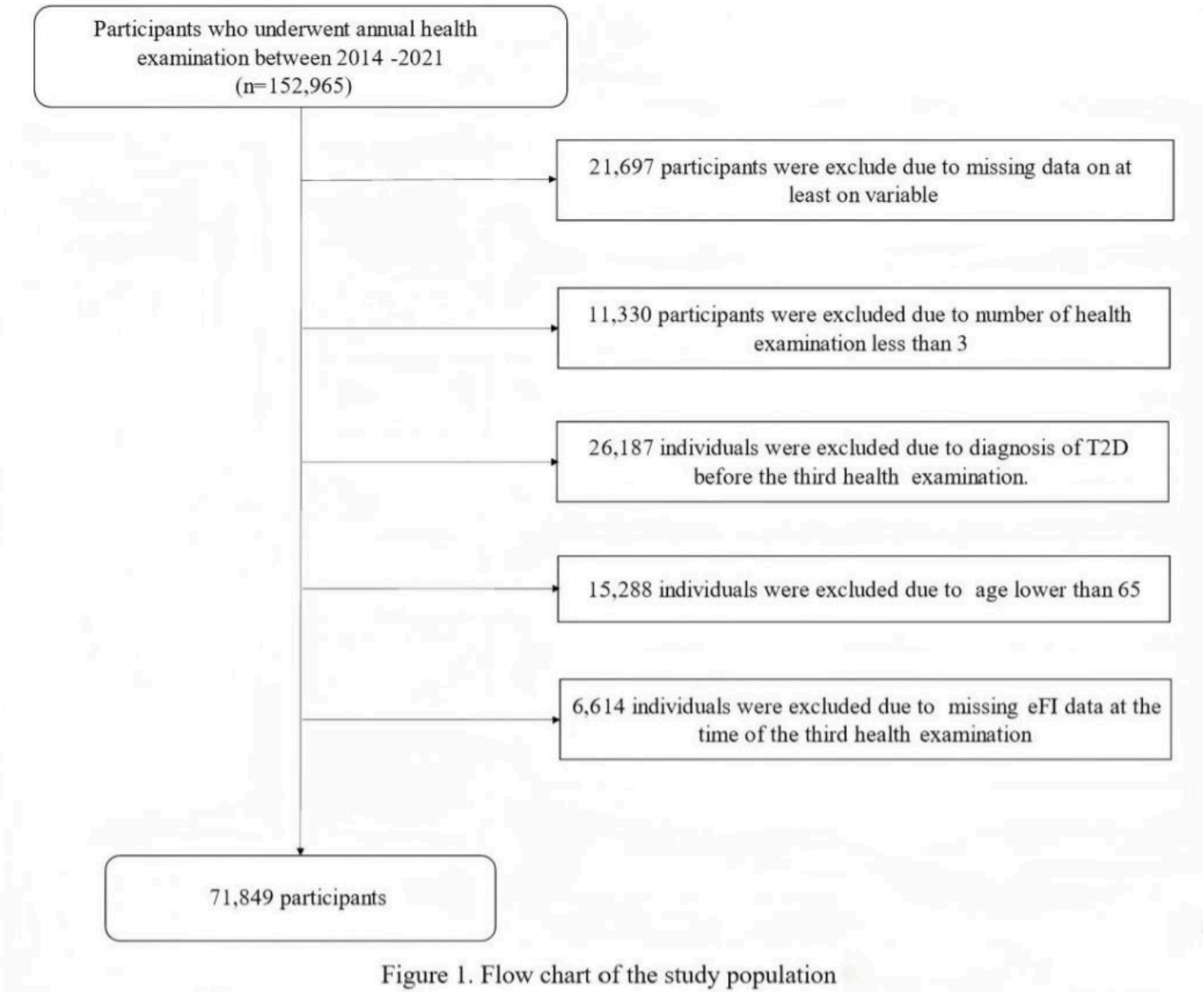


Figure 1. Flow chart of the study population

Figure 1

See image above for figure legend.

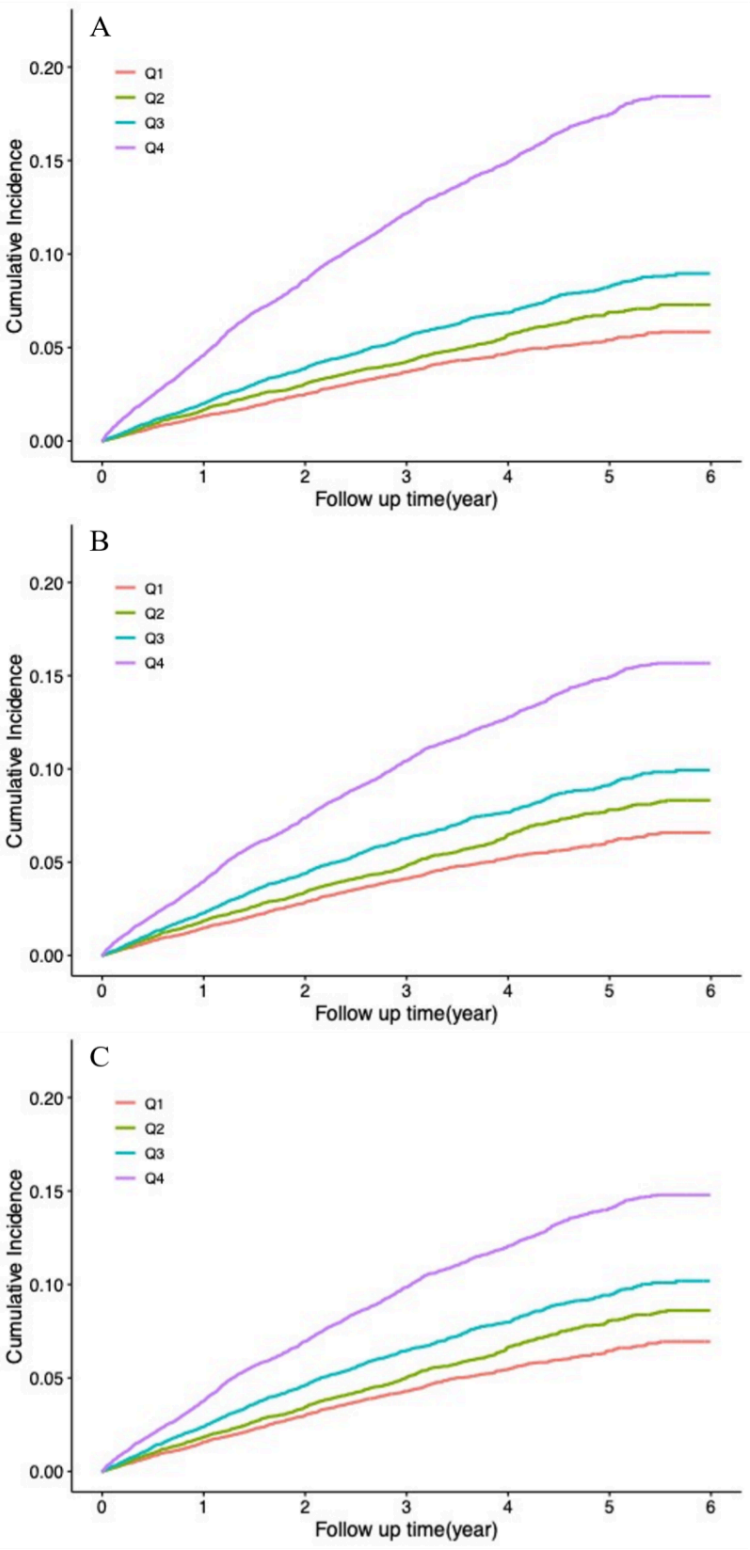


Figure 2

Cumulative incidence curves for the T2D events according to the quartiles of FPG variability (A: FPG-SD, B: FPG-CV, C: FPG-VIM, Q1: First quartile, Q2: Second quartile, Q3: Third quartile, Q4: Fourth quartile)

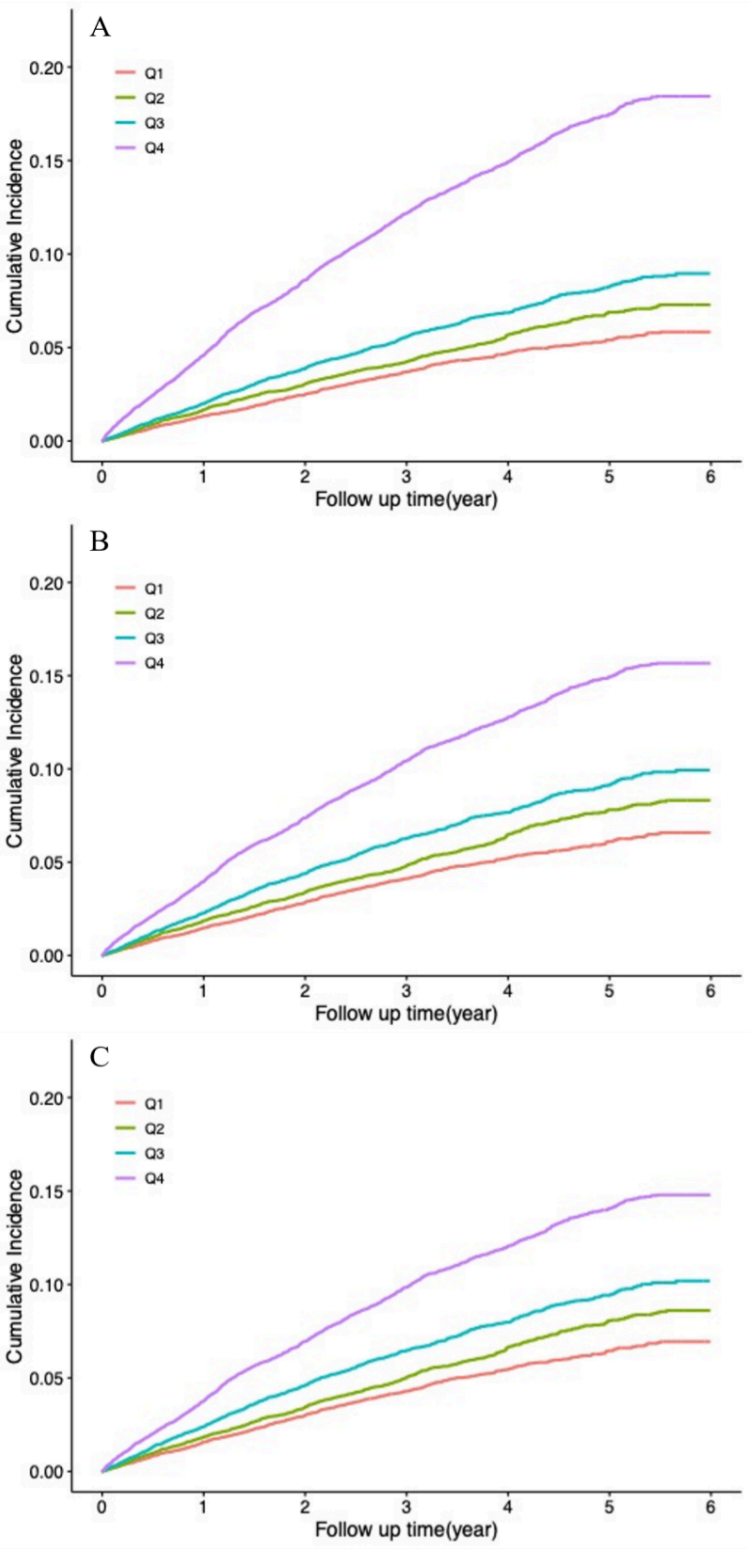


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