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The Association of Remnant Cholesterol with Endothelial Dysfunction and Subclinical Atherosclerosis in a Check-Up Population in China

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Aim: Vascular endothelial function and atherosclerosis are known to be important risk factors for cardiovascular disease. However, it remains unknown whether remnant cholesterol (RC) correlates with vascular endothelial function and atherosclerosis as represented by flow-mediated vasodilation (FMD) and brachial-ankle pulse wave velocity (baPWV). Therefore, in this study, we aimed to investigate this in the general population.

Methods: In this study, we examined 13,237 subjects who have undergone blood lipid, FMD, and baPWV measurements. Participants were divided into four groups based on RC quartiles. Multivariable linear regression models were used to calculate odds ratios for FMD and baPWV according to the RC levels.

Results: A significant negative relationship was found between RC and FMD ($\beta = -0.14$, $p = 0.014$), whereas RC was positively associated with baPWV ($\beta = 21.42$, $p < 0.001$), especially in the male and without chronic disease medication populations. The population was divided into three groups according to their lipids: dyslipidemia group, nondyslipidemia but RC increased group (RC > 0.78 mmol/L), and nondyslipidemia and RC normal group (RC ≤ 0.78 mmol/L). The FMD of the three groups was 7.09% ± 3.36%, 7.39% ± 3.38%, and 7.57% ± 3.54%, respectively. The baPWV of the three groups was 1445.26 ± 261.56 cm/s, 1425.04 ± 265.24 cm/s, and 1382.73 ± 267.75 cm/s. Significant differences were noted between the groups.

Conclusions: The findings indicated that a higher RC was an independent predictive factor for participants with endothelial function and atherosclerosis. It is important to use RC as a risk management indicator of vascular function, especially for those with normal conventional lipid parameters but increased RC.

Key words: Remnant cholesterol, Brachial-ankle pulse wave velocity, Flow-mediated vasodilation, Endothelial dysfunction, Subclinical atherosclerosis, Check-up population

Introduction

Cardiovascular diseases (CVD), in particular, ischemic heart disease and stroke, have been identified to be the leading cause of global mortality and a major contributor to disability worldwide. Arterial stiffness has been identified as an independent CVD risk factor and a predictor of all-cause mortality[1]. An increase in vascular stiffness is significantly associated with damage to target organs, including the heart, kidney, and brain, which may contribute to heart disease, renal dysfunction, and stroke[2]. Endothelial dysfunction is the subclinical event preceding CVD and is closely associated with arterial stiffness. Endothelial dysfunction is known to play a crucial role in the development of atherosclerosis, which can,

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in turn, lead to changes in the vessel intima and an increase in arterial stiffness[3, 4].

It has been shown that increased low-density cholesterol (LDL-C) is an independent risk factor for CVD[5]. The main lipid target for CVD prevention has been LDL-C, as per comprehensive evidence from observational studies, genetic studies, and randomized controlled trials[6]. However, after lowering LDL-C to the recommended target, CVD risk is noted to remain[7]. This could partly be due to remnant cholesterol (RC) in triglyceride-rich lipoproteins that are associated observationally and genetically, causally with an increased risk of CVD in large cohort studies and case-control consortia alike[8, 9]. RC is defined as the cholesterol content of triglyceride-rich lipoproteins, including chylomicron remnants, very low-density lipoprotein cholesterol, and intermediate-density lipoprotein (IDL) cholesterol. In previous studies, RC within triglyceride-rich lipoproteins has been associated with inflammation and with the development of ischemic heart disease, stroke, and nonalcoholic fatty liver disease[10-13]. Experimental studies have demonstrated that RC promotes the formation and development of endothelial dysfunction and atherosclerosis through adhesion and proinflammatory effects, which could lead to the occurrence of related diseases[14]. However, data on the predictive implications of RC for endothelial dysfunction and atherosclerosis in the general population remain to be lacking.

Measurement of flow-mediated vasodilation (FMD), which is an endothelium-dependent vasodilation in the brachial artery, has been used as a method to assess endothelial function. The lower the FMD value is, the worse the vascular endothelial function[15]. Brachial-ankle pulse wave velocity (baPWV) is the velocity at which a pulse wave travels along a specified artery segment and is considered the important standard for the noninvasive study of arterial stiffness[16]. The more rigid the artery is, the greater the PWV value[17]. At present, these two methods have been used in screening vascular diseases in large populations to evaluate endothelial dysfunction and vascular sclerosis. In this study, we intend to explore the associations of RC with vascular endothelial function and arteriosclerosis in a large-scale population and analyze the relationship between them in different subgroups, especially the different effects of high and normal RC on blood vessels in the population with normal conventional lipid parameters, to provide a basis intervention strategy for blood lipids in the population.

Subjects and Methods

Study Design and Populations

This cross-sectional study population comprised 13,237 individuals from a mixed urban and rural area who visited the health management center at the Third Xiangya Hospital in Changsha between January 1, 2015, and December 31, 2021. In addition to the physical and laboratory examination, personal details (health-related habits, family history, and self-reported disease history) were obtained from the National Physical Examination Questionnaire[18]. Anthropometric measurements included height, weight, waist circumference (WC), and blood pressure (BP); both height and weight were measured with light clothing without shoes. Body mass index (BMI) was calculated as body weight (kg) divided by the square of body height (m). BP was measured on the right upper arm in the sitting position after 10–15 minutes of rest between 7 and 9 AM using a validated digital automatic blood pressure monitor. Informed consent and the protocol of the overall physical examination were reviewed and approved by the Institutional Review Board at the Third Xiangya Hospital (No. 2018-S389). This study was approved by an independent ethics committee at the Third Xiangya Hospital, and all the participants provided written informed consent according to the general recommendations of the Declaration of Helsinki.

Measurements of FMD

We measured FMD according to the consensus paper of the European Society[15] using a vascular ultrasound system equipped with an edge-tracking system for 2D imaging and pulsed Doppler flow velocimeter for automatic measurement (UNEXEF18G; Unex Co. Ltd., Nagoya, Japan). Participants were examined between 8 and 12 AM by trained and experienced ultrasound doctors. In brief, the diameter of the brachial artery at rest was measured in the cubital region; subsequently, the cuff was inflated to 50 mmHg above systolic blood pressure for 5 min and deflated. The diameter at the same point of the artery was monitored continuously, and the maximum dilatation from 45 to 60 s after deflation was recorded. This method has been validated previously[19].

FMD was calculated from the following equation: FMD (%) = (maximum diameter–diameter at rest) × 100/diameter at rest.

Measurement of baPWV

As previously reported[20], the participants' baPWV was measured in a quiet, temperature-controlled room. After the participants rested for a

minimum of 5 min in the supine position, an automatic waveform analyzer (BP-203 RPE III, Omron Health Medical, Dalian, China) was used to measure the baPWV simultaneously. The cuffs were wrapped around the extremities (upper arm and ankle) and then connected to the plethysmography sensor (volume pulse form) and the oscillometric pressure sensor. Pressure waveforms were recorded at both the brachial and tibial arteries to assess the transmission time between the initial increases in these waves. The measurements were performed twice, and the average values of the left-side and right-side assessments were thereafter calculated.

Laboratory Measurements

Blood samples were collected according to the relevant guidelines at the Third Xiangya Hospital. All blood samples were measured using a 7600 and 7170 Hitachi automatic biochemical analyzer. Fasting blood samples were collected to test fasting serum glucose (FSG), total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) using LEADMAN test kits (Beijing LEADMAN Biochemical Co., Ltd. China), as well as serum creatinine (SCr) using Wako L-Type Creatinine M kits (Wako Pure Chemical Industries, Ltd. Japan). RC is defined as TC minus LDL-C minus HDL-C. Non-high-density lipoprotein cholesterol (non-HDL-C) is defined as TC minus HDL-C.

The calculation formulas of RC and non-HDL-C are as follows[21, 22]:

RC = TC − (LDL-C + HDL-C)

non-HDL-C = TC − HDL-C

The Main Chronic Disease Definition

Hypertension was defined as self-reported hypertension diagnosed by a physician, self-reported regular use of antihypertensive medications, or systolic blood pressure (SBP) /diastolic blood pressure (DBP) at recruitment ≥ 140/90 mmHg[23].

Dyslipidemia was defined as meeting any of the following criteria: (1) TC ≥ 6.22 mmol/L (240 mg/dl); (2) LDL-C ≥ 4.14 mmol/L (160 mg/dl); (3) HDL-C < 1.04 mmol/L (40 mg/dl); (4) TG ≥ 2.26 mmol/L (200 mg/dl); (5) use of lipid-lowering medicines; and (6) self-reported dyslipidemia diagnosed by a physician[24].

Diabetes mellitus was defined as self-reported diabetes diagnosed by a physician, self-reported regular use of antidiabetic medications, or FSG at recruitment ≥ 7.0 mmol/L[25].

CVD was defined as self-reported cardiovascular diseases diagnosed by a physician.

Statistical Analyses

Data were collected and cleaned using R version 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria) and analyzed using Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, version 22.0 for Windows). Continuous variables are shown as the means ± standard deviation, whereas categorical variables are reported as percentages (%) and numbers (n). Participants were divided into four groups according to the quartiles of RC. Continuous variables were compared using ANOVA with Tukey's test for multiple groups. Categorical values were compared using the χ^2 test. Recent studies have found that RC > 30 mg/dl (0.78 mmol/l) differentiated subjects at a higher risk of major adverse cardiovascular events compared with those at lower concentrations[26, 27]. This was used as a cutoff point to divide the population with normal lipids into two groups. Between-group differences were evaluated using the independent Student's *t*-test or rank sum test. Multivariable linear regressions were performed to evaluate the changes and their 95% confidence intervals (CIs) for FMD and baPWV by sex and menopause. The association of FMD and baPWV with sex in medicine subgroups was also assessed. Potential covariates were adjusted for age, sex, BMI, WC, SBP, DBP, FSG, SCr, blood urea nitrogen (BUN), uric acid (Ua), TC, LDL-C, HDL-C, baseline brachial artery diameter, alcohol and smoking status, physical activity, hypertension, diabetes mellitus, dyslipidemia, and cardiovascular disease. All *p*-values were two-tailed.

Results

The characteristics of the participants are summarized in **Table 1**. In total, 13,237 subjects were enrolled in the physical examinations. The mean age of the participants was 48.94 ± 9.96 years old, and 76.60% (n = 10,140) were male. Moreover, 23.81% of the participants were diagnosed with hypertension, 14.63% with diabetes mellitus, 38.23% with dyslipidemia, and 1.79% with cardiovascular disease. In total, 35.83% of the individuals were self-reported current smokers, whereas 45.78% of the individuals were self-reported current alcohol users. Meanwhile, 64.44% of the individuals self-reported current participation in sports. The mean values of RC from its lowest to highest quartiles were 0.40 mmol/L, 0.64 mmol/L, 0.93 mmol/L, and 1.88 mmol/L. For FMD, the mean values were as follows: 7.73%, 7.39%, 7.23%, and 7.09%. The mean value of FMD was 7.36% in the whole population. For baPWV, the mean values were as follows: 1363.58 cm/s, 1412.32

Table 1. Characteristics of participants in the whole study population and by quartile of remnant cholesterol (mean ± SD, N%)

Characteristics	Total	RC				F/x^2	P^2
		Q1	Q2	Q3	Q4		
N	13,237	3,264	3,227	3,362	3,384		
Age (years)	48.94 ± 9.96	48.94 ± 9.96	48.93 ± 9.97	48.67 ± 9.90	49.23 ± 10.01	1.804	0.144
BMI (kg/m^2)	25.31 ± 3.28	25.25 ± 3.25	25.24 ± 3.31	25.34 ± 3.34	25.42 ± 3.24	2.146	0.092
WC (cm)	86.61 ± 9.56	86.36 ± 9.47	86.38 ± 9.52	86.77 ± 9.74	86.91 ± 9.51	2.804	0.038
SBP (mmHg)	127.65 ± 17.25	127.58 ± 17.17	127.27 ± 17.3	127.87 ± 17.4	127.86 ± 17.13	0.909	0.436
DBP (mmHg)	80.31 ± 11.98	80.20 ± 12.04	80.19 ± 11.89	80.47 ± 12.00	80.37 ± 12.01	0.436	0.727
FSG (mmol/L)	5.66 ± 1.59	5.34 ± 1.12	5.49 ± 1.30	5.70 ± 1.55	6.11 ± 2.09	651.622	<0.001
SCr (mmol/L)	75.02 ± 19.90	70.41 ± 18.00	74.8 ± 20.82	77.01 ± 23.34	77.69 ± 15.84	437.725	<0.001
BUN (mmol/L)	4.98 ± 1.31	4.97 ± 1.32	5.00 ± 1.29	4.99 ± 1.33	4.97 ± 1.28	0.370	0.775
Ua (mmol/L)	351.92 ± 92.68	349.39 ± 93.89	351.58 ± 92.84	352.71 ± 92.87	353.91 ± 91.16	1.425	0.233
TC (mmol/L)	5.19 ± 0.98	4.77 ± 0.87	5.08 ± 0.90	5.27 ± 0.91	5.62 ± 1.02	1277.891	<0.001
TG (mmol/L)	2.17 ± 1.86	0.88 ± 0.31	1.40 ± 0.23	2.00 ± 0.34	4.29 ± 2.56	11704.211	<0.001
LDL-C (mmol/L)	2.86 ± 0.87	2.79 ± 0.79	3.05 ± 0.81	3.05 ± 0.82	2.57 ± 0.94	699.706	<0.001
HDL-C (mmol/L)	1.35 ± 0.34	1.58 ± 0.38	1.39 ± 0.30	1.28 ± 0.27	1.17 ± 0.26	2706.036	<0.001
RC (mmol/L)	0.97 ± 0.72	0.40 ± 0.08	0.64 ± 0.07	0.93 ± 0.11	1.88 ± 0.86	12408.291	<0.001
non-HDL-C (mmol/L)	3.84 ± 0.97	3.19 ± 0.82	3.69 ± 0.82	3.98 ± 0.83	4.45 ± 0.95	3011.461	<0.001
baPWV(cm/s)	1414.03 ± 266.5	1363.58 ± 272.59	1412.32 ± 263.71	1434.19 ± 265.69	1444.30 ± 256.85	267.485	<0.001
ABI	1.13 ± 0.08	1.12 ± 0.08	1.13 ± 0.08	1.13 ± 0.08	1.12 ± 0.08	8.094	<0.001
FMD (%)	7.36 ± 3.45	7.73 ± 3.61	7.39 ± 3.48	7.23 ± 3.36	7.09 ± 3.32	60.754	<0.001
Baseline brachial artery diameter (mm)	4.25 ± 0.67	4.01 ± 0.69	4.23 ± 0.65	4.33 ± 0.65	4.43 ± 0.62	721.585	<0.001
Max brachial artery diameter (mm)	4.56 ± 0.69	4.31 ± 0.71	4.53 ± 0.67	4.63 ± 0.67	4.74 ± 0.65	701.151	<0.001
Male % (n)	76.60 (10,140)	75.06 (2,450)	76.94 (2,483)	77.54 (2,607)	76.83 (2,600)	6.296	0.098
Current alcohol users % (n)	45.78 (6,061)	37.99 (1,208)	41.21 (1,330)	48.63 (1,635)	55.79 (1,888)	275.902	<0.001
Current smokers % (n)	35.83 (4,743)	26.19 (855)	33.52 (1,082)	37.18 (1,250)	45.98 (1,556)	293.542	<0.001
Physical activity % (n)	64.44 (8,530)	66.67 (2,176)	66.78 (2,155)	63.00 (2,118)	61.49 (2,081)	30.631	<0.001
Hypertension % (n)	23.81 (3,152)	18.19 (594)	23.95 (773)	26.23 (882)	36.68 (903)	82.993	<0.001
Dyslipidemia % (n)	38.23 (5,061)	7.72 (252)	11.65 (376)	33.43 (1,124)	97.78 (3,309)	7366.756	<0.001
Diabetes mellitus % (n)	14.63 (1,936)	8.92(291)	11.62 (375)	16.09 (541)	21.54 (729)	244.018	<0.001
CVD % (n)	1.79 (237)	1.59 (52)	2.44 (79)	1.75 (59)	1.38 (47)	11.787	0.008

Note: SD, standard deviance; BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; FSG, fasting serum glucose; SCr, serum creatinine; BUN, blood urea nitrogen; UA, uric acid; TC, total cholesterol; TG, triglycerides; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; RC, remnant cholesterol; non-HDL-C, non-high-density lipoprotein cholesterol; BaPWV, brachial-ankle pulse wave velocity; ABI, ankle brachial index; FMD, flow-mediated vasodilation.

cm/s, 1434.19 cm/s, and 1444.30 cm/s. The mean value of baPWV was 1414.03 cm/s in the whole population. No significant difference was noted in terms of age, sex, BMI, SBP, DBP, BUN, or Ua among the RC quartile groups. Subjects with higher RC levels had a higher proportion of alcohol users, smokers, patients with hypertension, patients with dyslipidemia, and patients with diabetes mellitus. They were found to have a higher FSG, higher SCr, higher TC, higher TG, higher non-HDL-C, larger baseline brachial artery diameter, larger max brachial artery diameter, and lower LDL-C levels.

Fig. 1 illustrates the relationship between FMD/baPWV and quartile RC in the whole population and in different sex groups. In the whole population, FMD decreased with the increase of RC, and differences were observed in the comparison of RC quartile between groups ($p<0.05$), except between Q3 and Q4. In males, the same trend was observed. No differences were noted between groups Q2 and Q3 or between Q3 and Q4. In females, differences existed only between Q1 and Q4 and between Q2 and Q4. In the whole population, baPWV increased with RC and differed in all group comparisons between RC quartiles ($p<0.05$), except between Q3 and Q4. In males, it was consistent with the whole population; in females, there was a significant difference between Q1 and the other groups but no significant difference between the other groups.

The population was divided into three groups

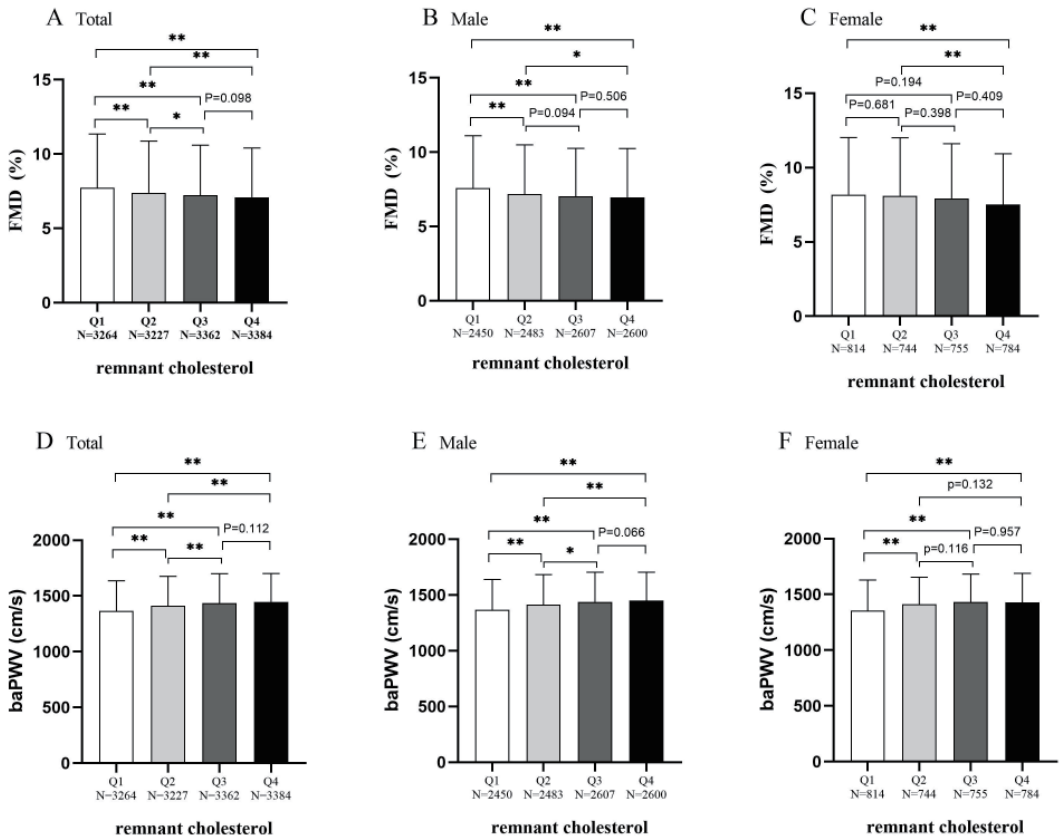

Fig. 1. Bar graphs showing FMD according to RC quartile subgroups in the total population (A), in males (B), and in females (C). Bar graphs showing baPWV according to RC quartile subgroups in the total population (D), in males (E), and in females (F)

The error bars indicate the standard deviation.
Note: $^{**}p<0.001$; $^{*}p<0.05$
baPWV, brachial-ankle pulse wave velocity; FMD, flow-mediated vasodilation; RC remnant cholesterol

according to their lipids, that is, dyslipidemia group, nondyslipidemia but RC increased group (RC >0.78 mmol/L), and nondyslipidemia and RC normal group (RC ≤ 0.78 mmol/L), as shown in **Fig. 2**. The FMD of the three groups was 7.09%±3.36%, 7.39%±3.38%, and 7.57%±3.54%, respectively, and the differences between the groups were statistically significant. The baPWV of the three groups was 1445.26±261.56 cm/s, 1425.04±265.24 cm/s, and 1382.73±267.75 cm/s, respectively. Significant differences were noted between the groups. The characteristics of the three groups are summarized in **Table 2**. There was no significant difference in terms of sex, BMI, WC, SBP, DBP, BUN, or Ua among the three groups. There was a significant difference in terms of age, FSG, SCr, TC, TG, LDL-C, HDL-C, non-HDL-C, proportion of alcohol users, smokers, patients with hypertension, and diabetes mellitus.

We used a multivariate linear regression model to analyze the associations of RC with FMD and baPWV. The results are shown in **Table 3**. We found that RC was negatively associated with FMD ($\beta=-0.14$, $p=0.014$ in model 3). A similar result was also observed in males ($\beta=-0.17$, $p=0.008$ in model 3). In females, RC was negatively associated with FMD in model 1 ($\beta=-0.37$, $p<0.001$) and model 2 ($\beta=-0.32$, $p<0.001$), but no significant relationship was found in model 3 ($\beta=-0.06$, $p=0.616$), whether menopausal or nonmenopausal. In addition, RC was positively associated with baPWV ($\beta=21.42$, $p<0.001$ in model 3). The same correlation was found in males ($\beta=22.76$, $p<0.001$ in model 3), but there was no significant relationship between RC and baPWV in females after adjusting for age, BMI, WC, SBP, and other factors ($\beta=8.37$, $p=0.285$ in model 3). Furthermore, among the nonmenopausal population, RC was positively correlated with baPWV ($\beta=33.14$, $p=0.012$ in model 3), but this correlation was not found in menopausal females. The population was grouped according to whether they took medicine (antihypertensive medicine, lipid-lowering medicine, and hypoglycemic medicine). After adjusting for the

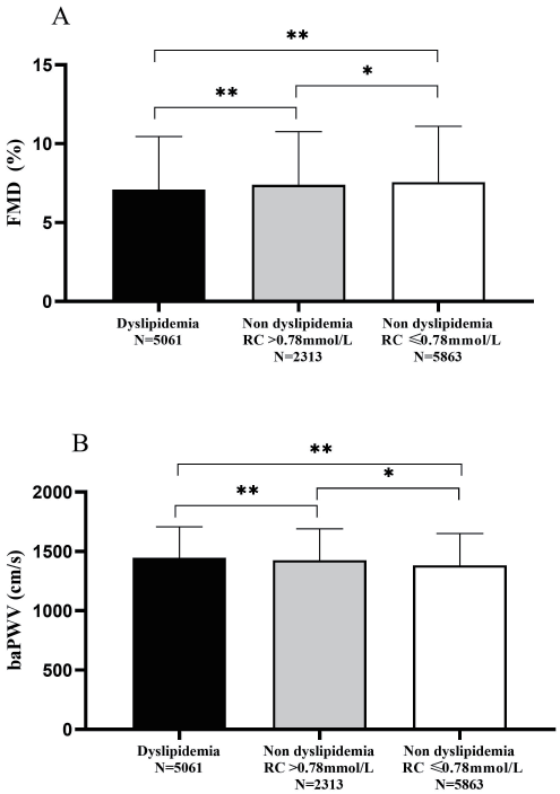

Fig. 2. Bar graphs showing FMD (A) and baPWV (B) in the dyslipidemia group, nondyslipidemia but RC increased group (RC > 0.78 mmol/L), and nondyslipidemia and RC normal group (RC ≤ 0.78 mmol/L)

Note: $^{**}p<0.001$; $^{*}p<0.05$
baPWV, brachial-ankle pulse wave velocity; FMD, flow-mediated vasodilation; RC remnant cholesterol

relevant factors, RC was found to be negatively associated with FMD in the population without medication ($p<0.001$) and in males ($p<0.001$) but not in females ($p=0.773$). RC was not associated with FMD in the medicated population. RC was positively associated with baPWV in the unmedicated population ($p<0.001$) and in the male subgroup ($p<0.001$), but not in the female subgroup ($p=0.104$). No association was determined between RC and baPWV in the medicated population ($p=0.275$).

We have also analyzed the associations of LDL-C and non-HDL-C with FMD and baPWV. The results are shown in **Supplementary Table 1 and Supplementary Table 2**. We found that LDL-C was negatively associated with FMD ($\beta=-0.09$, $p=0.025$ in model 3) in males, but not in all population ($\beta=-0.06$, $p=0.073$ in model 3) or females ($\beta=0.01$, $p=0.935$ in model 3). LDL-C was found to be positively associated with baPWV ($\beta=17.37$, $p<0.001$ in model 3). The same correlation was found in males ($\beta=14.34$, $p<0.001$ in model 3), but there was no significant relationship between LDL-C and baPWV in females ($\beta=-1.35$, $p=0.091$ in model 3). We have also found that non-HDL-C was negatively associated with FMD ($\beta=-0.14$, $p=0.014$ in model 3) and positively associated with baPWV ($\beta=21.42$, $p<0.001$ in model 3). Non-HDL-C was positively associated with baPWV ($\beta=24.75$, $p=0.031$ in model 3) in medicated subjects. However, there was no significant relationship between non-HDL-C and FMD in medicated subjects ($\beta=0.15$, $p=0.253$ in model 3).

Discussion

To the best of our knowledge, this is the first study to reveal the association between the RC level and vascular endothelial function and atherosclerosis in a large-scale retrospective observational study of 13,237 individuals in China. Many previous studies have focused on the cytological mechanisms by which RC causes endothelial dysfunction and atherosclerosis[28, 29], with limited data on the association between RC and both in the real-world, population-based setting.

RC is cholesterol-rich in TG lipoprotein, which consists of chylomicron remnants, IDL, and very-low-

Table 2. Clinical characteristics of dyslipidemia group, nondyslipidemia but RC increased group, and nondyslipidemia and RC normal group (mean ± SD, N%)

Characteristics	dyslipidemia group	nondyslipidemia but RC increased group	nondyslipidemia and RC normal group	F/x^2	P^2
N	5,061	2,313	5,863		
Age (years)	49.18 ± 9.90	48.49 ± 9.95	48.92 ± 10.01	3.807	0.022
BMI (kg/m^2)	25.35 ± 3.27	25.38 ± 3.32	25.25 ± 3.27	2.023	0.132
WC (cm)	86.74 ± 9.62	86.86 ± 9.62	86.39 ± 9.49	2.767	0.063
SBP (mmHg)	127.80 ± 17.33	127.90 ± 17.44	127.42 ± 17.10	0.951	0.386
DBP (mmHg)	80.35 ± 12.05	80.52 ± 12.01	80.18 ± 11.92	0.734	0.480
FSG (mmol/L)	5.97 ± 1.96	5.64 ± 1.43	5.40 ± 1.21	513.340	<0.001
SCr (mmol/L)	76.78 ± 17.59	76.96 ± 23.72	72.73 ± 19.9	238.800	<0.001
BUN (mmol/L)	5.01 ± 1.33	4.94 ± 1.24	4.98 ± 1.31	1.924	0.146
Ua (mmol/L)	353.37 ± 92.07	351.86 ± 92.54	350.69 ± 93.26	1.137	0.321
TC (mmol/L)	5.75 ± 1.07	5.03 ± 0.69	4.77 ± 0.71	2633.138	<0.001
TG (mmol/L)	3.50 ± 2.41	1.87 ± 0.29	1.13 ± 0.32	8586.921	<0.001
LDL-C (mmol/L)	2.96 ± 1.14	2.86 ± 0.63	2.78 ± 0.64	63.867	<0.001
HDL-C (mmol/L)	1.26 ± 0.33	1.27 ± 0.25	1.47 ± 0.35	1410.716	<0.001
RC (mmol/L)	1.53 ± 0.87	0.90 ± 0.12	0.51 ± 0.15	8945.872	<0.001
non-HDL-C (mmol/L)	4.49 ± 0.98	3.76 ± 0.64	3.29 ± 0.69	4260.003	<0.001
BaPWV (cm/s)	1445.26 ± 261.56	1425.04 ± 265.24	1382.73 ± 267.75	78.065	<0.001
ABI	1.12 ± 0.08	1.13 ± 0.08	1.13 ± 0.08	14.103	<0.001
FMD (%)	7.09 ± 3.36	7.39 ± 3.38	7.57 ± 3.54	60.427	<0.001
Baseline brachial artery diameter (mm)	4.36 ± 0.65	4.33 ± 0.64	4.12 ± 0.68	410.804	<0.001
Max brachial artery diameter (mm)	4.67 ± 0.67	4.64 ± 0.67	4.42 ± 0.70	396.363	<0.001
Male % (n)	76.98 (3,896)	77.04 (1,782)	76.10 (4,462)	1.466	0.480
Current alcohol users % (n)	52.03 (2,633)	48.03 (1,111)	39.52 (2,317)	176.840	<0.001
Current smokers % (n)	41.51 (2,101)	37.44 (866)	30.29 (1,276)	151.928	<0.001
Physical activity % (n)	42.50 (3,162)	43.47 (1,468)	66.52 (3,900)	20.516	<0.001
Hypertension % (n)	26.97 (1,365)	25.00 (578)	20.62 (1209)	62.515	<0.001
Diabetes mellitus % (n)	19.46 (985)	15.04(348)	10.28 (603)	183.627	<0.001
CVD % (n)	1.60 (81)	1.60 (37)	2.03 (119)	3.426	0.180

Note: SD, standard deviance; BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; FSG, fasting serum glucose; SCr, serum creatinine; BUN, blood urea nitrogen; UA, uric acid; TC, total cholesterol; TG, triglycerides; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; RC, remnant cholesterol; non-HDL-C, non-high-density lipoprotein cholesterol; BaPWV, brachial-ankle pulse wave velocity; ABI, ankle brachial index; FMD, flow-mediated vasodilation.

density lipoprotein[30]. As TG contents are gradually degraded by lipoprotein lipase in the bloodstream, the cholesterol in RC could also be involved in atherosclerotic plaque formation and subsequent cardiovascular events, and it has been recognized as more atherogenic and proinflammatory than LDL-C[31, 32]. Adverse cardiovascular events related to RC have also been observed in many clinical studies. High levels of RC have been reported to be associated with an increased risk of coronary artery disease, fatty liver disease, hypertension, and chronic kidney disease[11, 12, 33-35]. FMD, which is a marker of endothelium-dependent dilation of the brachial artery, reflects systemic endothelial function, as well as atherosclerotic risk burden at the time of FMD measurement. PWV reflects arterial stiffening that is increased by adverse structural and functional alterations in the vascular wall. These structural and functional abnormalities include endothelial dysfunction, medial hypertrophy, and elevated smooth muscle tone, which are associated with the development of atherosclerosis in the vascular wall. These two noninvasive vascular examination techniques have been widely used in the assessment of vascular function in patients with chronic diseases and in the screening of vascular diseases in the normal physical examination population.

In this study, RC was quartile grouped, and it was found that FMD was significantly lower in the higher RC group than in the lower RC group, and RC was negatively correlated with FMD. The baPWV was

Table 3. Adjusted associations of remnant cholesterol with FMD and baPWV in different groups

Variables	Model 1			Model 2			Model 3		
	β	95% CI	*P*	*β*	95% CI	*P*	*β*	95% CI	*P*
FMD									
All population									
Total (*n*=13,237)	-0.31	-0.39, -0.23	<0.001	-0.27	-0.35, -0.18	<0.001	-0.14	-0.25, -0.03	0.014
Male (*n*=10,140)	-0.29	-0.38, -0.20	<0.001	-0.25	-0.34, -0.16	<0.001	-0.17	-0.29, -0.04	0.008
Female (*n*=3,097)	-0.37	-0.56, -0.19	<0.001	-0.32	-0.50, -0.13	<0.001	-0.06	-0.31, 0.18	0.616
Non menopause (*n*=1,785)	-0.49	-0.78, -0.20	<0.001	-0.48	-0.78, -0.19	<0.001	-0.12	-0.53, 0.29	0.573
Menopause (*n*=1,312)	0.02	-0.21, 0.26	0.846	-0.01	-0.26, 0.23	0.906	-0.11	-0.42, 0.21	0.506
No medication									
Total (*n*=11,388)	-0.35	0, -0.44	<0.001	-0.30	0, -0.39	<0.001	-0.22	0, -0.35	0.001
Male (*n*=8,774)	-0.33	0, -0.43	<0.001	-0.29	0, -0.39	<0.001	-0.28	0, -0.42	<0.001
Female (*n*=2,614)	-0.39	0, -0.59	<0.001	-0.32	0, -0.52	0.002	-0.04	0.77, -0.32	0.773
Medication									
Total (*n*=1,849)	0.10	0.33, -0.1	0.327	0.11	0.28, -0.09	0.277	-0.03	0.85, -0.3	0.853
Male (*n*=1,366)	0.23	0.04, 0.01	0.042	0.22	0.05, 0	0.051	0.27	0.07, -0.02	0.068
Female (*n*=483)	-0.21	0.40, -0.70	.0397	-0.24	0.32, -0.73	0.320	-0.08	0.81, -0.71	0.812
baPWV									
All population									
Total (*n*=13,237)	32.68	26.38, 38.97	<0.001	35.06	28.67, 41.45	<0.001	21.42	13.54, 29.30	<0.001
Male (*n*=10,140)	33.39	26.18, 40.59	<0.001	36.27	28.97, 43.57	<0.001	22.76	13.66, 31.86	<0.001
Female (*n*=3,097)	29.78	16.83, 42.73	<0.001	30.70	17.48, 43.92	<0.001	8.37	-6.99, 23.74	0.285
Non menopause (*n*=1,785)	42.36	21.83, 62.89	<0.001	41.60	20.54, 62.67	<0.001	33.14	7.42, 58.86	0.012
Menopause (*n*=1,312)	14.38	-2.55, 31.31	0.096	16.96	-0.41, 34.32	0.056	9.61	-10.35, 29.57	0.345
No medication									
Total (*n*=11,388)	21.75	26.7, 39.55	<0.001	34.65	28.15, 41.16	<0.001	21.75	13.36, 30.14	<0.001
Male (*n*=8,774)	24.05	27.86, 42.65	<0.001	37.86	30.38, 45.33	<0.001	24.05	14.32, 33.78	<0.001
Female (*n*=2,614)	13.76	11.98, 37.85	<0.001	22.72	9.56, 35.88	<0.001	13.76	-2.85, 30.38	0.104
Medication									
Total (*n*=1,849)	-23.10	-40.81, -5.40	0.011	-15.09	-32.98, 2.79	0.098	12.84	-10.21, 35.88	0.275
Male (*n*=1,366)	-28.59	-48.95, -8.22	0.006	-22.00	-42.55, -1.44	0.036	19.16	-6.90, 45.22	0.149
Female (*n*=483)	-4.64	-40.74, 31.46	0.801	7.03	-29.69, 43.75	0.707	24.71	-22.12, 71.54	0.300

Model 1 was not adjusted for other factors.
Model 2 was adjusted for age, sex, body mass index, SBP, DBP, alcohol and smoking status, physical activity.
Model 3 was adjusted for age, sex, BMI, WC, SBP, DBP, FSG, SCr, BUN, Ua, TC, LDL-C, HDL-C, baseline brachial artery diameter, alcohol and smoking status, physical activity, hypertension, diabetes mellitus, dyslipidemia and cardiovascular disease.

significantly higher in the higher RC group than in the lower RC group, and RC was positively correlated with baPWV. This means that increased RC is associated with endothelial dysfunction and the development of vascular atherosclerosis. Previous studies have indicated an association between RC and arteriosclerosis. In Wang's study, it was found that higher RC was independently associated with higher baPWV, independent of other risk factors (OR=1.794, 95% CI: 1.267–2.539, p=0.001)[36]. In Qian's study, carotid artery intima-media thickness (cIMT) was used as an imaging marker of subclinical atherosclerosis. They found that the multivariable-adjusted OR (95% CIs) for the highest versus lowest quartile of RC were 2.06 (1.46–2.91) for abnormal mean cIMT and 1.70 (1.23–2.35) for abnormal maximum cIMT. Linear associations were determined between RC levels and both abnormal mean cIMT (p <0.001) and abnormal maximum cIMT (p=0.003)[37]. It has also been found that lowering RC with lipid-lowering drugs improves the cardioankle vascular index (an indicator of atherosclerosis)[38].

Furthermore, previous studies have shown that taking lipid-lowering drugs to reduce RC levels can improve endothelial function and atherosclerosis. After 6 months of atorvastatin therapy, RC

significantly decreased and FMD significantly improved compared to baseline values (5.1 vs. 3.6%, $p=0.04$)[39]. Nakamura's study found that the percent changes in FMD levels had a significant inverse correlation with the percent changes in RC ($r=-0.39$, $p<0.001$), so improvement of RC may be an important mediator for the relationship between improvement of endothelial dysfunction and LDL-lowering after statin treatment in patients with CAD[40].

Due to the large sample size of this study, statistically significant group differences were observed, while group differences in FMD and baPWV were found to be very small. Is this statistical difference clinically significant? We discussed this question in two ways. First, we calculated the effect size between the first and last FMD and baPWV groups according to the RC quartiles. Cohen's d effect size of FMD and baPWV were 0.2 and 0.3, respectively. Samsa[41] proposed an effect size of 0.2 as an estimate of minimal clinically important difference based on a literature review. Second, the clinical cut-off point of FMD was 4%[42], and FMD <4% was considered to indicate vascular endothelial dysfunction. The cutoff point of baPWV was 1800 cm/s[42], and baPWV >1800 cm/s was considered to indicate atherosclerosis. In the group with the lowest RC, 365 people (11.18%) were found to have FMD <4%, whereas 237 people (7.26%) had baPWV > 1800 cm/s. In the group with the highest RC, 483 people (14.27%) had FMD <4%, and 299 people (8.84%) had baPWV >1800 cm/s. According to the data, the population with endothelial dysfunction and vascular atherosclerosis is increased in the group with high RC, and the group differences in RC are clinically significant.

In this study, subgroup analysis of the population was performed by sex. After adjusting for relevant risk factors, it was found that RC and FMD had significant correlations in males, but this correlation was not found in females. We further divided the females into menopausal and nonmenopausal groups. RC and FMD were determined to be not correlated in either subgroup. To exclude vascular effects of medications, we have grouped the population according to whether they took relevant chronic disease medication. RC was not associated with FMD in the medicated population in either males or females. RC was associated with FMD in the nonmedicated population, but there was still no such association in females. The correlation between RC and baPWV in the subgroups was similar to that of FMD, except that RC and baPWV were correlated in the nonmenopausal group. Previous studies on the relationships of RC and endothelial function or atherosclerosis remain scarce and do not compare sex subgroups. However, previous studies have suggested that blood lipid profiles deteriorate and baPWV increases sharply in postmenopausal women[20]. TC and baPWV are not correlated in females[43], and metabolic markers and lipids are not key factors for baPWV in older and postmenopausal women[44, 45] but may be more likely to be related to hormonal changes[46].

We have considered that drugs can have an effect on lipid and vascular function, so we grouped the population according to whether they were taking medicine (antihypertensive medicine, lipid-lowering medicine, and hypoglycemic medicine) or not and found that RC was not associated with FMD and baPWV in medicated subjects, LDL-C was associated with baPWV only in females, and non-HDL-C was positively associated with baPWV in medicated subjects but not in males or females. From the statistical results, the correlation between non-HDL-C and arterial stiffness is noted to be more significant than RC and LDL-C in medicated subjects, which may be related to the lipid-lowering effect of lipid-lowering drugs on different lipid components in people of different ages and genders[47]. However, due to the more diverse and complex drugs taken by the medicated subjects in this study, it cannot be well described that kind of lipid components can be used as surrogate marker for endothelial dysfunction and arterial stiffness in medicated subjects.

Castaner's study[26] has explored the relationship between RC and cardiovascular outcome, wherein they found that a baseline RC level >30 mg/dl (0.78 mmol/l) was able to identify individuals at high risk of major adverse cardiovascular events independent of LDL cholesterol. In our study, the population was divided into dyslipidemia group, nondyslipidemia but increased RC group, and nondyslipidemia but normal RC group using 0.78 mmol/l as the cutoff point. Endothelial function and atherosclerosis were the worst in the dyslipidemia group; meanwhile, in the nondyslipidemia population, both endothelial function and atherosclerosis were more severe in the increased RC group than in the normal RC group.

In physical examination screening, our understanding was that hyperlipidemia was the main risk factor for vascular dysfunction and atherosclerosis, but according to our study, among people with normal lipids, those with increased RC were more likely to develop vascular dysfunction and atherosclerosis than those with normal RC. Therefore, in our clinical work of physical examination, we should pay more attention to people with normal

blood lipids but elevated RC, and lowering RC should also be an important task to improve vascular function.

Several limitations should be noted here. First, our study was a cross-sectional study; thus, the ability to clarify the cause-effect of RC and vascular endothelial function or atherosclerosis is deemed limited. Second, the enrolled participants were from one site. Thus, the generalizability of the findings to other populations is unclear. Third, patients without FMD and baPWV data were excluded, which may limit the generalizability of our findings. Fourth, vascular endothelial function and atherosclerosis were examined by different physicians. We could not analyze interrater variability for the measurements or explore the contributors to possible differences. However, we were able to perform consistency evaluation and quality control of the instrumentation and different doctors.

Conclusion

As per the findings of this study, it can further be confirmed that the higher RC was an independent predictive factor for participants with endothelial function and atherosclerosis in a large-scale population, which might enrich the research field of predictors of endothelial function and atherosclerosis. Thus, it is important to use RC as a risk management indicator of vascular function, especially for males and those with normal conventional lipid parameters but increased RC.

Conflict of Interest

The authors report no conflicts of interest.

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Author Contributions

Ying Li and Lijun Zhang produced data for analysis. Quling Shi and Pingting Yang wrote the manuscript. Quling Shi, Jiangang Wang and Pingting Yang designed the study. Saiqi Yang and Qian Chen included patients for the study. All authors reviewed and edited the manuscript. Quling Shi, Pingting Yang and Ying Li handled funding and supervision. All authors read and approved the final manuscript.

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Supplementary Table 1. Adjusted associations of low-density lipoprotein cholesterol with FMD and baPWV in different groups

Variables	Model 1			Model 2			Model 3		
	β	95% CI	*P*	*β*	95% CI	*P*	*β*	95% CI	*P*
FMD									
All population									
Total (*n*=13,237)	-0.06	-0.13, 0.01	0.081	-0.07	-0.14, 0	0.037	-0.06	-0.13, 0.01	0.073
Male (*n*=10,140)	-0.07	-0.15, 0	0.056	-0.08	-0.16, -0.01	0.031	-0.09	-0.17, -0.01	0.025
Female (*n*=3,097)	-0.02	-0.17, 0.13	0.795	-0.04	-0.19, 0.11	0.564	0.01	-0.15, 0.16	0.935
No medication									
Total (*n*=11,388)	-0.10	-0.18, -0.03	0.008	-0.11	-0.19, -0.04	0.003	-0.11	-0.19, -0.03	0.006
Male (*n*=8,774)	-0.11	-0.20, -0.03	0.007	-0.12	-0.20, -0.04	0.004	-0.15	-0.24, -0.06	<0.001
Female (*n*=2,614)	-0.06	-0.23, 0.11	0.473	-0.08	-0.25, 0.08	0.325	0.01	-0.17, 0.18	0.954
Medication									
Total (*n*=1,849)	0.01	-0.15, 0.17	0.874	0.03	-0.13, 0.18	0.716	-0.03	-0.11, 0.39	0.253
Male (*n*=1,366)	-0.02	-0.19, 0.14	0.776	0.00	-0.17, 0.17	0.965	0.17	0, 0.35	0.055
Female (*n*=483)	0.10	-0.26, 0.46	0.592	0.09	-0.26, 0.45	0.604	0.16	-0.21, 0.53	0.407
baPWV									
All population									
Total (*n*=13,237)	15.83	10.61, 21.05	<0.001	15.52	10.30, 20.74	<0.001	17.37	12.48, 22.27	<0.001
Male (*n*=10,140)	16.96	10.97, 22.95	<0.001	16.46	10.46, 22.46	<0.001	19.98	14.34, 25.63	<0.001
Female (*n*=3,097)	12.10	1.49, 22.70	.025	12.35	1.73, 22.97	0.023	8.49	-1.35, 18.33	0.091
No medication									
Total (*n*=11,388)	18.52	13.11, 23.93	<0.001	17.96	12.57, 23.35	<0.001	18.69	13.41, 23.97	<0.001
Male (*n*=8,774)	18.07	11.84, 24.30	<0.001	17.35	11.12, 23.57	<0.001	20.52	14.42, 26.62	<0.001
Female (*n*=2,614)	20.09	9.31, 30.87	<0.001	19.94	9.20, 30.67	<0.001	12.64	2.06, 23.23	0.019
Medication									
Total (*n*=1,849)	31.12	17.67, 44.58	<0.001	27.19	13.74, 40.63	<0.001	10.84	-10.21, 30.88	0.175
Male (*n*=1,366)	39.07	23.48, 54.66	<0.001	35.12	19.49, 50.74	<0.001	20.89	4.75, 37.02	0.011
Female (*n*=483)	6.88	-19.79, 33.56	0.612	3.57	-23.25, 30.39	0.794	-17.43	-44.82, 9.97	0.212

Model 1 was not adjusted for other factors.
Model 2 was adjusted for age, sex, BMI, SBP, DBP, alcohol and smoking status, physical activity.
Model 3 was adjusted for age, sex, BMI, WC, SBP, DBP, FSG, SCr, BUN, Ua, TC, LDL-C, HDL-C, baseline brachial artery diameter, alcohol and smoking status, physical activity, hypertension, diabetes mellitus, dyslipidemia and cardiovascular disease.

Supplementary Table 2. Adjusted associations of non-high-density lipoprotein cholesterol with FMD and baPWV in different groups

Variables	Model 1			Model 2			Model 3		
	β	95% CI	*P*	*β*	95% CI	*P*	*β*	95% CI	*P*
FMD									
All population									
Total (*n*=13,237)	-0.22	-0.28, -0.16	<0.001	-0.20	-0.26, -0.14	<0.001	-0.14	-0.25, -0.03	0.014
Male (*n*=10,140)	-0.22	-0.28, -0.15	<0.001	-0.20	-0.27, -0.13	<0.001	-0.17	-0.29, -0.04	0.008
Female (*n*=3,097)	-0.21	-0.35, -0.08	0.002	-0.20	-0.33, -0.06	0.004	-0.06	-0.31, 0.20	0.662
No medication									
Total (*n*=11,388)	-0.28	-0.34, -0.21	<0.001	-0.25	-0.32, -0.19	<0.001	-0.22	-0.35, -0.09	<0.001
Male (*n*=8,774)	-0.28	-0.35, -0.2	<0.001	-0.26	-0.33, -0.18	<0.001	-0.28	-0.42, -0.14	<0.001
Female (*n*=2,614)	-0.26	-0.40, -0.11	<0.001	-0.23	-0.38, -0.08	0.002	-0.04	-0.32, 0.24	0.773
Medication									
Total (*n*=1,849)	0.06	-0.08, 0.21	0.401	0.08	-0.06, 0.22	0.274	0.15	-0.11, 0.42	0.253
Male (*n*=1,366)	0.09	-0.06, 0.25	0.236	0.11	-0.05, 0.26	0.182	0.26	-0.02, 0.55	0.070
Female (*n*=483)	-0.01	-0.35, 0.32	0.932	-0.03	-0.36, 0.30	0.847	-0.03	-0.36,0.31	0.887
baPWV									
All population									
Total (*n*=13,237)	30.65	26.00, 35.3	<0.001	31.35	26.68, 36.02	<0.001	21.42	13.54, 29.30	<0.001
Male (*n*=10,140)	32.21	26.85, 37.56	<0.001	33.03	27.66, 38.40	<0.001	22.76	13.66, 31.86	<0.001
Female (*n*=3,097)	25.34	15.93, 34.75	<0.001	25.74	16.25, 35.22	<0.001	16.86	1.05, 32.68	0.037
No medication									
Total (*n*=11,388)	32.97	28.20, 37.74	<0.001	33.09	28.31, 37.86	<0.001	21.75	13.36, 30.14	<0.001
Male (*n*=8,774)	34.07	28.56, 39.59	<0.001	34.60	29.08, 40.12	<0.001	24.05	14.32, 33.78	<0.001
Female (*n*=2,614)	25.34	15.93, 34.75	<0.001	27.57	18.09, 37.06	<0.001	13.76	-2.85, 30.38	0.104
Medication									
Total (*n*=1,849)	15.18	2.67, 27.70	0.017	15.87	3.42, 28.33	0.013	24.75	2.25, 47.24	0.031
Male (*n*=1,366)	18.91	4.40, 33.41	0.011	18.89	4.43, 33.35	0.011	19.32	-6.70, 45.33	0.145
Female (*n*=483)	3.79	-21.11, 28.68	0.765	6.33	-18.61, 31.26	0.618	1.54	-34.45, 38.03	0.964

Model 1 was not adjusted for other factors.
Model 2 was adjusted for age, sex, BMI, SBP, DBP, alcohol and smoking status, physical activity.
Model 3 was adjusted for age, sex, BMI, WC, SBP, DBP, FSG, SCr, BUN, Ua, TC, LDL-C, HDL-C, baseline brachial artery diameter, alcohol and smoking status, physical activity, hypertension, diabetes mellitus, dyslipidemia and cardiovascular disease.