Investigating the inverse association between glycaemia and abdominal aortic dilatation in a large Chinese hypertensive population: a cross-sectional study

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Background: There is epidemiological evidence that diabetes has a protective effect on the occurrence and development of abdominal aortic aneurysms (AAAs). However, information on the role of glucose level on abdominal aortic diameter is limited. This study sought to assess the relationship between fasting plasma glucose (FPG) and infra-renal aortic diameter in a Chinese hypertensive population.

Methods: The prospective participants comprised candidates from 2 large population-based studies on the clinical presentation and management of hypertension in China. In total, 18,034 hypertensive participants (6,942 male and 11,092 females, with a mean age of 64.72±7.41 years) were included in the study. The maximal diameter of the infra-renal aorta was measured by ultrasound scanning. Multivariate linear regression analyses were conducted to assess the specific association between FPG and abdominal aortic diameter. The interaction terms between the baseline covariables and the aortic diameter were used to determine if a variable affected the association between FPG and abdominal aortic diameter.

Results: Of these, 22 cases of AAA were identified, and the prevalence of diabetes was lower in those with AAA than those without. A significant negative association was also found between FPG and aortic diameter in both sexes. A dose-dependent decrease in the prevalence of diabetes across quartiles of aortic diameter was also observed, with an estimated odds ratio (OR) of 0.60 (95% CI: 0.50–0.72) for men and 0.72 (95% CI: 0.63–0.82) for women for the top quartiles compared to the bottom quartiles. Cigarette smoking only interacted with the association between FPG level and aortic diameter in women. The association did not differ with other subgroups.

Conclusions: Our findings indicate that glycaemia may plays a protective role in the early stage of aortic dilatation in both sexes in a Chinese hypertensive population. Prospective studies need to be conducted to confirm our findings and explore the mechanism underlying this association in different populations.

Keywords: Diabetes; glycaemia; aortic dilatation; abdominal aortic aneurysm (AAA); hypertension

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Introduction

Abdominal aortic aneurysm (AAA), which is defined as a permanent dilatation of the abdominal aorta, is a life-threatening condition that affects up to 9% of men over the age of 65 years (1). AAA ruptures are catastrophic events, and the decision to either observe the progression of or repair an aneurysm is difficult for both surgeons and patients. Thus, the early identification of patients at risk for AAA, and the development of preventative interventions for AAA are important. AAA and atherosclerosis share several common risk factors, including age, smoking, hypercholesterolemia, and hypertension; however, the strength of the association between these factors and the expression of the pathology varies between AAA and atherosclerosis. Additionally, while diabetes is a risk factor for atherosclerosis, diabetes is a protective factor for AAA, which indicates a difference in the pathogenesis of these 2 clinical conditions (2).

According to epidemiological evidence (2), patients with diabetes have a lower prevalence and incidence of AAA. A meta-analysis (3) revealed that the prevalence of diabetes was lower in patients without AAA than patients with AAA. Diabetes has also been associated with decreased growth rates of AAA (4,5), and lower rates of AAA rupture (6). A recent study (7) found an inverse association between diabetes and the diameter of the infra-renal and ascending aorta in patients with coronary artery disease. These findings indicate that diabetes has a potential protective effect on the development and progression of AAA. The mechanism underlying the association between diabetes and AAA has been investigated in selected studies (8,9); however, the pathophysiology and molecular biology linking diabetes and AAA are unclear. Knowledge of the negative association between the fasting plasma glucose (FPG) level, diabetes, and aortic diameter may extend our understanding of AAA, and thus accelerate the development of novel clinical therapies for AAA.

Our study was the first to specifically investigate the association between the FPG level and aortic diameter in both sexes, in a large study population of over 18,000 Chinese participants with hypertension. Our aim was to determine (I) the relationship between diabetes, FPG, and aortic diameter, and (II) the extent to which aortic diameter can be explained by FPG when covariant factors known to affect AAA development and progression are controlled. We present the following article in accordance with the STROBE reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-1256/rc).

Methods

Study participants

The prospective participants came from 2 large population-based studies on the clinical presentation and management of hypertension in China. Both studies used the same inclusion and exclusion criteria for participant selection and the same follow-up schedule. The first study, the China Stroke Primary Prevention Trial (CSPPT), was a randomized, double-blind clinical trial that was conducted from May 19, 2008, to August 24, 2013 (clinicaltrials.gov identifier: NCT00794885). A 2nd cohort of patients was enrolled from the same regions as those of the CSPPT, and that study followed the same protocol with the exception that the 2nd cohort of patients was not strictly treated with the designated drugs used in the CSPPT. At the last follow-up visit of participants in these 2 large cohort studies in July and August 2013, measurements of aortic diameter were obtained to investigate abdominal aortic diameter and the prevalence of AAA in a large hypertensive population in China.

The medical charts of the 22,693 candidates were screened, after which 4,659 participants were excluded. The data of 18,034 participants were entered into the analysis. The flow chart of the participant screening process is shown in *Figure 1*.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from each participant before data collection. The study was approved by the Human Subject Committee at the Biomedical Institute of Anhui Medical University, Hefei, China (FWA assurance number FWA00001263) (ethical approval No: CH1032-D). Prof.

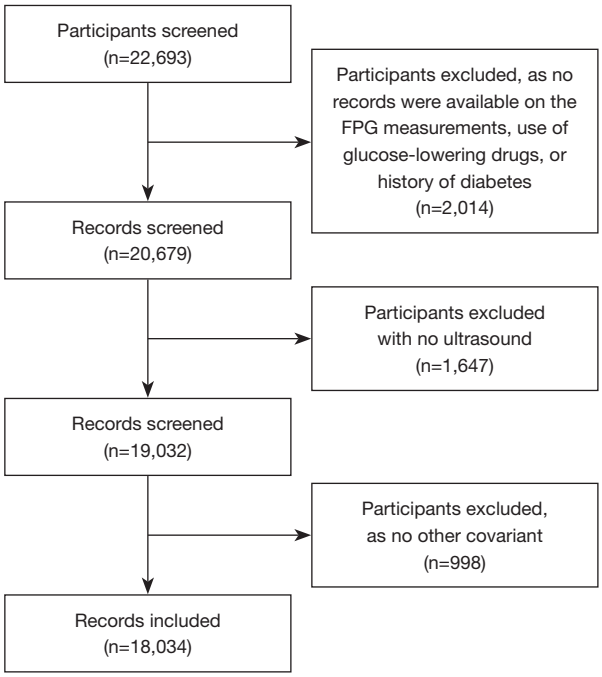

Figure 1 Flow diagram of the screening and enrollment of participants. FPG, fasting plasma glucose.

Xianhui Qin and Xiping Xu were worked in Anhui Medical University at the beginning of CSPPT study.

Evaluation of the abdominal aorta

The maximal diameter of the infra-renal aorta was measured by ultrasound scanning, performed by experienced technicians, using a professional ultrasound machine (SonoScape Technologies, Shenzhen, China) with a 3.5-MHz real-time sector scanner. After completing a longitudinal scan of the aorta from the level of the renal arteries to the aortic bifurcation, the diameter of the abdominal aorta was measured between 2 reference points, the 1st of which was located just inferior to the level of the renal arteries, and the 2nd of which was just superior to the aortic bifurcation. If an obvious dilation of the aorta was identified between these 2 reference points, the diameter at its widest point was also measured. AAA was defined as a dilation >50% than the diameter of the normal adjacent regions of the aorta.

Inter- and intra-observer measurement reliability was also assessed. For the determination of reliability, 100 cases were randomly sampled from the whole study population with approximately equal numbers of men and women. Inter- and intra-observer agreement was assessed using the methods proposed by Bland and Altman. There were no significant differences between the within (intra) or between (inter) observers (10).

Data collection

A standard questionnaire was administered by trained staff to obtain information on the demographic characteristics, personal and family medical history, and lifestyle risk factors, such as cigarette smoking and alcohol consumption, of the participants. The interview included questions related to the diagnoses and treatment of diabetes, hypertension, dyslipidemia, stroke, and cardiovascular events.

Laboratory tests

A venous blood sample was obtained from each participant after 12 to 15 hours of fasting. Serum or plasma samples were separated within 30 min and stored at –70 ℃. Concentrations of FPG, serum homocysteine, creatinine, and lipids [including total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and triglycerides] were measured using automatic clinical analyzers (Beckman Coulter) at the core laboratory of the National Clinical Research Center for Kidney Disease at Nanfang Hospital, Guangzhou, China.

Statistical analysis

The data are presented as the mean ± standard deviation (SD) for the continuous variables and the proportion for the categorical variables. Between-group comparisons were performed using chi-squared tests for categorical variables and 2 sample *t* tests for continuous variables. A diagnosis of diabetes was based on a self-reported history of diabetes, the current use of hypoglycemic agents, or a FPG level ≥7.0 mmol/L. A multivariate logistic regression analysis was conducted to evaluate the associations between abdominal aortic diameter and diabetes. Multivariate linear regression analyses were conducted to assess the specific association between FPG and abdominal aortic diameter. FPG was evaluated as a continuous variable and by categories using the following cutoff values: normal glucose tolerance, FPG <5.6 mmol/L; impaired glucose tolerance, 5.6≤ FPG <7.0 mmol/L; and diabetes, FPG ≥7.0 mmol/L. The trend tests were conducted by modeling the FPG category medians as continuous variables. We adjusted for age, body mass index (BMI), heart rate, and systolic blood pressure (SBP), cigarette smoking, TC, triglycerides, HDL-C,

Table 1 Characteristics of the study population

Characteristics	Overall (n=18,034)	Men (n=6,942)	Women (n=11,092)	P value
Age, years	64.72±7.41	65.82±7.43	64.02±7.31	<0.001
Body mass index, kg/m^2	24.84±3.84	23.98±3.60	25.38±3.89	<0.001
Heart rate, beats/min	76.89±11.49	75.70±11.76	77.63±11.25	<0.001
Systolic blood pressure, mmHg	136.86±17.96	134.13±17.56	138.57±17.99	<0.001
Diastolic blood pressure, mmHg	82.05±11.00	82.32±11.45	81.89±10.72	0.01
Cigarette smoking				<0.001
Never	12,378 (68.60%)	1,763 (25.40%)	10,615 (95.70%)	
Former	1,930 (10.70%)	1,750 (25.20%)	180 (1.60%)	
Current	3,726 (20.70%)	3,429 (49.40%)	297 (2.70%)	
Fasting plasma glucose, mmol/L	6.26±2.00	6.21±1.93	6.29±2.05	0.013
Total cholesterol, mmol/L	5.28±1.09	5.03±1.03	5.44±1.09	<0.001
Triglycerides, mmol/L	1.77±1.39	1.54±1.32	1.92±1.41	<0.001
HDL-C, mmol/L	1.28±0.31	1.28±0.33	1.27±0.29	0.021
Creatinine, μmol/L	68.33±25.96	80.23±31.54	60.89±18.14	<0.001
Homocysteine, μmol/L	13.60±7.03	15.57±9.11	12.36±4.94	<0.001
Self-reported stroke	918 (5.10%)	390 (5.60%)	528 (4.80%)	0.011
Self-reported cardiovascular disease	450 (2.50%)	188 (2.70%)	262 (2.40%)	0.147
Self-reported diabetes	1,320 (7.30%)	357 (5.10%)	963 (8.70%)	<0.001
Use of glucose-lowering drugs	1,186 (6.60%)	313 (4.50%)	873 (7.90%)	<0.001
Aortic diameter, mm	14.66±2.19	15.66±2.21	14.04±1.93	<0.001

HDL-C, high-density lipoprotein cholesterol.

creatinine, homocysteine, self-reported cardiovascular disease, and self-reported stroke in the final model. The interaction term between a covariable (as a categorical variable) and aortic diameter (as a continuous variable) was examined to evaluate if the variable affected the association between FPG and abdominal aortic diameter.

All analyses were performed with the statistical software packages R (http://www.R-project.org, The R Foundation), and Free Statistics (version 1.5, http://www.clinicalscientists.cn/freestatistics/). A 2-sided significance level of 0.05 was used to evaluate the statistical significance.

Results

Characteristics of the study population

The descriptive characteristics of the 18,034 participants included in our analysis are set out in *Table 1*, and are reported both for the total study sample and by sex. The study group comprised 6,942 men and 11,092 women, with a mean age of 64.72±7.41 years. There were no sex-specific differences in terms of self-reported cardiovascular disease. However, there were significant sex-specific differences in relation to other measured characteristics of the study population. Notably, compared to the female group, the male group was older, had higher diastolic blood pressure (DPB), a higher proportion of current smokers, higher levels of HDL-C, creatinine, and homocysteine, a higher proportion of self-reported stroke and cardiovascular disease, and a larger abdominal aortic diameter. Additionally, compared to the female group, the male group had a lower BMI, heart rate, and SBP, lower levels of FPG, TC, and triglycerides, a lower proportion of self-reported diabetes, and used fewer glucose-lowering drugs.

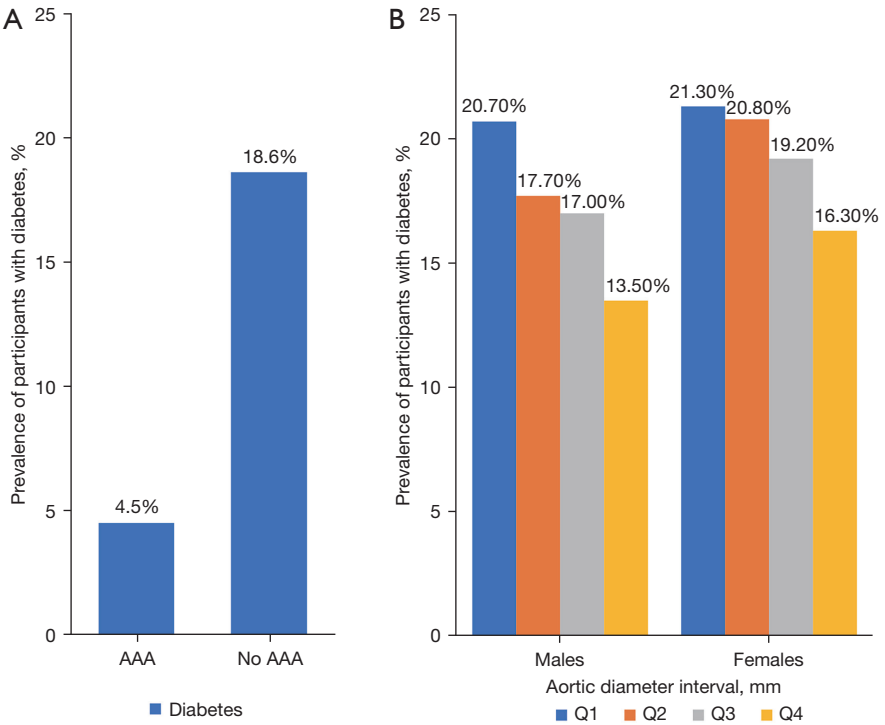

Figure 2 Prevalence of diabetes according to different group. (A) Prevalence of diabetes according to positive or negative identification of AAA; (B) prevalence of diabetes for the quartiles of infra-renal aortic diameter according to sex. AAA, abdominal aortic aneurysm.

Relationship between AAA, aortic diameter, and diabetes

In total, 22 cases of AAA were found in the 18,034 participants in our hypertensive study population. The prevalence of diabetes was lower in participants with AAAs than those without an AAAs (4.5% *vs.* 18.6%, P=0.23; see *Figure 2A*). Additionally, the prevalence of diabetes was significantly lower between quartiles of aortic diameter (men, 20.7% *vs.* 17.70% *vs.* 17.0% *vs.* 13.5%, P<0.001; women, 21.30% *vs.* 20.80% *vs.* 19.20% *vs.* 16.30%, P<0.001; see *Figure 2B*).

The univariate regression models revealed a significant negative association between aortic diameter and diabetes. The regression model predicted a significant 9% reduction in the prevalence of diabetes in men, and 6% in women for every 1-mm increase in aortic diameter. A dose-dependent decrease in the prevalence of diabetes across the quartiles of the aortic diameter was also observed, with an estimated odds ratio (OR) of 0.60 (95% CI: 0.50–0.72) for men, and 0.72 (95% CI: 0.63–0.82) for women for the top quartiles compared to the bottom quartiles. These associations remained unchanged after further adjustment of the regression model for age, BMI, heart rate, SBP, cigarette smoking, TC, triglycerides, HDL-C, creatinine, homocysteine, and self-reported cardiovascular disease and stroke (P<0.001 for all; see *Table 2*).

Association between FPG and aortic diameter in the participants not using glucose-lowering drugs

As glucose-lowering drugs affect FPG, only 16848 of the total 18,034 participants with no history of using glucose-lowering drugs were included in the further analyses. After adjusting for the covariates, a negative linear association between FPG and aortic diameter was found (see *Figure 3*). As FPG increased, the aortic diameter significantly decreased between the different categories of FPG (i.e., <5.6 mmol/L, 5.6–7.0 mmol/L, and ≥7.0 mmol/L) in both sexes (all P values <0.01; see *Table 3*). According to the linear models, every 1-mmol/L increase in FPG was associated with a significant 0.08 mm decrease in aortic diameter for men (P<0.001) and a 0.04 mm decrease for women (P<0.001). A dose-dependent decrease in the aortic diameter across the categories of FPG was also observed, with an estimated coefficient of –0.40 for FPG ≥7.0 mmol/L as compared to FPG <5.6 mmol/L

Table 2 Dose-response relationship between aortic diameter and diabetes according to sex

Variables	Men (n=6,942)			Women (n=11,092)		
	Diabetes (N, %)	Crude, OR (95% CI)	Adjusted*, OR (95% CI)	Diabetes (N, %)	Crude, OR (95% CI)	Adjusted*, OR (95% CI)
Aortic diameter, 1 mm	1,195 (17.2)	0.91 (0.88, 0.93)	0.93 (0.90, 0.96)	2,147 (19.4)	0.94 (0.91, 0.96)	0.95 (0.92, 0.97)
Aortic diameter, mm						
Quartile 1	349 (20.70)	1.00	1.00	590 (21.30)	1.00	1.00
Quartile 2	307 (17.70)	0.83 (0.70, 0.98)	0.88 (0.73, 1.05)	513 (20.80)	0.97 (0.85, 1.11)	1.03(0.90, 1.18)
Quartile 3	303 (17.00)	0.79 (0.66, 0.93)	0.84 (0.71, 1.01)	584 (19.20)	0.87 (0.77, 0.99)	0.94 (0.82, 1.07)
Quartile 4	236 (13.50)	0.60 (0.50, 0.72)	0.67 (0.56, 0.81)	460 (16.30)	0.72 (0.63, 0.82)	0.76 (0.66, 0.87)
P value for trend		<0.001	<0.001		<0.001	<0.001

*, adjusted for age, body mass index, heart rate, systolic blood pressure, cigarette smoking, total cholesterol, triglycerides, high-density lipoprotein cholesterol, creatinine, homocysteine, self-reported cardiovascular disease and self-reported stroke. OR, Odds ratio; CI, Confidence Interval.

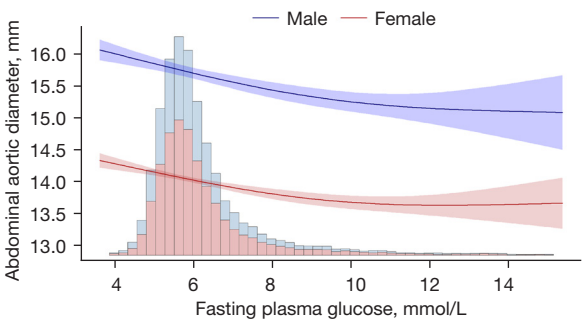

Figure 3 The smooth curve fitting of FPG and infra-renal aortic diameter in the participants who did not use glucose-lowering drugs, reported by sex and adjusted for age, body mass index, heart rate, systolic blood pressure, cigarette smoking. Red box representative histogram of abdominal aortic diameter in female, and blue box representative histogram of abdominal aortic diameter in male. FPG, fasting plasma glucose.

for men (P<0.001), and an estimated coefficient of −0.19 for women for the same FPG categories (P=0.002). In men, the association between FPG and aortic diameter remained unchanged after further adjustment of the model for the covariates. Conversely, the adjusted model remained linear for women, but was no longer significant (see *Table 2*).

Additionally, the possible modulating effects of age and other variables, including BMI and cigarette smoking, on the FPG-aortic diameter relationship was evaluated (see *Table 4*). The FPG-aortic diameter relationship remained consistent for both men and women across different ages, BMIs, and cigarette smoking habits. In women, cigarette smoking produced an intriguing significant interaction whereby in current smokers, every 1 mmol/L increase in FPG was associated with a 0.13-mm decrease in aortic diameter, while in former smokers, every 1-mmol/L increase in FPG was associated with a 0.04-mm increase in aortic diameter. However, these contrasting associations were not significant, which may have been due to the small number of current and former smokers in the female group. Interaction effects between aortic diameter and other covariables were also evaluated, but none were significant.

Discussion

In this observational study of 18,034 hypertensive adults, we found that the prevalence of diabetes was lower in patients with AAA than patients without AAA, and that there was a significant negative association between aortic diameter and diabetes. FPG level was also shown to have an inverse relationship with a continuum of aortic diameters, including the non-aneurysmal range, in both sexes. An inverse relationship was also observed in participants with high FPG who were not using glucose-lowing drugs, and those without diabetes. Our findings suggest that a general elevation in glucose, and not one that is only diabetes-related, may play a protective role in the early stage of aortic dilatation, and that this effect is contrary to that of glucose in the stenosis of small arteries.

Epidemiological evidence (2) indicates that the prevalence and incidence of AAA are lower in patients with

Table 3 Multivariate linear regression between FPG and infra-renal aortic diameter in participants who did not use glucose-lowering drugs

Variables	Diameter (mm)		Crude		Adjusted*	
	N	Mean ± SD	β (SE)	P value	β (SE)	P value
Men						
FPG, 1 mmol/L	6,629	15.68±2.22	–0.08 (0.02)	<0.001	–0.05 (0.02)	0.005
FPG, mmol/L						
<5.6	2,814	15.77±2.22	0	–	0	–
5.6–7.0	2,933	15.69±2.28	–0.08 (0.06)	0.178	–0.03 (0.06)	0.625
≥7.0	882	15.38±2.00	–0.40 (0.09)	<0.001	–0.25 (0.09)	0.004
P value for trend			<0.001		0.004	
Women						
FPG, 1 mmol/L	10,219	14.06±1.94	–0.04 (0.01)	<0.001	–0.02 (0.01)	0.064
FPG, mmol/L						
<5.6	4,503	14.13±1.94	0	–	0	–
5.6–7.0	4,442	14.04±1.92	–0.09 (0.04)	0.027	–0.07 (0.04)	0.09
≥7.0	1,274	13.94±2.01	–0.19 (0.06)	0.002	–0.12 (0.06)	0.05
P value for trend			0.002		0.048	

*, adjusted for age, body mass index, heart rate, systolic blood pressure, cigarette smoking, total cholesterol, triglycerides, high-density lipoprotein cholesterol, creatinine, homocysteine, self-reported cardiovascular disease, and self-reported stroke. FPG, fasting plasma glucose; SD, standard division; SE, standard error.

diabetes. A meta-analysis (3) showed that the prevalence of diabetes in patients without AAA ranged from 17% to 36%, while the prevalence in patients with AAA was only 6% to 14%. The incidence of diabetes is also significantly lower in patients with AAA than those without AAA (OR =0.65, 95% CI: 0.60–0.70; P<0.001). In our study the prevalence of diabetes in participants with and without AAA was 4.5% and 18.6%, respectively. Further, in patients with diabetes, every 1-mm increase in aortic diameter was associated with a significant 9% reduction in the prevalence of diabetes in men, and a 6% reduction in women. Thus, diabetes may play a protective role on aortic dilatation.

Diabetes has also been associated with decreased AAA growth rates (4). The RESCAN study (11) provided evidence of a 0.51-mm/year lowering of the growth rate of AAA in diabetic patients compared to a matched cohort without diabetes. Additionally, Theivacumar *et al.* (6) assessed the relationship between diabetes and aortic aneurysm rupture, and found that the rate of diabetes was significantly higher in patients with a non-ruptured AAA than patients with a ruptured AAA rupture, with rates of diabetes of 12.4% and 6.4% for the diabetic and non-diabetic groups, respectively. They also reported that diabetic patients with AAA were significantly less likely to experience a rupture or die from a rupture of the aneurysm, which indicates that diabetes may have a protective effect on aortic aneurysm rupture. Based on this evidence, the surveillance of AAAs may represent a better option than operative repair in patients with diabetes given the lower risk for rupture and high risk associated with repair. Future controlled trials and surveillance studies need to be conducted to confirm our findings before they are implemented in practice.

Few studies have investigated the specific association between diabetes, FPG, and aortic diameter. Le *et al.* (2) were the first to report an inverse relationship between FPG levels and the continuum of aortic diameters, which included a non-aneurysmal range of aortic diameters, in non-diabetic men. Recently, Tanaka *et al.* (7) found an inverse association between diabetes and the diameter of the infra-renal and ascending aorta in patients with advanced coronary artery disease. Our results confirm those of Le *et al.* (2) We also extended on these previous findings by demonstrating that this relationship exists across a continuum of FPG levels, including diabetic levels in patients not using glucose-

Table 4 Subgroup analysis between fasting plasma glucose and Infra-renal aortic diameter according to age, body mass index, and cigarette smoking in participants not using glucose-lowering drugs

Variables	Aortic diameter, mm		FPG (β, SE, P value)	P value for interaction
	N	Mean	Continuous (mmol/L)	
Men				
Age, years				0.136
<65	2,948	15.56±2.13	–0.03 (0.02) 0.241	
≥65	3,681	15.78±2.29	–0.07 (0.02) 0.006	
BMI, kg/m^2				0.460
<25	4,211	15.69±2.29	–0.05 (0.02) 0.021	
≥25	2,418	15.67±2.10	–0.04 (0.02) 0.082	
Smoking				0.564
Never	1,681	15.71±2.22	–0.02 (0.03) 0.603	
Former	1,634	15.65±2.13	–0.05 (0.03) 0.139	
Current	3,314	15.68±2.26	–0.06 (0.02) 0.009	
Women				
Age, years				0.118
<65	5,681	14.07±1.84	–0.01 (0.02) 0.483	
≥65	4,538	14.06±2.06	–0.03 (0.02) 0.075	
BMI, kg/m^2				0.779
<25	5,003	13.97±1.95	–0.02 (0.02) 0.216	
≥25	5,216	14.15±1.93	–0.02 (0.02) 0.186	
Cigarette smoking				0.034
Never	9,783	14.06±1.93	–0.02 (0.01) 0.085	
Former	159	13.97±2.13	0.04 (0.08) 0.653	
Current	277	14.16±2.25	–0.13 (0.10) 0.186	

Adjusted for age, body mass index, heart rate, systolic blood pressure, cigarette smoking, total cholesterol, triglycerides, high-density lipoprotein cholesterol, creatinine, homocysteine, self-reported cardiovascular disease, and self-reported stroke. FPG, fasting plasma glucose; SE, standard error; BMI, body mass index.

lowering drugs. For participants not using glucose-lowering drugs, every increase of 1 mmol/L in FPG was associated with a significant decrease of 0.08 mm in aortic diameter in men, and 0.04 mm in women. After adjusting the model for other variables associated with aortic diameter, the association between FPG and aorta diameter was no longer significant in women, but the significance of the association was maintained for men. These results indicate a possible weaker association between FPG and aortic diameter in women. Similar sex-specific effects on the association between diabetes and AAA have been identified in a meta-analysis, (12) which showed that the cumulative inverse association between diabetes and AAA was less evident in the 391,234 women in the study group (OR 0.9; 95% CI: 0.66–1.22; P=0.48) than the 214,774 men (OR 0.84; 95% CI: 0.73–0.96; P=0.01). We also found that smoking had a significant interaction effect between FPG and aortic diameter in women, suggesting that cigarette smoking may play a larger role in the association between FPG and aortic diameter in women.

Knowledge of the negative association between aortic diameter and diabetes or FPG could improve our

understanding of the development of AAA. However, the pathophysiology and molecular biology of diabetes on AAA remains unclear (8,9). An improved understanding of the disease process may accelerate the development of novel clinical therapies for AAA.

First, consideration must be given to the association between elevated glucose, the classical feature of diabetes, and the advanced glycation of the extracellular matrix (ECM) proteins (13). Elevated glucose in diabetic patients with AAA stimulates the formation of advanced glycation end-products (AGEs), (4,11) and induces the cross-linking of collagen lattices in the aortic media, rendering it less prone to proteolysis, and thereby directly decreasing aortic wall degradation. This pathway provides a plausible explanation for the apparent protective role of elevated glucose in AAA patients. Norman *et al.* (14) reported that the serum levels of the concentrations of the AGE carboxymethyllysine (CML) were significantly lower in diabetic men with AAAs than diabetic men without AAAs. However, this finding contrasts with other report of negative associations between AGEs and occlusive manifestations of cardiovascular disease (15). Thus, while advanced glycation may be a feature of the inverse association between diabetes and AAA, it has a direct effect on occlusive arterial disease. However, in a recent study, serum CML concentration did not predict the rate of expansion, or growth of AAAs detected by screening (4).

Second, consideration must be given to the effect of monocyte-macrophages interactions in the pathophysiology of AAA (16). A previous study has reported that reduced levels of matrix metalloproteinase-2 (MMP-2) and MMP-9 in diabetic patients with AAA reduce the breakdown and remodeling of the ECM proteins of the aortic wall (17). Given the lower growth rate of AAA in diabetic patients compared to non-diabetic patients (4), the marked decrease in MMPs and interlukin-6 secretion, as shown in *in vitro* experiments, might be the mechanism protecting aortic media from degradation in diabetic patients. Miyama *et al*. (18) found reduced aortic mural macrophage infiltration, elastolysis, and neovascularization in a combined mice model of AAA and diabetes, compared to a model of AAA only, which suggest that hyperglycemia has a protective effect on the extracellular matrix of the aortic wall, which would limit AAA formation.

Third, consideration must be given to the role of genetics in mediating the protective role of diabetes on AAA development and growth (19). Additionally, based on the hypothesis of Le *et al.* (2) that lower levels of homocysteine in pre-diabetic states and early in the course of type 2 diabetes may affect the association between FPG and AAA, we evaluated the specific interaction effect of homocysteine level in our models, and found that different homocysteine levels had no effect on the association between FPG and AAA.

We consider the outcomes of our study to be reliable, and are of the view that they provide credible evidence of the association between FPG, diabetes, AAA, and infra-renal aortic diameter. Future prospective studies need to be conducted to further evaluate the association between FPG, diabetes, and the incidence and development of AAA. Our study, measured FPG and aortic diameter obtained at the same time point using a well-characterized, community-based design, and included a large population sample of 18,034 hypertensive Chinese participants. In the interpretation and application of outcomes of this study, consideration must be given to the limitations of our study. This is a cross-sectional study of a defined hypertensive population, and thus the association between FPG and aortic diameter may not be causal. A prospective study needs to be conducted to confirm the association. Our analysis of the association between FPG and AAA was conducted in a hypertensive population that did not use glucose-lower drugs, and thus we cannot evaluate the potential effects of these drugs on aortic diameter and AAA, and more studies are required to clarify the effects of use of insulin and oral glucose-lowering medications on the disease process of AAA. Additionally, the prevalence of AAA in our study population was low, which may be indicative of different population-specific characteristics of AAA. Future studies should evaluate the prevalence of diabetes in groups with and without AAA (in this study, we compared the prevalence of AAA in groups with and without diabetes).

In summary, we found evidence of a significant negative association between aortic diameter and diabetes, and between FPG level and the continuum of aortic diameters, including the non-aneurysmal range of diameters. These associations were consistent in both sexes, and in individuals with diabetes who did not use glucose-lowering drugs and non-diabetic individuals. Our findings also indicate possible differences in the prevalence of diabetes and AAA in a hypertensive population of Chinese descent. Together, our findings indicated that elevated glucose plays a protective role in the early stage of aortic dilatation in both sexes. Prospective studies need to be conducted to confirm our findings and explore the mechanism underlying this

association in different populations.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Human Subject Committee at the Biomedical Institute of Anhui Medical University, Hefei, China (FWA assurance number FWA00001263) (ethical approval No: CH1032-D). Written informed consent was obtained from each participant before data collection.

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