Glycated Hemoglobin and Risk of Arterial Stiffness in Chinese Han Population: A Longitudinal Study

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Abstract

Background: Glycated hemoglobin (HbA1c) is related to the risk and the progression of arterial stiffness, and such association can be found between fasting blood glucose (FBG), postprandial blood glucose (PBG), triglyceride-glucose index (TyG Index) and arterial stiffness. But the relationship in different studies is inconsistent, such longitudinal studies were sparse, and the comparison in effects of these four parameters on arterial stiffness was less conducted. We aimed to explore the longitudinal relationship between HbA1c and arterial stiffness adjusting for confounding factors in Chinese Han population and compare the risk effect of HbA1c, FBG, PBG, and TyG index on arterial stiffness.

Methods: Data were collected from 2011-2012 and 2018-2019 survey in the Beijing Health Management Cohort（BHMC）study and 3048 participants were enrolled. Cox proportional hazard models were fitted to investigate the association between HbA1c, FBG, PBG, TyG index and arterial stiffness after adjusting for multiple general confounding factors.

Results: Among the 3048 subjects, 591 were diagnosed as arterial stiffness during the follow-up. The adjusted HRs (95% confidence interval (CI)) for arterial stiffness compared with the lowest quartile HbA1c group were 1.22 (95% CI: 0.93-1.62), 1.52 (95% CI: 1.17-1.98) and 2.05 (95% CI: 1.59-2.63) of the three higher quartile groups respectively, which were higher than those of FBG, PBG and TyG index. Each 1% increasing of HbA1c indicated a 39% (HR: 1.39, 95% CI: 1.25-1.53) higher risk of arterial stiffness. Sensitivity analysis showed the consistent results treating the parameters as continuous variable. No significant association was found between TyG index and the risk of arterial stiffness, neither in continuous nor in polytomous form. The restricted cubic spline showed nonlinear association between HbA1c, PBG and arterial stiffness, but such association was not found for FBG and TyG index.

Conclusion: HbA1c can be treated as an important risk factor of arterial stiffness. Individuals with higher level of HbA1c had higher risk of arterial stiffness compared with PBG, FBG and TyG index.

Background

Arterial stiffness, an important pre-stage status of disease, has a dramatic effect on the progression of severe vascular diseases [1]. Many studies have investigated the risk factors of arterial stiffness [2]. Some previous studies showed that as one of the products in the process of long-term adverse glycation, HbA1c would describe the risk of not only arterial stiffness, but cardiovascular diseases [3], and the risk increases with the increasing HbA1c level. Many indicators diagnosing arterial stiffness or the progression of atherosclerosis are adopted [4–7] in different studies. Brachial-ankle pulse wave velocity (baPWV) and ankle brachial index (ABI) are two effective methods for the definition of arterial stiffness. Many studies have explored the relationship of arterial stiffness and HbA1c [6–9]. Specially, some studies illustrated that HbA1c presented higher discriminatory power predicting increasing risk of arterial stiffness in the non-diabetic group [10]. But in some other studies such association of arterial stiffness and HbA1c did not exist [5, 11]. The two diseases, arterial stiffness and diabetes mellitus, influence each

other mutually. Recently many studies have investigated the relationship between plasma glucose parameters and arterial stiffness [12–14], such as fasting blood glucose (FBG) and postprandial blood glucose (PBG). Compared with FBG and PBG, HbA1c is more predictive in diabetes or non-diabetes population [15, 16]. However, the results among different studies are inconsistent [12, 15, 17]. As an index of insulin resistance, it is proved that TyG index is closely associated with arterial stiffness and atherosclerosis [18, 19], and according to some known mechanisms insulin resistance is associated with the progression of arterial stiffness. However, to our known, there is no study about such comparison between HbA1c and TyG index in risk of arterial stiffness.

Currently some studies have been performed to mainly explore the relationship between HbA1c and risk of arterial stiffness, but longitudinal studies comparing the performance of HbA1c, FBG, PBG and TyG index on arterial stiffness are sparse. Additionally, most of the studies are cross-sectional [15, 16], and the results of multiple studies are inconsistent [4, 20, 21]. Longitudinal studies to clarify the association are required.

In this cohort study, we aimed to explore the longitudinal relationship between HbA1c and the risk of arterial stiffness mainly, compare the effect of HbA1c, PBG, FBG and TyG index on arterial stiffness, and provide effective information for population with different levels of HbA1c, PBG, FBG and TyG index.

Methods

Study Population

As a cohort study, Beijing Health Management Cohort (BHMC) study aims to explore the important chronic diseases and general factors among participants at work or in retirement in Beijing. At the 2011-2012 baseline survey, 8917 participants took the diagnostic test of arterial stiffness. Of 8917 participants, 2555 participants with cardiovascular diseases, cancer or atherosclerosis and without information about HbA1c were excluded. 3314 participants failed to take the final diagnostic test at the end point of the cohort study in 2018-2019 survey. 3048 participants finishing the follow-up were enrolled in the study (Figure 1). We obtained the ethical approval from the Ethics Committee of the Capital Medical University (number 2013SY26) and informed consents from all of the participants.

Data Collection

The physical examination and measurement was conducted by trained medical professionals in the whole process based on the 1964 Declaration of Helsinki and the updated version.

Participants were required to take off shoes and heavy clothes to take the anthropometric measurement. Body mass index (BMI) is the measure of dividing the weight (kg) by the square of the height (m^2). After at least 5 minutes' rest and 30 minutes' against caffeine, mean arterial pressure (MAP) was calculated as diastolic blood pressure (DBP) plus one third of pulse pressure, and the latter was measured as systolic blood pressure (SBP) minus DBP. Participants were supposed to keep calm in the sitting position, and the

technology should be put at the height of heart, as well as the tested right arm. Such test should be conducted at least three times with 1-2 minutes' intervals, and the mean of the records was applied.

After at least 12 hours' overnight fast, the blood samples were collected from participants, and the following main indexes were tested by a chemistry analyzer, Beckman LX 20, Beckman, Brea, CA, USA: HbA1c, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), FBG and PBG. All analyses, such as samples transportation and the enzymatic method, were performed according to the manufacturer's recommendations.

Demographic data can be obtained according to the questionnaire. Briefly, information about age, gender, and behavioral factors, including physical activity intensity (low, moderate and high intensity), education level (lower than high-school education and over or equal to high-school education), excessive salt intake (>6g/day), drinking status (past/current alcohol drinker), smoking status (past/current smoker), sleep duration (<6h/day, 6-8h/day and >8h/day) and medication history of hypertension and hyperlipidemia, was collected mainly.

Definition of arterial stiffness

We defined arterial stiffness as baPWV >1800m/s or ABI <0.9 [22-24] in this study. And the above two criteria were tested with an automatic arterial stiffness analyzer. The requirement of the participants was similar with that when testing the blood pressure. We calculated ABIs as the ratio of SBP at the ankle to that on the upper arm on each side, and the minimum ratio was applied. BaPWV was calculated based on pressure in ankles and upper arms and the distance tailored to the height of each participant by the analyzer automatically, and the maximum record was applied.

Statistical Methods

We stratified the study population into quartiles based on HbA1c level (Q1 group: participants with HbA1c ≤5.29%, Q2 group: participants with HbA1c range of 5.30-5.52%, Q3 group: participants with HbA1c range of 5.53-5.81%, Q4 group: participants with HbA1c >5.81%). TyG index was calculated as the ln[fasting TG (mg/dl) × FBG (mg(dl)/2].

Continuous variables are summarized with mean ± standard deviation or median with interquartile range (IQR). Categorical variables are presented as numbers and proportions. We used ANOVA test for non-paired samples of normally distributed parameters and the Kruskal-Wallis test for non-parametric variables. The Chi-Squared test was applied for the comparison of categorical variables among four groups.

Three-step stepwise multivariable-adjusted Cox proportional hazard regression models were conducted to explore the potential association between these parameters and the risk of the arterial stiffness. Model 1 was adjusted for age and gender. Model 2 was adjusted for variables in model 1, as well as education level, smoking status, drinking status, physical activity intensity, sleep duration, excessive salt intake and

medication history. Model 3 was adjusted for variables in model 2 plus BMI, MAP, LDL-C, HDL-C and TG. As for TyG index, we excluded TG from model 3 considering the calculation.

Sensitivity analysis was performed by treating the four parameters (HbA1c, FBG, PBG and TyG index) as continuous variable in Cox analysis. The restricted cubic spline was used to assess the dose-response relationship between the average HbA1c, PBG, FBG and TyG index and the risk of arterial stiffness.

For all analyses, a two-tailed *P* value <0.05 was considered to be statistically significant. All statistical analyses were performed using R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria), SAS version 9.4 (SAS Institute, Cary, North Carolina, USA) and Stata version 15 (College Station TX StataCorp LLC).

Results

Baseline characteristics of the study population

In this cohort study, 3048 qualified participants finished the follow-up. The baseline characteristics in different groups stratified by HbA1c quartiles were summarized in Table 1. In detailed, 2311 men and 737 women were investigated. 591 participants were diagnosed as arterial stiffness in the follow-up. The distribution of participants developing arterial stiffness in the highest HbA1c quartile group compared with other quartile groups was significantly different. The distribution of age, education level and medication history among the HbA1c quartile groups was significantly different. Individuals in the higher HbA1c quartile group had significantly higher level of LDL-C, HDL-C, TG, MAP and BMI. A significant difference was not observed among different HbA1c quartile groups for physical activity intensity, smoking status, drinking status, excessive salt intake and sleep duration. The distribution of HbA1c, PBG, FBG and TyG index at baseline among individuals with and without arterial stiffness is shown in Fig. 2.

Table 1
Demographic and clinical characteristics of participants according to quartiles of HbA1c at baseline

Variables	Total	Quartiles of HbA1c				*P*
		Q1 (≤ 5.29%)	Q2 (5.30%-5.52%)	Q3 (5.53%-5.81%)	Q4 (> 5.81%)	
No. of participants, n	3048	774	772	748	754	
Arterial stiffness, n (%)	591 (19.39)	90 (11.63)	113 (14.64)	149 (19.92)	239 (31.70)	< 0.0001
Male, n (%)	2311 (75.82)	582 (75.19)	568 (73.58)	547 (73.13)	614 (81.43)	0.0004
Age, median (IQR), years	56 (48–63)	45 (52–58)	47 (54–61)	51 (57–64)	54 (59–67)	< 0.0001
Age ≥ 65, n (%)	667 (21.88)	103 (13.31)	137 (17.75)	182 (24.33)	245 (32.49)	< 0.0001
Over or equal to high-school, n (%)	2995 (98.26)	767 (99.10)	762 (98.70)	734 (98.13)	732 (97.08)	0.0165
Physical activity intensity, n (%)						0.2358
Low	623 (20.47)	143 (18.48)	152 (19.69)	169 (22.65)	159 (21.14)	
Moderate	2358 (77.46)	617 (79.72)	599 (77.59)	560 (75.07)	582 (77.39)	
High	63 (2.07)	14 (1.81)	21 (2.72)	17 (2.28)	11 (1.46)	
Past/current smoker, n (%)	276 (9.06)	67 (8.66)	61 (7.90)	78 (10.43)	70 (9.28)	0.3681
Past/current alcohol drinker, n (%)	374 (12.27)	97 (12.53)	90 (11.66)	97 (12.97)	90 (11.94)	0.8651
Excessive salt intake						0.0543
(> 6 g/day), n (%)	174 (5.71)	45 (5.81)	30 (3.89)	53 (7.09)	46 (6.10)	
Sleep duration, n (%)						0.3240
< 6 h/day	72 (2.36)	16 (2.07)	21 (2.72)	22 (2.94)	13 (1.72)	

HbA1c glycated hemoglobin, *IQR* interquartile range, *MAP* mean arterial pressure, *BMI* body mass index, *LDL-C* low-density lipoprotein cholesterol, *TG* triglycerides, *HDL-C* high-density lipoprotein cholesterol

Variables	Total	Quartiles of HbA1c				*P*
		Q1 (≤ 5.29%)	Q2 (5.30%-5.52%)	Q3 (5.53%-5.81%)	Q4 (> 5.81%)	
6–8 h/day	2868 (94.36)	731 (94.44)	729 (94.43)	702 (93.85)	706 (93.63)	
> 8 h/day	108 (3.54)	27 (3.49)	22 (2.85)	24 (3.21)	35 (4.64)	
Medication history of hyperlipidemia, n (%)	82 (2.69)	10 (1.29)	19 (2.46)	16 (2.14)	37 (4.91)	0.0001
Medication history of hypertension, n (%)	947 (31.07)	189 (24.42)	202 (26.17)	227 (30.35)	329 (43.63)	< 0.0001
MAP, median (IQR), mmHg	92.67 (84.67-100.33)	92.33 (84.00-100.00)	91.33 (83.67–99.33)	92.00 (84.33–100.00)	94.33 (86.67–102.00)	< 0.0001
BMI, median (IQR), kg/m2	25.51 (23.62–27.54)	24.91 (23.26–26.82)	25.25 (23.26–27.19)	25.47 (23.48–27.56)	26.40 (24.55–28.50)	< 0.0001
LDL-C, median (IQR), mmol/L	3.08 (2.52–3.70)	3.01 (2.51–3.59)	3.14 (2.57–3.74)	3.20 (2.64–3.82)	2.98 (2.38–3.65)	< 0.0001
TG, median (IQR), mmol/L	1.39 (1.01–2.05)	1.29 (0.95–1.89)	1.38 (0.98-2.00)	1.42 (1.03–2.06)	1.56 (1.11–2.22)	< 0.0001
HDL-C, median (IQR), mmol/L	1.20 (1.05–1.40)	1.23 (1.07–1.46)	1.22 (1.08–1.41)	1.22 (1.06–1.39)	1.12 (1.04–1.30)	< 0.0001

HbA1c glycated hemoglobin, *IQR* interquartile range, *MAP* mean arterial pressure, *BMI* body mass index, *LDL-C* low-density lipoprotein cholesterol, *TG* triglycerides, *HDL-C* high-density lipoprotein cholesterol

Association between arterial stiffness and the glucose parameters

The results indicated that compared with the lowest HbA1c quartile group, people in higher HbA1c quartile group had higher hazard ratio. The HRs (95% CI, *P* value) are 1.22 (0.93–1.62, *P* = 0.1540) for Q2 group, 1.52 (1.17–1.98, *P* = 0.0019) for Q3 group and 2.05 (1.59–2.63, *P* < 0.0001) for Q4 group

respectively with the covariates of Model 3 controlled. The effect of HbA1c did not change when more covariates entered into the model. To compare the effect of HbA1c, FBG, PBG and TyG index on the occurrence of arterial stiffness, the Cox-regression analysis was also conducted for FBG, PBG and TyG index. The risk of arterial stiffness increased across the quartiles of the blood glucose parameters, and obviously those in higher HbA1c quartile group (HR: 2.05, 95% CI: 1.59–2.63 of the highest quartile group) had the highest risk of arterial stiffness in contrast to FBG (HR: 1.42, 95% CI: 1.13–1.79 of the highest quartile group) and PBG (HR: 1.68, 95% CI: 1.29–2.20 of the highest quartile group). However, the significant relationship between TyG index and the risk of arterial stiffness was not found ($P > 0.05$) according to the result (Table 2).

Table 2
Hazard ratio (95% CI) of the parameters of the quartile groups with arterial stiffness

Variables	Model 1: HR (95% CI)	*P* value	Model 2: HR (95% CI)	*P* value	Model 3: HR (95% CI)	*P* value
Quartiles HbA1c (%)						
Q1 (≤ 5.29)	Reference		Reference		Reference	
Q2 (5.30–5.52)	1.18 (0.89–1.55)	0.2529	1.18 (0.89–1.56)	0.2423	1.22 (0.93–1.62)	0.1540
Q3 (5.53–5.81)	1.45 (1.11–1.89)	0.0058	1.47 (1.13–1.91)	0.0043	1.52 (1.17–1.98)	0.0019
Q4 (> 5.81%)	2.07 (1.61–2.64)	< 0.0001	1.92 (1.50–2.46)	< 0.0001	2.05 (1.59–2.63)	< 0.0001
FBG (mmol/L)						
Q1 (≤ 5.13)	Reference		Reference		Reference	
Q2 (5.14–5.45)	1.06 (0.82–1.36)	0.6663	1.02 (0.79–1.31)	0.9904	1.00 (0.78–1.29)	0.9926
Q3 (5.46–5.96)	1.09 (0.85–1.39)	0.5070	1.02 (0.80–1.31)	0.8547	1.00 (0.78–1.29)	0.9795
Q4 (> 5.96)	1.63 (1.30–2.05)	< 0.0001	1.48 (1.18–1.86)	0.0009	1.42 (1.13–1.79)	0.0028
PBG (mmol/L)						
Q1 (≤ 5.4)	Reference		Reference		Reference	
Q2 (5.5–6.2)	1.11 (0.83–1.50)	0.4746	1.05 (0.78–1.42)	0.7317	1.01 (0.75–1.37)	0.9430
Q3 (6.3–7.5)	1.52 (1.16-2.00)	0.0027	1.42 (1.08–1.88)	0.0122	1.40 (1.06–1.85)	0.0182
Q4 (> 7.5)	1.98 (1.52–2.57)	< 0.0001	1.75 (1.34–2.28)	< 0.0001	1.68 (1.29–2.20)	0.0001

Model 1: adjusted for age and gender.

Model 2: adjusted for variables in model 1, as well as education level, smoking status, drinking status, physical activity intensity, sleep duration, excessive salt intake and medication history.

Model 3: adjusted for variables in model 2 plus BMI, MAP, LDL-C, HDL-C and TG.

HbA1c glycated hemoglobin, *PBG* postprandial blood glucose, *FBG* fasting blood glucose, *TyG index* triglyceride-glucose index, *HR* Hazard ratio, *CI* confidence interval

Variables	Model 1: HR (95% CI)	*P* value	Model 2: HR (95% CI)	*P* value	Model 3: HR (95% CI)	*P* value
TyG						
Q1 (≤ 9.08)	Reference		Reference		Reference	
Q2 (9.09–9.45)	1.16 (0.93–1.47)	0.1946	1.09 (0.86–1.37)	0.4799	0.93 (0.73–1.17)	0.5230
Q3 (9.46–9.85)	1.43 (1.05–1.94)	0.0225	1.34 (0.99–1.82)	0.0624	0.99 (0.77–1.27)	0.9390
Q4 (> 9.85)	1.80 (1.21–2.68)	0.0040	1.66 (1.11–2.47)	0.0137	1.10 (0.84–1.44)	0.4930
Continuous						
HbA1c (%)	1.40 (1.27–1.55)	< 0.0001	1.39 (1.25–1.54)	< 0.0001	1.39 (1.25–1.53)	< 0.0001
FBG (mmol/L)	1.16 (1.10–1.23)	< 0.0001	1.16 (1.09–1.23)	< 0.0001	1.15 (1.08–1.22)	< 0.0001
PBG (mmol/L)	1.10 (1.07–1.14)	< 0.0001	1.09 (1.06–1.13)	< 0.0001	1.09 (1.06–1.12)	< 0.0001
TyG	1.33 (1.15–1.54)	0.0002	1.24 (1.07–1.45)	0.0045	1.16 (0.96–1.39)	0.1170
Model 1: adjusted for age and gender.						
Model 2: adjusted for variables in model 1, as well as education level, smoking status, drinking status, physical activity intensity, sleep duration, excessive salt intake and medication history.						
Model 3: adjusted for variables in model 2 plus BMI, MAP, LDL-C, HDL-C and TG.						
HbA1c glycated hemoglobin, *PBG* postprandial blood glucose, *FBG* fasting blood glucose, *TyG index* triglyceride-glucose index, *HR* Hazard ratio, *CI* confidence interval						

Dose-response analysis between four glucose parameters and arterial stiffness

Multivariable adjusted restricted cubic spline model with 3 knots showing the dose-response association with 95% CI applied. The result showed that there was no association between HbA1c and risk of arterial stiffness when HbA1c < 5.88%. The increasing HbA1c level above or equal to 5.88% has a significantly non-linear relationship with increasing risk of arterial stiffness. And the non-linear relationship between arterial stiffness and PBG level higher or equal to 7.7 mmol/L was also observed. However, we did not find such relationship between FBG, TyG index and the risk of arterial stiffness in its varying range (Fig. 3).

Sensitivity analysis

After adjusting for confounding variables in model 3, the risks of arterial stiffness were in the order of HbA1c (HR = 1.39, 95% CI: 1.25–1.53), FBG (HR = 1.15, 95% CI: 1.08–1.22) and PBG (HR = 1.09, 95% CI: 1.06–1.12). The association between TyG index and the risk of arterial stiffness was not significant (P = 0.1170). It is indicated that different forms of the parameters in models did not change the results (Fig. 4).

Discussion

In our longitudinal study, HbA1c in both categorical and continuous form has a significantly positive relationship with the risk of arterial stiffness after adjusting for confounding factors. And the result of dose-response analysis showed that in participants with HbA1c ≥ 5.88% the risk increased nonlinearly with the HbA1c level increased. Among the whole study population, higher level of HbA1c is significantly associated with the highest risk of arterial stiffness compared with PBG and FBG, while the same relationship was not found between TyG index and arterials stiffness.

Our result illustrated the important effect of HbA1c on arterial stiffness partly because of the glycation process. Diabetes mellitus has an adverse effect on arterial stiffness [25]. Hyperglycemia and insulin resistance are two important conditions of diabetes mellitus, and they could trigger the development of arterial lesions [26]. Insulin would moderate the stiffness of artery, while insulin-resistance would hurt this process [27]. Insulin-resistance is the important mechanism of type 2 diabetes, and some studies had illustrated the great curative effect of hypoglycemic agents on arterial stiffness with the significant reduction of HbA1c among diabetics [28]. HbA1c is an indicator of long-term blood glucose variation and advanced glycation products, so it is of vital importance as an indicator of the risk of arterial stiffness. Moreno [29] found that independent of general factors, HbA1c could express the differences of the risk of arterial stiffness between the groups with controlled and uncontrolled diabetes mellitus. And Johansen [30] found that HbA1c increasing over time or measured in baseline would have an impact on aortic stiffness. Some studies had illustrated that chronic hyperglycemia with long-term high level of HbA1c among diabetics can promote protein glycosylation and accelerate the progression of arterial stiffness [31]. In the long process of glycation, some intermediate or end glycation products would accumulate in the blood, and cellular signaling, the reaction of inflammation and oxidative stress and release of some plasma substances would be activated. Those would result in the pathological change of arterial wall and endothelial cell dysfunction, and would accelerate the progression of arterial stiffness and other vascular diseases. The decrease of NO reserve would also result in oxidative stress, contribute to decline of the ability of vasodilatation and further lead to cellular injury [32].

In our study, we found that HbA1c can be treated as the best risk indicator of arterial stiffness compared with other three glucose parameters. Some previous studies had investigated the effect of TyG index, an essential indicator of insulin-resistance, on arterial stiffness in different groups of population [29, 33–35], however, the result is inconsistent with ours. It may result from the difference of the study population, such as the distribution of health condition and the sample size. Partly because of the specific mechanism of insulin resistance on diabetes mellitus and less consideration of the participation of

diabetics in our study population, the negative association was obtained between TyG index and arterial stiffness. Also such comparison of TyG index and glucose parameters was seldom conducted, so the specific result could not be found and compared. Previously, some cross-sectional studies had investigated the role of PBG and FBG on arterial stiffness. However, the role of HbA1c had not been intensively explored, and the comparison of the effect of PBG, FBG and HbA1c on arterial stiffness had not been conducted. So our study supplies practical information when it comes to compare the potential risk among these glucose parameters of arterial stiffness. As another two important parameters about plasma glucose and diabetes mellitus, we found the lower risk of arterial stiffness of PBG and FBG compared with HbA1c, partly because of the characteristics of HbA1c as an indicator of advanced glycation end products and long-term weighted blood glucose level [36, 37]. The measurement of PBG was conducted after the meal, and the physiological process would impact the level of blood glucose. While the diet pattern, food groups and variability of the measurement would make a difference. What is more, PBG level higher or equal to 7.8 mmol/L is also treated as a disease condition, and the level of HbA1c from 4–6% can be treated as the normal condition of blood glucose. So our results of the non-linear relationship of PBG ≥ 7.7 mmol/L and HbA1c ≥ 5.88% with arterial stiffness are reliable. Although those criteria are far from strict compared with those of diabetes mellitus, they could not be ignored.

In many studies, the positive association between HbA1c and arteriosclerosis disappeared [38] after adjusting for general confounding factors. The endpoint of the present study is the occurrence of arterial stiffness diagnosed by baPWV and ABI. Many other studies investigated the relationship between HbA1c and arterial stiffness diagnosed by angiography examination. The angiography examination can reflect the progression and condition of arteriosclerosis [39], but is weaker when it comes to assess the risk of arterial stiffness at the initial stage of arteriosclerosis. According to the previous study, baPWV and ABI, as the simple and harmless measurement, can serve as a routine clinic examination of arterial stiffness [24]. The differences among these studies about diagnosis criteria would cause the contradictory results. On the other hand, some important covariates, such as age, gender and behavior characteristics, would inevitably have effects on the risk of arterial stiffness. The inconsistent results would be obtained if some important confounding factors were not included in the adjusted models. Additionally, among the studies, the classification of HbA1c is different, the sample sizes of the study population are distinct [11], and the study population is composed of individuals with different characteristics. Li [40] had illustrated that the individuals with increasing of HbA1c level only in range from 5.7–6.4% and impaired glucose tolerance had increased risk of arterial stiffness. So the differences about classification and study population should be noted. Because of the composition of health check-up participants of our study population, the result of our analysis could be applied to general population.

There are several strengths in this study. It should be emphasized that this is a longitudinal study investigating the positive association of HbA1c and arterial stiffness and enriching the evidence in such field, while previous studies were limited by their cross-sectional designs. Besides HbA1c, we additionally explored the association of PBG, FBG and TyG index with arterial stiffness and compared the potential risk among these parameters. The result highlighted the highest risk of high level of HbA1c in arterial

stiffness. The sensitivity analysis is the third strengths, and the results are stable when we treat the parameters as continuous variable.

The present study has some certain limitations. First, in this study we included all qualified individuals taking the physical examination, and some similar studies could be found [15, 44], in order that we can make our conclusion accessible to the general population. However, more participants from different nationalities or races should be enrolled. Subgroup or stratified analyses are required in our further studies. Second, we should take the long-term variation of the parameters into consideration in our future research.

Conclusions

In this longitudinal study, HbA1c is significantly associated with arterial stiffness assessed by baPWV and ABI among a Chinese Han population, and as HbA1c increases, the risk of arterial stiffness increases when HbA1c level ≥ 5.88%. Abnormal HbA1c has the highest risk of arterial stiffness compared with PBG, FBG and TyG index in the population. This study suggests the necessity for early detection and management of arterial stiffness in population with high level of HbA1c.

Abbreviations

HbA1c: Glycated hemoglobin; FBG: Fasting blood glucose; PBG: Postprandial blood glucose; TyG Index: Triglyceride-glucose index; BHMC: Beijing Health Management Cohort; baPWV: Brachial-ankle pulse wave velocity; ABI: Ankle brachial index; BMI: Body mass index; MAP: Mean arterial pressure; DBP: Diastolic blood pressure; SBP: Systolic blood pressure; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; TG: Triglycerides; HR: Hazard ratio; IQR: Interquartile range; CI: Confidence interval

Declarations

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Authors' contributions

The responsibilities of the authors were as follows—ZH and L-XT: came up with the idea and made the design of the study; X-PK made contribution to the data; ZH and J-QW conducted the statistical analysis; ZH drafted the primary manuscript; ZH, JL, JZ, J-QW, YL and Z-YW revised the manuscript and provided important advice for the modification; All authors read and approved the final manuscript.

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Availability of data and materials

The datasets analyzed in this study are not publicly available because of the private information, but are available from the corresponding author with reasonable request.

Ethics approval and consent to participate

The study was conducted obeying the rule of Declaration of Helsinki. We obtained the ethical approval from the Ethics Committee of the Capital Medical University (number 2013SY26) and informed consents from all of the participants.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

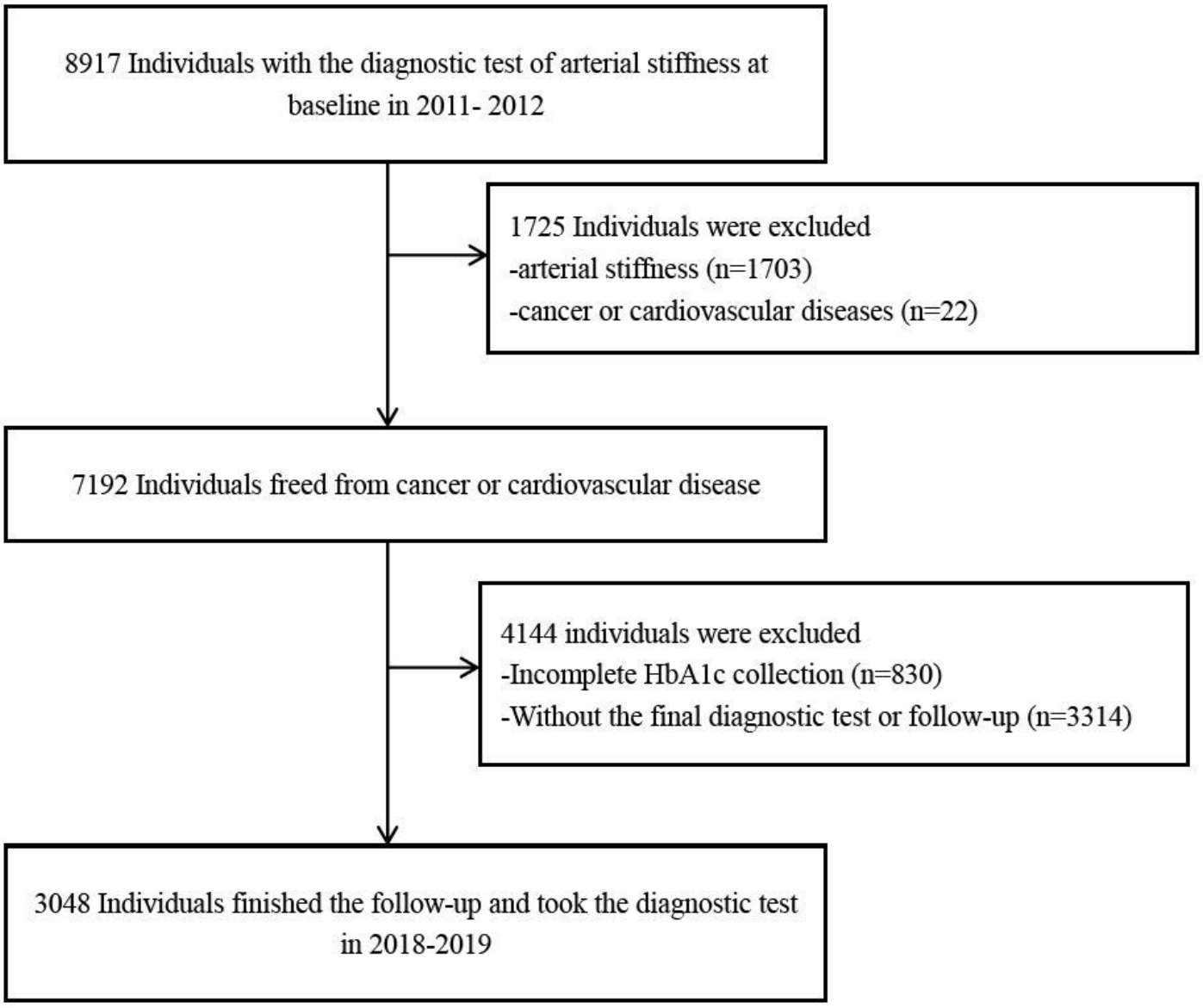
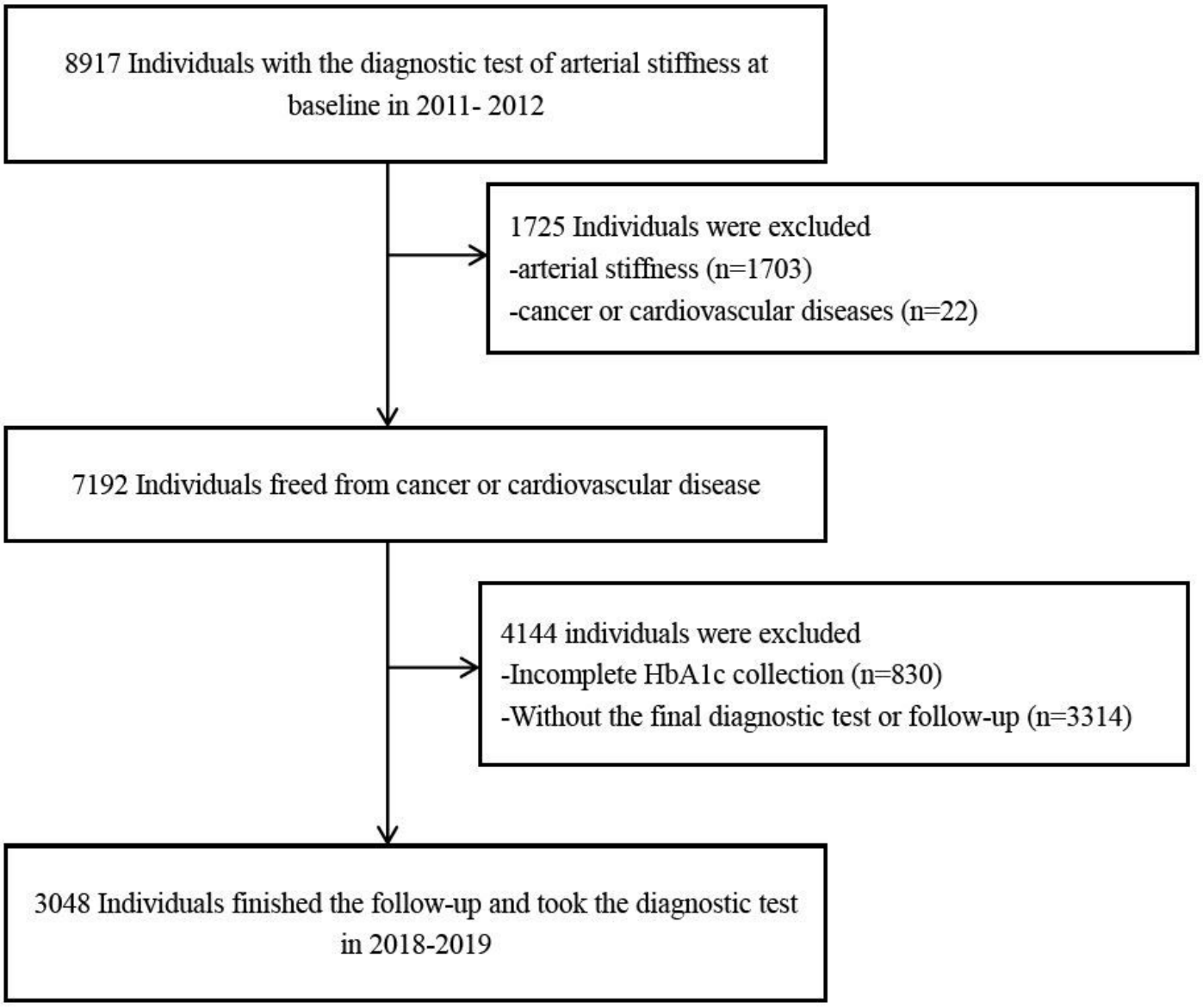


Figure 1

Flow table of the study population in Beijing Health Management Cohort from 2011-2012 to 2018-2019. HbA1c glycated hemoglobin



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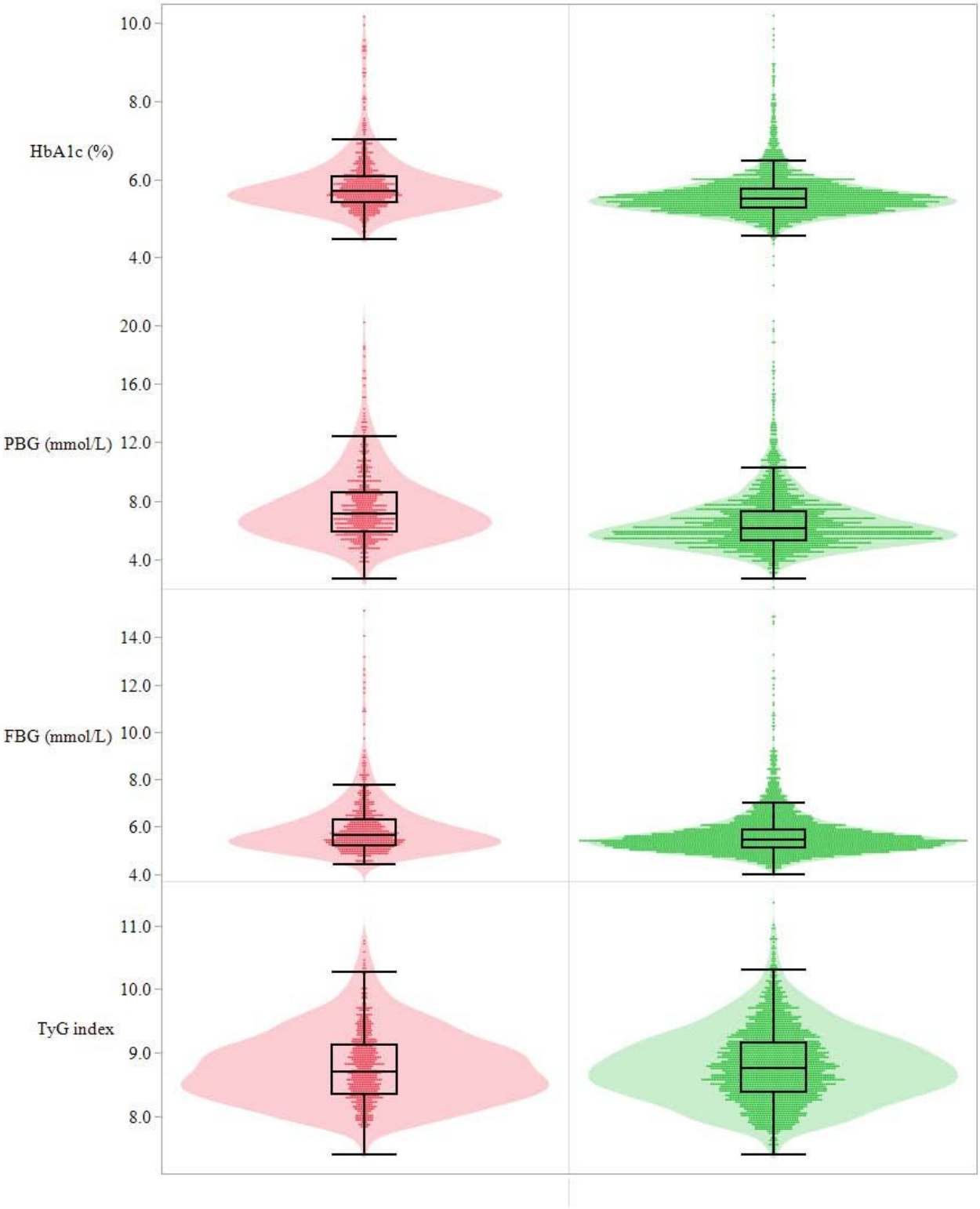
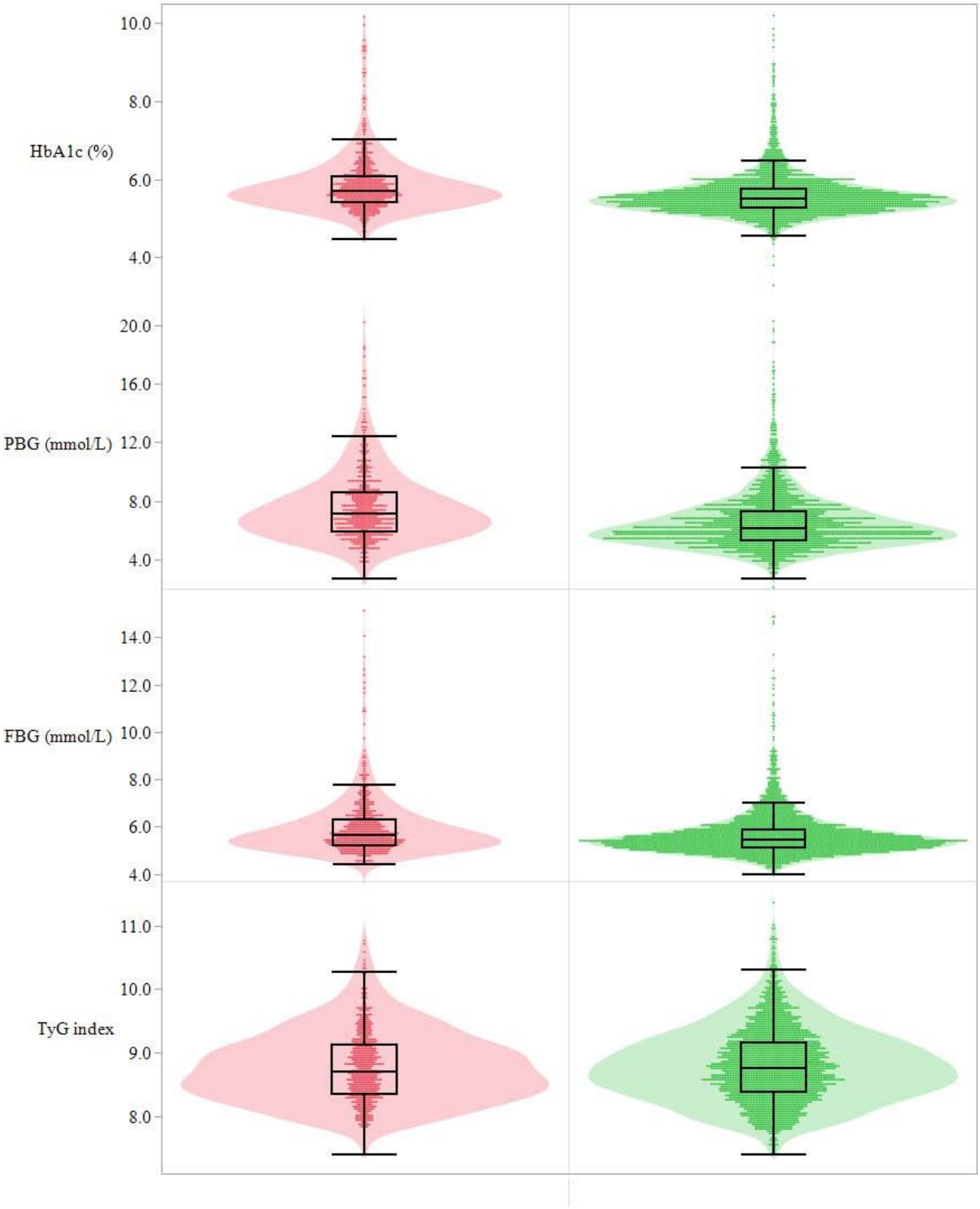


Figure 2

Distribution of the parameters at baseline among individuals with and without arterial stiffness. HbA1c glycated hemoglobin, PBG postprandial blood glucose, FBG fasting blood glucose, TyG index triglyceride-glucose index



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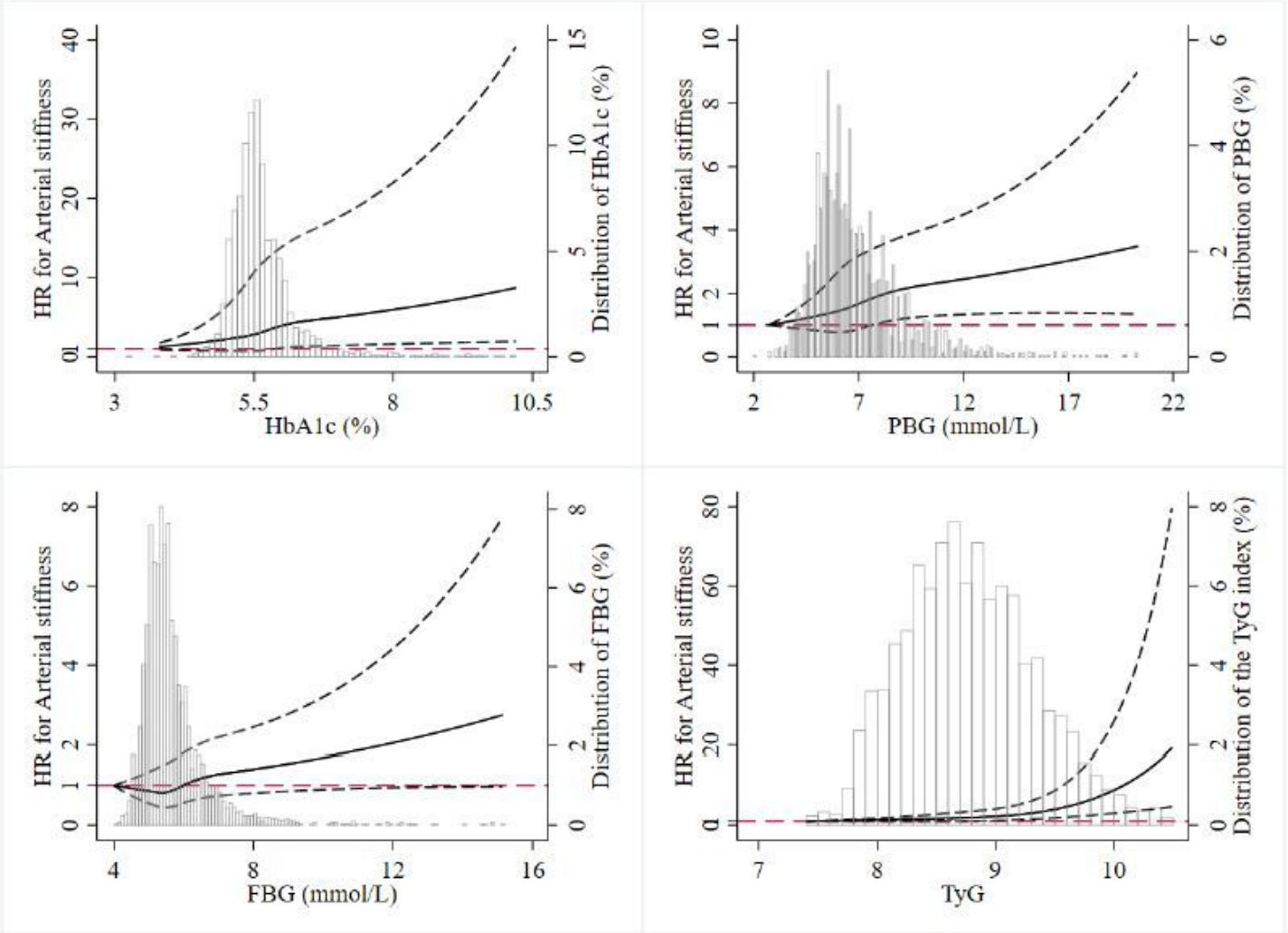
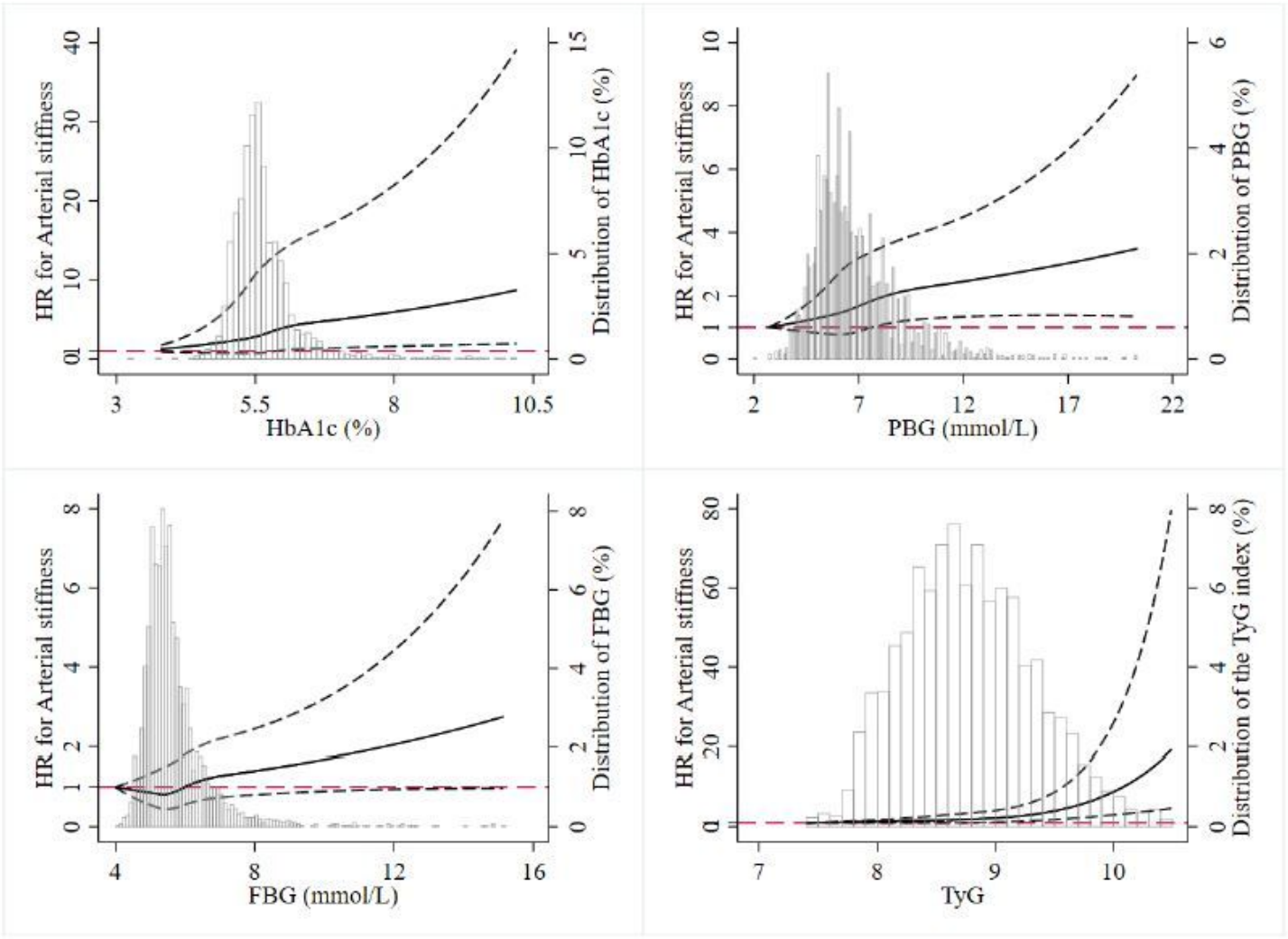


Figure 3

Dose–response relationship between the glucose parameters and the risk of arterial stiffness. HbA1c glycated hemoglobin, PBG postprandial blood glucose, FBG fasting blood glucose, TyG index triglyceride-glucose index, HR Hazard ratio



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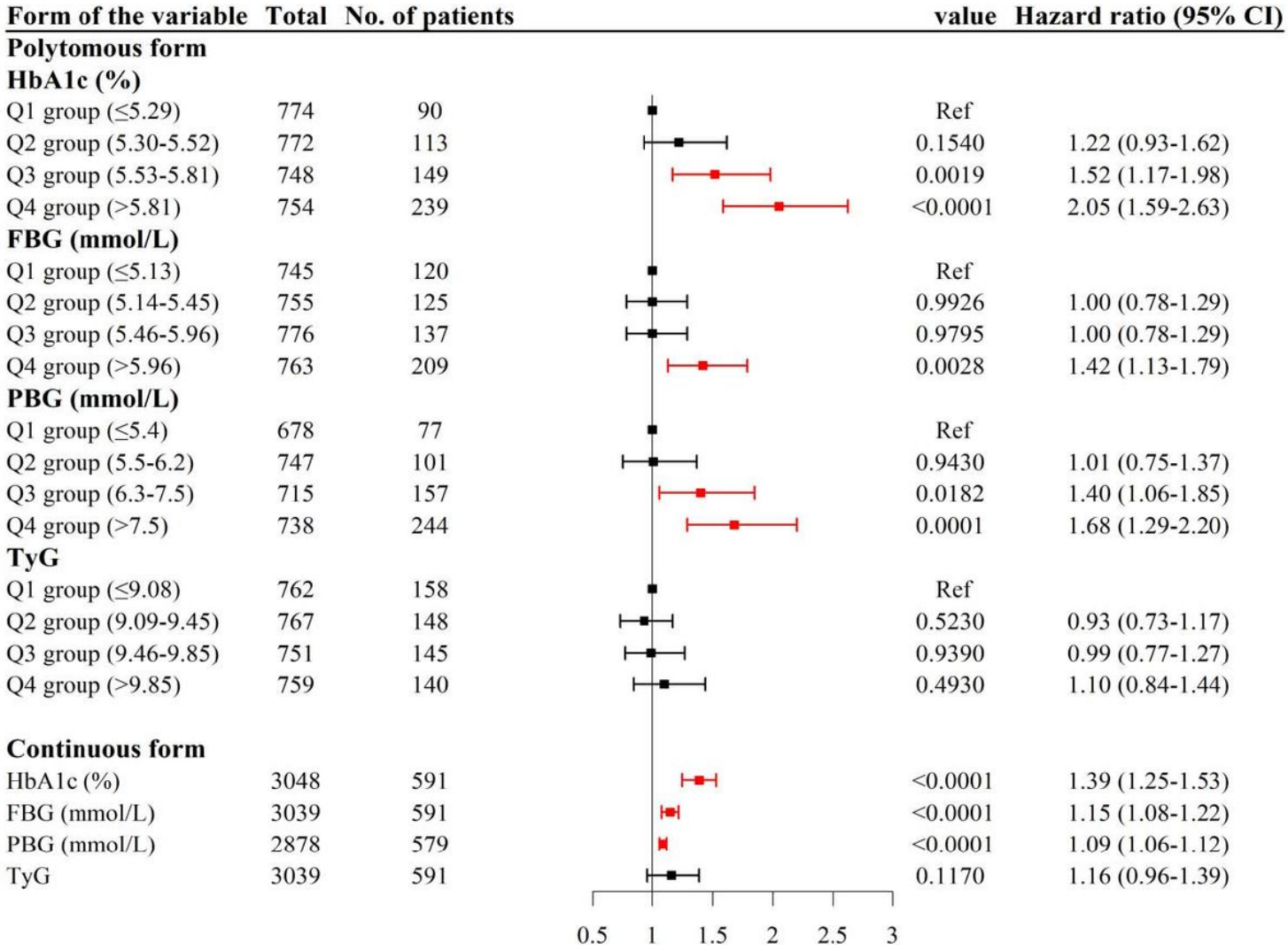
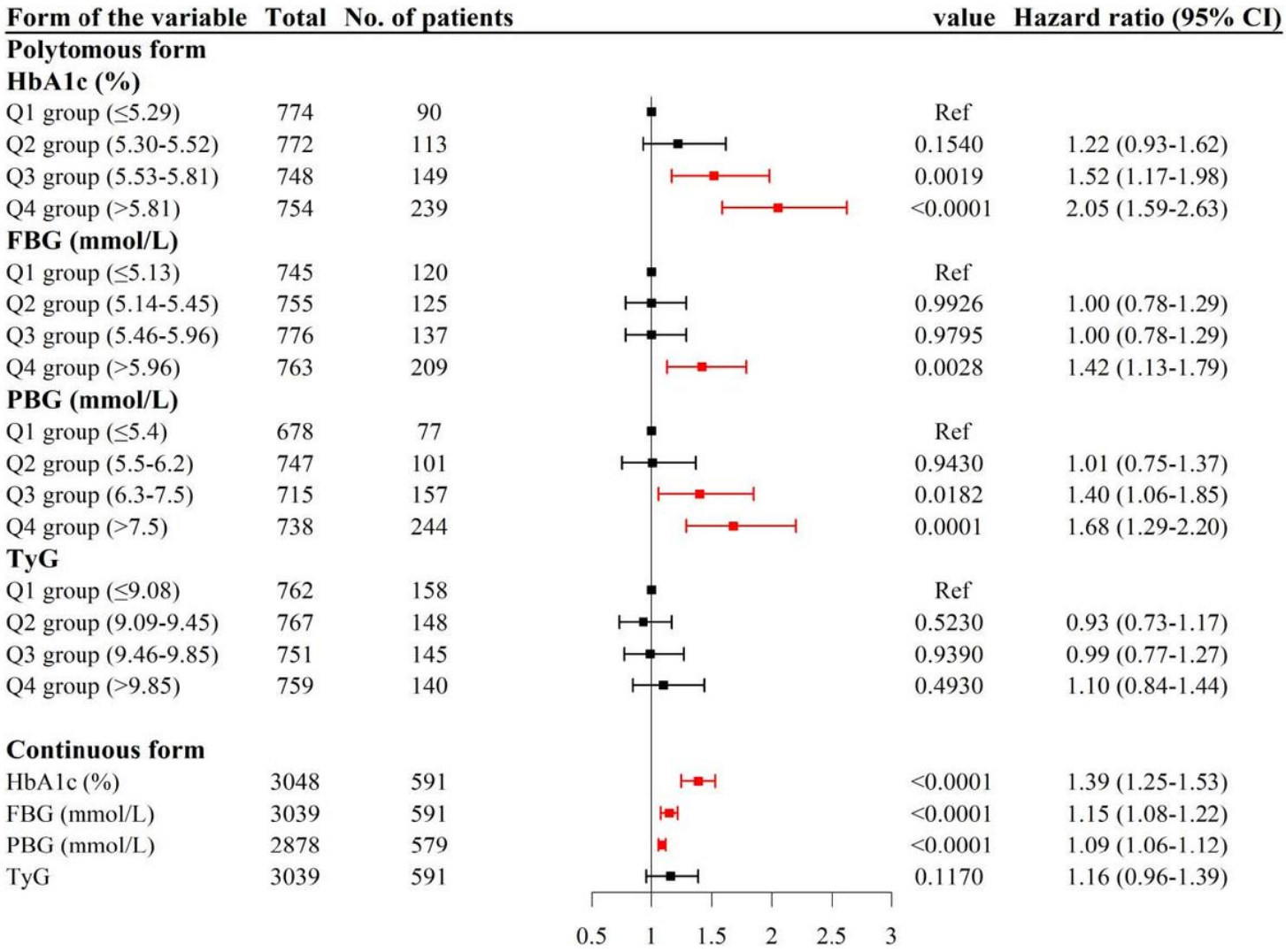


Figure 4

Association between the risk of arterial stiffness and the glucose parameters. HbA1c glycated hemoglobin, PBG postprandial blood glucose, FBG fasting blood glucose, TyG index triglyceride-glucose index, CI confidence interval



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