

Association Between Glucose Metabolism And Vascular Aging In Chinese Adults: A Cross-Sectional Analysis In The Tianning Cohort Study

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Aim: Fasting glucose has been associated with vascular aging, but the association between HbA1c and vascular aging has been limitedly studied in Chinese and other ethnic populations. We aimed to examine this association in a large sample of Chinese adults.

Methods: In the Tianning Cohort (N=5142), fasting glucose, HbA1c, carotid-femoral pulse wave velocity (cfPWV), and pulse pressure (PP) were measured. Vascular aging was defined as having the highest quartile level of cfPWV or PP. We applied quantile regression models to examine the association between glucose metabolism and vascular aging.

Results: The median cfPWV was significantly increased as increasing quintiles of fasting glucose ($\beta=0.14$, $P<0.001$) and HbA1c ($\beta=0.07$, $P=0.0056$), respectively. Per 1-mmol/L increment of fasting glucose was significantly associated with a higher risk of having vascular aging defined by cfPWV (OR=1.05, $P=0.022$), PP (OR=1.06, $P=0.048$), or either (OR=1.08, $P=0.002$). Similarly, per 1% increment of HbA1c was significantly associated with a higher risk of having vascular aging defined by cfPWV (OR=1.06, $P=0.044$), PP (OR=1.10, $P=0.012$), or either (OR=1.12, $P=0.042$).

Conclusion: Glucose metabolism was significantly and positively associated with vascular aging in Chinese adults, but the causality is uncertain.

Keywords: vascular aging, glucose metabolism, Chinese, fasting glucose

Introduction

Vascular aging, a latent and continuous physiological process, is an established risk factor of cardiovascular disease (CVD) morbidity and mortality¹⁻³ but can be detectable and modifiable in the whole life cycle. One of the hallmarks of vascular aging is an increase in arterial stiffness, which can be measured in various ways,⁴ including the most common noninvasive methods - pulse wave velocity (PWV)^{5,6} and pulse pressure (PP). These indices have been established to be independent predictors of CVD risks.^{7,8} Identification of potential biomarkers of vascular aging may help move forward the window of primary prevention and management of CVD.⁹

A wide range of mechanisms has been found to accelerate the process of vascular aging, such as oxidative stress, inflammation, and endothelial dysfunction.^{4,10-12} These pathologic responses also emerged in the conditions of glucose metabolic disorders, e.g., insulin resistance, hyperglycemia, and diabetes mellitus,¹³⁻¹⁵ indicating a potential role of glucose metabolism in vascular aging.¹⁶ This hypothesis has also been suggested by prior studies. For example, an in vitro experiment found an increased excretion of inflammatory biomarkers in human aortic endothelial cells exposed to high glucose.¹⁷

This phenomenon was also demonstrated in an animal experiment.¹⁶ In humans, genetic polymorphisms at several genes involved in glucose metabolism have been associated with vascular disorders even in non-diabetic individuals.¹⁸ To date, the association between fasting glucose and arterial stiffness has been studied in populations,^{2,19–21} but these studies were mainly conducted in individuals with European ancestry and there appeared an ethnic-difference in the magnitude of this association.²² Besides, the association between hemoglobin A1c (HbA1c), another index reflecting long-term glycemic control,²³ and vascular aging is not well studied in Chinese, as well as other ethnic populations. Moreover, some novel behavioral factors, e.g., physical inactivity^{24–26} and sleep inefficiency,^{27,28} were not well controlled in previous studies. The present study aimed to intensively investigate the association between glucose metabolism (assessed by fasting glucose and HbA1c) and vascular aging independent of behavioral factors in more than five thousand Chinese adults in the Tianning Cohort. Considering the potential time-dependent vascular responses to high glucose in the body,^{29,30} we also examined the association between glycemic status and vascular aging.

Methods

Study Participants

The Tianning Cohort is an on-going multi-center community-based prospective longitudinal study designed to search for new risk factors and potential therapeutic targets of CVD and related risk factors in Chinese adults. This study was initiated on May 25, 2018, and recruited participants aged over 18 years in conformity with the principle of voluntariness from 9 communities residing in a traditional but economically developed district (Tianning) in the center of Changzhou, China. After giving a signed written informed consent, a total of 5,199 participants have received a face-to-face interview, physical examination, urine and blood drawn and would be followed by phone every two years to collect CVD events and repeatedly examined every five years to monitor their cardiovascular health. The protocols of this study were approved by the Ethics Committee of Soochow University (approval No. ECSU-201800051) and this study was conducted following the Declaration of Helsinki. After excluding participants with missing data on either glucose metabolism or vascular aging (N=57), a total of 5,142 participants were included in the final analysis.

Measurement Of Glucose Metabolic Indices

Fasting glucose and HbA1c were determined in overnight fasting blood samples by Hexokinase methods (Siemens Healthcare Diagnostic Inc., Co Antrim, UK) and latex agglutination test methods (Siemens Healthcare Diagnostic Inc., Newark, USA), respectively. All tests were performed by the Simens ADVIA Chemistry XPT system in the Jiangsu Key Laboratory of Preventive and Translational Medicine for Geriatric Diseases. The laboratory staff was blinded to the health conditions of study participants. The criteria of diabetes diagnosis were to meet one of the following: (1) self-reported history of diabetes, (2) measured fasting glucose ≥ 7.0 mmol/L in this examination, (3) measured HbA1c $\geq 6.5\%$ in this examination.

Measurement Of Vascular Aging

Arterial stiffness, assessed by carotid-femoral PWV (cfPWV) and PP, was used to evaluate vascular aging in our study. Measurement of cfPWV was performed by the use of cuffs placed around the carotid and femoral to record the time of arrival of the pulse wave oscillometrically applying a validated device AS-2000 (Hong Kong Biomedical Holdings LTD., Hong Kong, China). Briefly, after the participants had rested for at least 15 mins, trained technicians and physicians placed the pressure cuffs on carotid and femoral and performed the measurement in the supine position. The device simultaneously measures pulse waves of the carotid and femoral arteries using an oscillometric cuff technique. The device estimates the travel path by subtracting the carotid-sternal notch distance from the femoral-sternal notch distance and automatically computes cfPWV as the ratio of the travel path divided by the time difference between the pulse waves that are transmitted to the carotid and femoral arteries. Blood pressure was measured 3 times by trained staff using a standard mercury sphygmomanometer and a cuff of appropriate size, according to a standard protocol,³¹ after the participants had been resting for at least 5 mins in a relaxed, sitting position. The first and fifth Korotkoff sounds were recorded as systolic blood pressure (SBP) and diastolic blood pressure (DBP), respectively. The mean of the 3 measurements was used in statistical analyses. PP was calculated as the difference between SBP and DBP. Vascular aging was defined as individuals with a cfPWV in the highest quartile (≥ 8.84 m/s), a PP in the highest quartile (≥ 54 mmHg), or either.

Assessment Of Confounding Factors

Cigarette smoking was classified as current smoking, past smoking, and never smoking. Current smoking was defined as having smoked cigarettes regularly and smoking currently. Past smoking was defined as having smoked cigarettes regularly in the past but not smoking currently. Never smoking was defined as never smoked cigarettes. Alcohol consumption was classified as current drinkers or not. Current drinkers were those who had consumed any alcohol during the past year. Education level was estimated as years of under education. Bodyweight (kg) and height (cm) were measured when participants wore light clothes and no shoes by trained staff. Body mass index (BMI) was calculated by dividing weight in kilograms by the square of height in meters (kg/m^2). Physical activity was determined using the Global Physical Activity Questionnaire (GPAQ) which was developed by the WHO for physical activity surveillance in developing countries.³² It collects information on physical activity at work, commuting, and recreational activities as well as sedentary behavior. The measured data were processed according to the GPAQ Analysis Guide, and MET-minutes per week values were calculated and used in data analysis. Sleep was assessed by a total score of the Pittsburgh Sleep Quality Index (PSQI), a widely used and well-validated measure of sleep quality.³³ Blood lipids including low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) were measured by the Simens ADVIA Chemistry XPT system using commercial reagents (Siemens Healthcare Diagnostic Inc., Co Antrim, UK).

Statistical Analysis

Characteristics of study participants were presented in diabetic and non-diabetic participants, respectively. To examine the association between fasting glucose and cfPWV, we constructed a median regression model in which cfPWV was the dependent variable and fasting glucose (continuous or categorized as quintiles) was the independent variable, adjusting for age, sex, education level, cigarette smoking, alcohol consumption, BMI, LDL-C, HDL-C, and SBP. The median regression model was used here to account for the skewed distribution of cfPWV. The associations between fasting glucose and PP, between HbA1c and cfPWV, between HbA1c and PP, were similarly examined. To facilitate data interpretation, we further constructed logistic regression models to examine whether fasting glucose and HbA1c were associated with advanced vascular aging defined as cfPWV or PP values within the highest quartile. A two-tailed

P-value less than 0.05 was considered statistically significant. All statistical analyses were conducted using SAS statistical software, version 9.4 (SAS Institute, Cary, NC).

Sensitivity Analysis

To examine whether physical activity and sleep, two behavioral factors ignored by prior studies, affect the association between glucose metabolism and vascular aging, physical activity, sedentary behavior, and PSQI score were additionally adjusted. To examine whether hypertension, diabetes, and prevalent CVD influence our results, participants with prevalent hypertension, diabetes and CVD were excluded.

Results

Baseline Characteristics

A total of 5,142 participants (mean age 50.97 ± 15.63 years, 58.52% of women) were included in the current study. Of them, 579 (11.26%) participants had prevalent diabetes including 462 under hypoglycemic treatments, and 1043 (20.28%) participants had prediabetes. 2203 (42.84%) participants were classified as having vascular aging referring to individual cfPWV ($N=1291$), individual PP ($N=1282$), or either. The baseline characteristics of study participants are shown in Table 1. Diabetic participants had significantly higher levels of PP (mean: 54.7 vs 46.6 mmHg, $P < 0.001$) and cfPWV (median: 7.4 vs 6.7 m/s, $P = 0.003$) than those without diabetes. Compared to non-diabetic participants, those with diabetes were more likely to be older, male, past smoking and to have higher levels of blood pressure, lipids and more hypertension, dyslipidemia, and CVD (all $P < 0.05$). Sleep quality, sedentary behavior, and education level seemed to be lower in participants with diabetes than those without (all $P < 0.05$). No significant difference in other listed variables was identified between these two groups.

Association Between Fasting Glucose And Vascular Aging

The median level of cfPWV was significantly increased as increasing quintile levels of fasting glucose (Figure 1, $\beta = 0.14$, $P < 0.0001$). Table 2 shows the associations of fasting glucose with vascular aging. Regression using continuous fasting glucose as the independent variable showed that per 1-mmol/L increment of fasting glucose was significantly associated with a higher risk of having vascular aging defined by individual cfPWV (OR=1.05, $P = 0.022$), individual PP (OR=1.06, $P = 0.048$), or either (OR=1.08, $P = 0.002$). Regression using quintiles of fasting glucose as the independent variable

Table 1 Baseline Characteristics Of Study Participants

Characteristics	Prevalent Diabetes		P-value
	Without	With	
No. of participants	4563	579	
Age, years	49.4±15.4	63.3±11.5	<0.001
Sex, men (%)	1839 (40.30)	294 (50.78)	<0.001
Cigarette smoking, n (%)			
Current smoking	897 (19.66)	132 (22.80)	0.075
Past smoking	217 (4.76)	59 (10.19)	<0.001
Never smoking	3449 (75.59)	388 (67.01)	<0.001
Current drinking, n (%)	847 (18.56)	111 (19.17)	0.723
Hypertension history, n (%)	1295 (28.38)	350 (60.45)	<0.001
CVD, n (%)	189 (4.14)	74 (12.78)	<0.001
Education level, years	10.89±3.92	9.37±3.57	<0.001
Body mass index, kg/m ²	23.96±3.69	24.89±3.32	<0.001
Systolic blood pressure, mmHg	123.2±16.5	132.3±17.0	<0.001
Diastolic blood pressure, mmHg	79.6±10.4	77.5±9.9	0.018
Total cholesterol, mmol/L	4.80±0.93	4.84±1.03	0.264
Triglycerides, mmol/L	1.73±1.24	2.05±1.25	<0.001
LDL cholesterol, mmol/L	2.76±0.79	2.71±0.83	0.290
HDL cholesterol, mmol/L	1.23±0.31	1.13±0.30	<0.001
Pulse pressure, mmHg	46.6 ±11.8	54.7 ±14.5	<0.001
cfPWV, m/s, median (IQR)	6.7 (5.3–8.7)	7.4 (5.3–9.2)	0.003
PSQI score	3.6±3.1	4.2±3.6	<0.001
Physical activity, MET-minutes/week	5222.9±8066.8	5018.9±8182.4	0.686
Sedentary behavior, minutes/day	364.9±216.0	348.6±232.0	0.010

Notes: Results were expressed with mean±SD unless otherwise noted.

Abbreviations: LDL, low-density lipoprotein; HDL, high-density lipoprotein; CVD, cardiovascular disease; cfPWV, carotid-femoral pulse wave velocity; IQR, interquartile range; PSQI, Pittsburgh sleeps quality index.

revealed similar associations in the same direction. Compared to participants with the lowest quintile of fasting glucose, those with the highest quintile had a 31%, 49%, and 45% higher risk of having vascular aging defined by cfPWV (OR=1.31, $P=0.023$), PP (OR=1.49, $P=0.016$), or either (OR=1.45, $P=0.001$), respectively.

Association Between HbA1c And Vascular Aging

The median level of cfPWV was significantly increased as increasing quintile levels of HbA1c (Figure 1, $\beta=0.07$,

$P=0.0056$). Table 3 shows the associations of HbA1c with vascular aging. Regression using continuous HbA1c as the independent variable showed that per 1% increment of HbA1c was significantly associated with a higher risk of having vascular aging defined by individual cfPWV (OR=1.06, $P=0.044$), individual PP (OR=1.10, $P=0.012$), or either (OR=1.12, $P=0.042$). Regression using quintiles of HbA1c as the independent variable revealed similar associations in the same direction. Compared to participants with the lowest quintile of HbA1c, those with the highest quintile had a 52% higher risk of having vascular

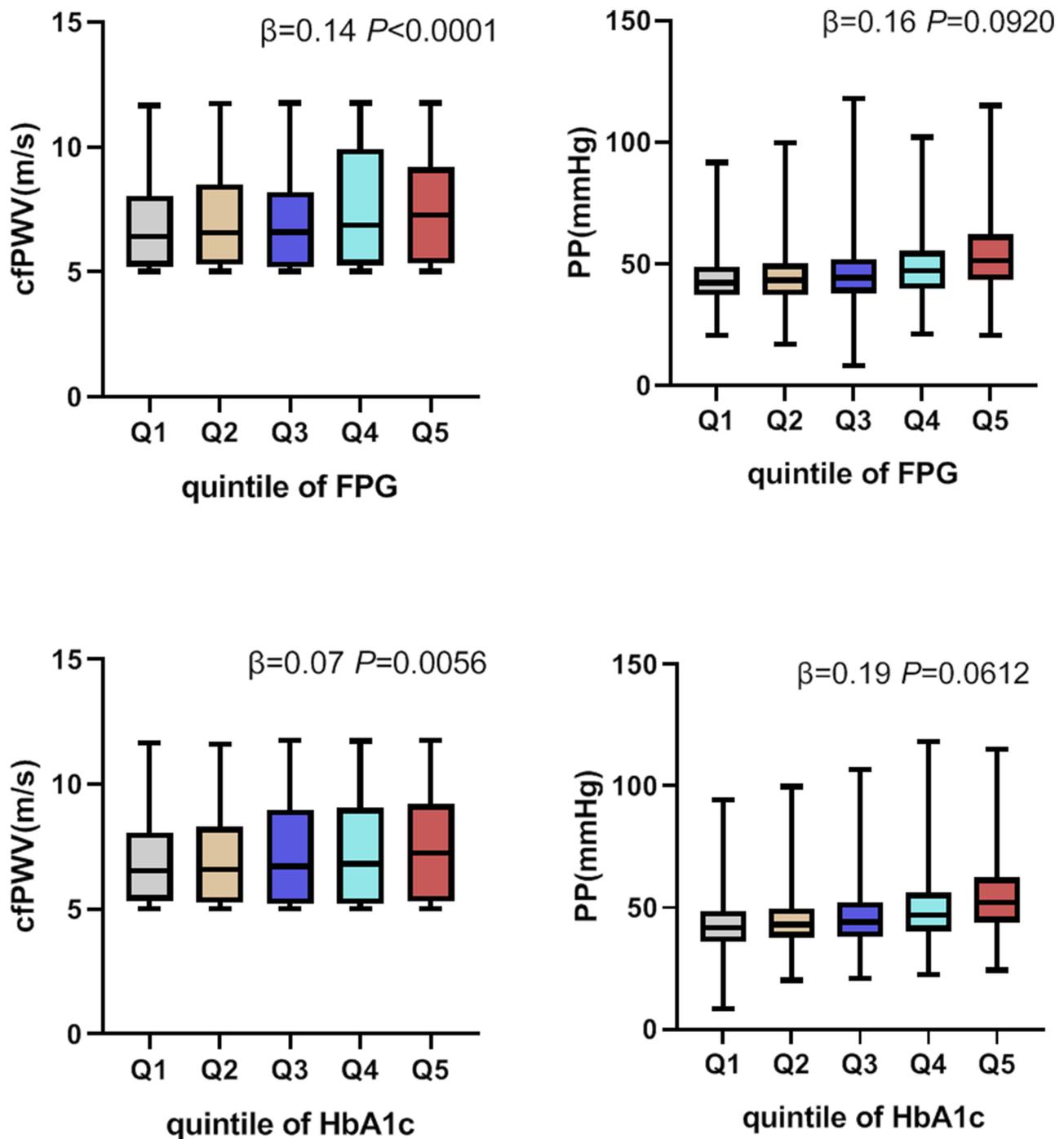


Figure 1 An illustration of the median levels of cfPWV and PP according to quintiles of fasting glucose and HbA1c. β indicates the median increase in cfPWV and PP associated with the increasing quintiles of fasting glucose and HbA1c, independent of age, sex, education level, cigarette smoking, alcohol drinking, body mass index, low- and high-density lipoprotein cholesterol, and systolic blood pressure.

aging defined by PP (OR=1.52, $P=0.015$). We failed to observe significantly increased risks of having vascular aging defined by cfPWV for the highest quintile of HbA1c compared to those with the lowest quintile.

Association Between Diabetic Status And Vascular Aging

Compared to participants with a normal glucose metabolic condition, participants with diabetes had a 35% higher risk

Table 2 Multivariate *Adjusted Associations Of Fasting Glucose With Vascular Aging

Fasting Glucose (mmol/L)	PP \geq 54 mmHg			cPWV \geq 8.84 m/s			PP \geq 54 mmHg And/Or cPWV \geq 8.84 m/s		
	N (%)	OR (95% CI)	P-value	N (%)	OR (95% CI)	P-value	N (%)	OR (95% CI)	P-value
Per unit	1282 (24.93)	1.06 (1.00–1.12)	0.048	1291 (25.11)	1.05 (1.01–1.10)	0.022	2203 (42.84)	1.08 (1.03–1.13)	0.002
Quintiles									
FPG<4.3	113 (13.26)	1.00 (ref)		182 (21.36)	1.00 (ref)		265 (31.10)	1.00 (ref)	
4.3≤FPG<4.6	158 (16.31)	1.08 (0.76–1.54)	0.679	226 (23.32)	1.08 (0.86–1.36)	0.498	343 (35.40)	1.08 (0.87–1.34)	0.498
4.6≤FPG<4.9	224 (20.42)	1.16 (0.83–1.63)	0.378	240 (21.88)	1.00 (0.80–1.24)	0.966	405 (36.92)	1.02 (0.82–1.26)	0.863
4.9≤FPG<5.5	330 (28.37)	1.28 (0.92–1.77)	0.142	343 (29.49)	1.47 (1.18–1.83)	<0.001	577 (49.61)	1.51 (1.23–1.87)	<0.001
5.5≤FPG	457 (43.07)	1.49 (1.08–2.06)	0.016	300 (28.28)	1.31 (1.04–1.65)	0.023	613 (57.78)	1.45 (1.16–1.82)	0.001

Notes: *Adjust for age, sex, education level, cigarette smoking, alcohol consumption, body mass index, low- and high-density lipoprotein cholesterol, and systolic blood pressure.
Abbreviations: PP: pulse pressure; cPWV, carotid-femoral pulse wave velocity.

Table 3 Multivariate * Adjusted Associations Of HbA1c With Vascular Aging

HbA1c (%)	PP \geq 54 mmHg			cPWV \geq 8.84 m/s			PP \geq 54 mmHg And/Or cPWV \geq 8.84 m/s		
	N (%)	OR (95% CI)	P-value	N (%)	OR (95% CI)	P-value	N (%)	OR (95% CI)	P-value
Per unit	1282 (24.93)	1.10 (1.02–1.18)	0.012	1291 (25.11)	1.06 (1.00–1.12)	0.044	2203 (42.84)	1.12 (1.00–1.11)	0.042
Quintiles									
HbA1c<5.1	120 (12.64)	1.00 (ref)		205 (21.60)	1.00 (ref)		298 (31.40)	1.00 (ref)	
5.1≤HbA1c<5.3	139 (15.98)	1.30 (0.90–1.87)	0.165	199 (22.87)	1.03 (0.82–1.29)	0.808	303 (34.83)	1.04 (0.84–1.30)	0.723
5.3≤HbA1c<5.6	248 (20.31)	1.09 (0.77–1.52)	0.635	320 (26.21)	1.23 (1.00–1.51)	0.056	500 (40.95)	1.12 (0.92–1.38)	0.262
5.6≤HbA1c<6.0	323 (30.16)	1.35 (0.96–1.88)	0.082	278 (25.96)	1.16 (0.93–1.46)	0.183	512 (47.81)	1.15 (0.93–1.43)	0.207
6.0≤HbA1c	452 (43.84)	1.52 (1.08–2.13)	0.015	289 (28.03)	1.25 (0.99–1.58)	0.065	590 (57.23)	1.25 (0.99–1.57)	0.056

Notes: *Adjust for age, sex, education level, cigarette smoking, alcohol consumption, body mass index, low- and high-density lipoprotein cholesterol, and systolic blood pressure.
Abbreviations: PP: pulse pressure; cPWV, carotid-femoral pulse wave velocity.

humans, a study including 697 Korea non-diabetic participants found that fasting glucose was significantly associated with vascular aging assessed by brachial-ankle PWV.² This phenomenon was also observed in another study including 1,312 participants,²² where the ethnic difference in the contribution of fasting glucose to vascular aging appeared to exist. However, the association between fasting glucose and vascular aging is limited studied in Chinese. To our knowledge, only one study including more than 5000 participants found that fasting glucose was not only cross-sectionally but also prospectively associated with vascular stiffness measured by baPWV in Chinese.^{19,21} Our study provided another evidence that fasting glucose may accelerate vascular aging in Chinese, not limited to white populations. Most of these results including ours were generated from observational study designs that cannot elucidate the causality between fasting glucose and vascular aging. The prospective association between glucose metabolism and vascular aging has been reported in very few studies with mixed results and most studies did not focus on glucose metabolism.^{19,38–41} However, a Mendelian Randomization study conducted in 2,853 individuals from Malmö Diet and Cancer study found that genetically elevated fasting glucose was associated with vascular aging assessed by cfPWV.²⁰ Together with prior studies, our study added the possibility that fasting glucose may be a risk factor of vascular aging. In addition to fasting glucose, HbA1c, another indicator of glucose metabolism, may also be associated with vascular aging, but this hypothesis, to the best of our knowledge, has been rarely studied. We also examined and found that HbA1c was also significantly associated with vascular aging. All these results suggested that glucose metabolism, not limited to the specific indicator, may play a role in vascular aging. As expected, abnormal glucose metabolic conditions, e.g., diabetes and prediabetes, have been consistently associated with advanced vascular aging in our and other studies.^{42–44}

To examine whether hypertension, diabetes, and CVD affect the association between glucose metabolism and vascular aging, we applied sensitivity analysis and found that excluding participants with hypertension, diabetes, and CVD did not change our results. This finding indicated that the association between glucose metabolism and vascular aging may not be driven by these conditions. Two important behavioral factors, e.g., sleep and physical activity, that may play confounding effects on the association between glucose metabolism and vascular aging have been ignored by prior studies. We additionally adjusted for these

two factors and found that the association between glucose metabolism and vascular aging persisted. Our findings added to the literature that the vascular toxicity of glucose may be independent of sleep and physical activity. Moreover, these sensitivity analyses revealed a robust association between glucose metabolism and vascular aging.

The mechanisms underlying the identified association between glucose metabolism and vascular aging needed to be discussed to deepen our understanding of the vascular toxicity of glucose. Increased arterial stiffness is a clinically important phenotype associated with vascular aging in humans and generally associated with vascular oxidative stress and endothelial dysfunction.⁴⁵ Researchers have found that hyperglycemia, particularly the fluctuation of glucose levels, caused a significant degree of oxidative stress through decreasing endothelial nitric oxide synthase (eNOS) expression, reducing nitric oxide (NO) bioavailability, and impairing NO metabolism,^{46,47} and thereby leading to endothelial dysfunction. Glucose-induced increased vascular oxidative stress and endothelial dysfunction would ultimately accelerate vascular aging which is strongly linked to cardiovascular disease. Vascular aging could serve as an intermediate marker of the link between hyperglycemia and vascular complications.⁴⁸ Therefore, strict glycemic control might achieve positive long-term protection against cardiovascular disease, at least partially through delay and reverse vascular aging.

Our study provides initial evidence that glucose metabolism may play a potential role in vascular aging, independent of lifestyle and metabolic factors. There are some strengths in our study including comprehensive adjustment for lifestyle and metabolic factors, application of fasting glucose and HbA1c as glucose metabolic indicators and cfPWV and PP as vascular aging measurements, and relatively large sample size. Several limitations of this study should be considered. First, in our study, all the participants were Han Chinese. The generalizability of our findings to other ethnic populations is unclear. Second, based on its cross-sectional design, we are unable to determine the causal association between glucose metabolism and vascular aging. Further studies are needed to confirm causality. Third, our results showed that glucose and HbA1c were consistently associated with cfPWV in both quantile and logistic regression models, whereas the association between glucose metabolism and the other vascular aging index PP was not statistically significant in the quantile regression model (Figure 1). The inconsistent results should be interpreted by cautious.

In conclusion, our results indicate that higher levels of HbA1c and fasting glucose were significantly associated

with advanced vascular aging in Chinese adults, independent of behavioral and metabolic factors. These findings may suggest that dysregulated glucose metabolism may embed adverse effects on cardiovascular health through accelerating vascular aging. The causality between glucose metabolism and vascular aging and the underlined mechanisms warranted further investigation.

Abbreviations

BMI, body mass index; CVD, cardiovascular disease; fPWV: carotid-femoral pulse wave velocity; DBP, diastolic blood pressure; GPAQ, the Global Physical Activity Questionnaire; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PWV, pulse wave velocity; PSQI, the Pittsburgh Sleep Quality Index; SBP, systolic blood pressure.

Data Availability

The data are available on request from the corresponding author at penghao@suda.edu.cn.

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Disclosure

The authors report no conflicts of interest in this work.

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