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ARTICLE

Sex-specific association between serum immunoglobulin-M and brachial ankle pulse wave velocity in a Chinese population: Danyang Study

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Abstract

Emerging evidence supports a causal role for the immunoglobulin-M (IgM) as a protector of atherosclerosis. Since arterial stiffness is an index of subclinical atherosclerosis, we propose that IgM may play an important role in arterial stiffness. As the level of IgM differs between sexes, we investigate the sex-specific association of serum IgM with arterial stiffness in a Chinese population. The study subjects were recruited from Danyang in 2017. Using the Omron VP-1000 system, we measured brachial ankle pulse wave velocity (baPWV). Serum IgM concentration was measured by the immunoturbidimetry method. The 1030 study participants (mean age = 54.3 ± 9.0 years) included 407 men (39.5%), 428 hypertensive (41.6%), 80 diabetic (7.8%), and 512 arterial stiffness patients (49.7%). Serum IgM concentration was lower in men than women (0.97 vs. 1.26 μg/mL, $P < 0.001$) and negatively with alcohol intake ($r = -0.11$ in men and $r = -0.07$ in women, $P \le 0.09$). In multiple regression analyses, serum IgM concentration was negatively associated with baPWV in women (−0.82 m/s per 10-time increase in serum IgM concentration, $P = 0.009$) but not in men. In multivariable logistic regression analyses, elevated serum IgM concentration was associated with lower risks for arterial stiffness in women (OR = 0.26; 95% CI 0.08–0.82; $P = 0.02$) but not in men (OR = 0.66; 95% CI 0.17–2.62; $P = 0.55$). Categorical analyses produced similar results. Serum IgM is negatively associated with baPWV and accordingly associated with a lower risk of arterial stiffness in women.

Key words Arterial stiffness · Brachial ankle pulse wave velocity · Immunoglobulin-M

Introduction

Immunoglobulin-M (IgM) antibodies, mainly produced by B1 lymphocytes [1], have been shown to protect against atherosclerosis in recent animal experiments [2–4] and human studies [5–7]. The atheroprotective effects of IgM antibodies may be mediated by neutralizing the proinflammatory properties of oxidized low-density lipoproteins (ox-LDL), inhibiting the uptake of oxidized low-density lipoproteins by macrophages, and by promoting apoptotic cell clearance [8]. Arterial stiffness caused by decreased arterial compliance is one of the major signs of vascular aging [9]. Previous study showed that increased ox-LDL contributed to decreased arterial compliance [10], which might lead to arterial stiffness. In addition, elevated arterial stiffness was an index of subclinical atherosclerosis [11] because some studies have reported the reversibility of arterial stiffness after reduction of atherosclerotic risk

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factors. Taken together, serum IgM is, therefore, considered as a protector of arterial stiffness by regulation of ox-LDL and anti-atherosclerosis. To date, as to humans, evidence for IgM and arterial stiffness association is still lacking. On this point, an important notion has attracted increasing interests is that IgM may also play an important role in arterial stiffness. If the hypothesis is true, this would open a new pathway to a possible therapy of vascular aging.

Sex differences have been observed in serum IgM concentrations. Men have an absolute lower level of serum IgM than women [12]. Therefore, the association between serum IgM and arterial stiffness may differ between sexes. Accordingly, the present study aims to investigate sex-specific association of serum IgM with arterial stiffness in a Chinese population.

Methods

Study population

The Danyang Study is an ongoing, longitudinal, and multistage cohort study with the objective of investigating the comprehensive cardiovascular risk factors in Chinese. Subjects were recruited if they were (1) at least 30 years old, (2) local residents from communities in Danyang, and (3) available for long-term follow-up. Exclusion criteria included (1) severe cardiac disease or end-stage renal disease, (2) stroke history within 3 months, (3) autoimmune disease, and (4) malignant tumor with life expectancy <5 years. The Danyang Study was authorized and financially supported by the provincial government of Jiangsu (Grant ID BE2015730) and was approved by the Ethics Committee of Jiangsu Province Hospital of Traditional Chinese Medicine. All patients gave informed written consent prior to their inclusion in the study.

From 3 June 2017 to 29 June 2017, we visited five villages of Station Community randomly selected from Danyang County, a plain area approximately 70 km east of Nanjing. We invited all inhabitants aged at least 30 years to take part. Of the 1154 invited, 1035 (89.7%) participated. Of these 1035 participants, we excluded five subjects from this analysis because of missing information on brachial ankle pulse wave velocity ($n = 3$), or serum IgM ($n = 2$). Thus, the number of participants analyzed totaled 1030.

Anthropometric, biochemical, and immunoglobulin-M measurements

One trained physician measured each patient's blood pressure 3 × consecutively using a validated Omron 7130 oscillometric blood pressure monitor (Omron, Kyoto, Japan) [13] after the patients had rested for at least 5 min in the sitting position. The same observer also administered a standardized questionnaire to collect information on socio-demographics medical history, lifestyle, and use of medications. A trained nurse measured body height and body weight. Body mass index (BMI) was calculated as the body weight in kilograms divided by the body height in meters squared.

Venous blood samples were drawn after overnight fasting for the measurement of plasma glucose, serum creatinine, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides. Serum IgM was measured by the immunoturbidimetry method using IMMAGE 800 analyzers (Beckman Coulter Inc., Brea, CA, USA).

Hypertension was defined as a blood pressure of at least 140 mm Hg systolic or 90 mm Hg diastolic, or as the use of antihypertensive drugs. Diabetes mellitus was defined as a fasting plasma glucose of at least 7.0 mmol/L or as the use of anti-diabetic agents.

Brachial ankle pulse wave velocity measurements

Brachial ankle pulse wave velocity (baPWV) was measured using the Omron VP-1000 device (Omron HealthCare, Kyoto, Japan) as described previously [14, 15]. In brief, the travel path from body height was extrapolated and baPWV was computed automatically by dividing time difference between the pulse waves that were transmitted to the brachial and ankle arteries by the travel path with Omron Colin device [16]. Because no uniform cutoff values are available for baPWV, arterial stiffness was defined as a baPWV >14.88 m/s in current study [17].

Statistical methods

For database management and statistical analysis, we used SAS software (version 9.2, SAS institute, Cary, NC, USA). Serum IgM concentration was logarithmically transformed for statistical analysis. To compare means and proportions, we used the Student *t*-test and Fisher's exact test, respectively. We searched for possible correlates of IgM and baPWV using stepwise multiple regression with the *P*-value for potential covariates to enter and stay in the model set at 0.10. We then performed sex-specific multiple linear and logistic regression analyses to study the association of serum IgM concentration with baPWV, with continuous and dichotomous variables, respectively, while controlling for the identified correlates. A two-sided value of $P < 0.05$ was considered statistically significant.

Table 1 Characteristics of the participants by sex

Characteristic	Men ($n = 407$)	Women ($n = 623$)	P
Age (years)	55.4 ± 9.1	53.5 ± 8.9	0.001
Body mass index (kg/m^2)	24.7 ± 3.1	23.6 ± 3.2	< 0.001
Systolic blood pressure (mm Hg)	128.6 ± 16.7	123.5 ± 19.3	< 0.001
Diastolic blood pressure (mm Hg)	85.8 ± 10.2	80.6 ± 10.3	< 0.001
Heart rate (beats/minute)	71.3 ± 9.5	74.5 ± 9.9	< 0.001
Current smoking, *n* (%)	267 (65.6)	1 (0.2)	< 0.001
Alcohol intake, *n* (%)	225 (55.3)	28 (4.5)	< 0.001
Hypertension, *n* (%)	209 (51.4)	219 (35.2)	< 0.001
Diabetes mellitus, *n* (%)	39 (9.6)	41 (6.6)	0.08
Taking antihypertensive drugs, *n* (%)	118 (29.0)	121 (19.4)	< 0.001
Taking antihyperglycemic drugs, *n* (%)	17 (4.2)	18 (2.9)	0.26
Plasma glucose (mmol/L)	5.57 ± 1.53	5.32 ± 1.10	0.005
Total cholesterol (mmol/L)	4.80 ± 0.89	4.98 ± 1.03	0.003
HDL cholesterol (mmol/L)	1.43 ± 0.32	1.61 ± 0.33	< 0.001
LDL cholesterol (mmol/L)	2.86 ± 0.73	2.91 ± 0.74	0.33
Triglyceride (mmol/L)	1.46 (0.99–2.38)	1.34 (0.99–1.91)	0.002
Serum creatinine (μmol/L)	76.5 ± 11.3	58.7 ± 9.3	< 0.001
Brachial ankle PWV (m/s)	15.6 ± 2.6	15.0 ± 2.5	0.001
Arterial stiffness, *n* (%)	223 (54.8)	289 (46.4)	0.008
Immunoglobulin type M (g/L)	0.97 (0.70–1.31)	1.26 (0.92–1.70)	< 0.001

Data are mean ± standard deviation, median with interquartile range in parenthesis, or number with percentage in parenthesis

For definitions of hypertension, diabetes, and arterial stiffness, see Methods

HDL high-density lipoprotein, *LDL* low-density lipoprotein, *PWV* pulse wave velocity

Results

Characteristics of the study participants

The 1030 participants (mean age 54.3 ± 9.0 years) included 407 men (39.5%), 428 had hypertension (41.6%), 80 had type 2 diabetes mellitus (7.8%), and 512 had arterial stiffness (49.7%). Table 1 summarizes the characteristics of the study participants by sex. Men and women had similar rates for diabetes and taking antihyperglycemic drugs, and LDL cholesterol levels. Men were older (+ 1.9 years) and had a greater BMI (+ 1.1 kg/m^2), higher systolic/diastolic blood pressure (+ 5.1/5.2 mm Hg), higher serum creatinine (+ 17.8μmol/L), higher plasma glucose (+ 0.25 mmol/L), serum triglycerides (+ 0.12 mmol/L), lower serum total (−0.18 mmol/L), and HDL cholesterol concentrations (−0.18 mmol/L), and lower heart rate (−3.2 beats/minute), and higher rates for hypertension (51.4% vs. 35.2%) or taking antihypertensive drugs (29.0% vs. 19.4%) and higher proportions of current smoking (65.6% vs. 0.2%) and alcohol intake (55.3% vs. 4.5%) ($P \le 0.005$).

Men, compared with women, had lower serum IgM concentration (0.97 vs. 1.26 g/L; $P < 0.001$) but higher baPWV (15.6 vs. 15.0 m/s; $P = 0.001$) and proportion of arterial stiffness (54.8% vs. 46.4%; $P = 0.008$).

Correlates of serum IgM concentration and baPWV

In sex-specific stepwise multiple regression analyses, age, body mass index, mean arterial pressure, heart rate, current smoking (not in women because of small numbers) and alcohol intake, the use of antihypertensive and antihyperglycemic drugs, the presence of hypertension and diabetes, plasma glucose, serum total, and high-density lipoprotein cholesterol were considered as potential correlates.

We identified that serum IgM concentration was associated with alcohol intake and baPWV with age, mean arterial pressure, heart rate and body mass index in men as well as women ($r = 0.10$ to 0.57 or -0.11 to -0.07, $P \le 0.06$, Table 2). IgM was additionally negatively associated with age in women ($r = -0.15$, $P = 0.0003$). BaPWV was additionally associated with the presence of diabetes and use of antihypertensive drugs in men ($r = 0.08$ to 0.11, $P \le 0.05$, Table 2).

Relationship between IgM concentration and baPWV

Because men and women had different IgM and baPWV, we performed multiple regression analyses in men and women separately and adjusted for above-mentioned correlates, i.e., age, mean arterial pressure, heart rate, body mass index, current smoking (not in women because of small numbers) and alcohol intake, the use of antihypertensive and antihyperglycemic drugs, the presence of hypertension and diabetes, plasma glucose, serum total, and high-density lipoprotein cholesterol. These multiple regression analyses demonstrated that serum IgM concentration was significantly negatively associated with baPWV (0.82 m/s decrease per 10-time increase in serum IgM concentration, $P = 0.009$) in women but not in men ($P > 0.10$, Table 3). Similarly, compared to those in the lowest tertile of serum IgM level, subjects in the highest tertile had a significantly lower baPWV in women (14.9 vs. 15.3 m/s, $P = 0.01$) but not in men (15.5 vs. 15.7 m/s, $P = 0.39$, Fig. 1).

Table 2 Correlates of serum immunoglobulin-M (IgM) concentration and brachial ankle pulse wave velocity by sex

	Men ($n = 407$)		Women ($n = 623$)	
	Partial r	P	Partial r	P
Serum IgM concentration				
Alcohol intake	−0.11	0.03	−0.07	0.09
Age (years)	-	> 0.10	−0.15	0.0003
Brachial ankle pulse wave velocity				
Age (years)	0.57	< 0.0001	0.57	< 0.0001
Mean arterial pressure (mm Hg)	0.38	< 0.0001	0.40	< 0.0001
Heart rate (beats/minute)	0.17	< 0.001	0.19	< 0.0001
Body mass index (kg/m^2)	0.11	0.03	0.10	0.06
Diabetes mellitus	-	> 0.10	0.11	0.006
Use of antihypertensive drugs, n (%)	-	> 0.10	0.08	0.05

In a sex-specific stepwise multiple regression model, we considered age, body mass index, mean arterial pressure, heart rate, current smoking (not in women because of small numbers), and alcohol intake, the use of antihypertensive and antihyperglycemic drugs, the presence of hypertension and diabetes, plasma glucose, serum total and high-density lipoprotein cholesterol for entry and stay at a significance level of $P \leq 0.10$. The variables are listed in an order of the size of the absolute value of the correlation coefficients in men. For definitions of hypertension, diabetes mellitus, see Methods.

Relationship between IgM concentration and arterial stiffness

We next performed multiple logistic regression analysis to investigate whether serum IgM level was associated with the risks for arterial stiffness in men and women separately. After adjusted for aforementioned covariates, elevated serum IgM concentration was significantly associated with lower risks for arterial stiffness in women (OR = 0.26; 95% CI 0.08–0.82; $P = 0.02$) but not in men (OR = 0.66; 95% CI 0.17–2.62; $P = 0.55$), respectively (Table 4). Similar results were obtained by logistic regression using non-transformed IgM as a categorical variable (data not show).

Discussion

The main finding of our study is that IgM decreases with alcohol intake in both men and women and declines with age in women, and is negatively associated with baPWV and accordingly associated with a lower risk of arterial stiffness in women. As baPWV is a measure of arterial stiffness and is also predictive of cardiovascular events and mortality [14, 18, 19], our finding, therefore, may have clinical implications for arterial stiffness and cardiovascular events prevention by increasing the production of serum IgM in women.

To the best of our knowledge, our study is the first that has showed significant association of serum IgM concentration with a lower risk of arterial stiffness as assessed by baPWV in women. Among 623 Chinese women in our study, each logarithmically transformed increase in serum IgM concentrations are associated with −0.82 m/s lower baPWV, and 74% lower risk of arterial stiffness. This finding is in keeping with recent findings on inverse association between IgM autoantibodies to oxidized low-density lipoprotein and carotid artery atherosclerosis [5] and coronary artery disease [6]. Indeed, arterial stiffness is closely related to atherosclerosis [20]. Study conducted by Huynh et al. [21] suggested that arterial stiffening may affect endothelial function with aging and promote atherosclerosis. Arterial stiffness and atherosclerosis commonly coexist with aging and they share some common pathophysiological mechanisms. That to some extent explains why the association between IgM and atherosclerosis can partly translate to arterial stiffness.

The mechanism underlying the protective effect of serum IgM on arterial stiffness has not been clear. Mounting evidences from recent animal-based studies suggest that IgM plays an important role in atherosclerosis. Ldlr$^{-/-}$ mice deficient in serum IgM has accelerated cholesterol crystal formation and increases smooth muscle cell stiffness in aortic root lesions [2]. Moreover, Kyaw et al. [3] demonstrates that natural IgM secreted by B1 lymphocytes offered atheroprotection by depositing IgM in atherosclerotic lesions, which reduces the necrotic cores of lesions. As vascular smooth muscle cell stiffness [22] and inflammation [23] contribute to arterial stiffness, we therefore speculate that lower serum IgM might have a detrimental effect on arterial stiffness by above-mentioned mechanisms. However, future studies are needed to clarify the exact mechanisms of serum IgM in the development of arterial stiffness.

The sex differences on the association between serum IgM and baPWV that we found are probably explained by a difference in serum IgM between men and women. Women have a relatively higher level of IgM than men [12]. Indeed, women have a 0.29 g/L higher IgM concentration in our study. In addition, Lewis et al. [2] demonstrates that increased atherosclerosis is observed in female serum IgM deficient LDLR$^{-/-}$ mice compared to control irrespective of type of diet. Another possible explanation on the sex-specific association may be dependent on the status of menopause in women. Previous studies suggested that post-menopausal women had a lower level of IgM than pre-menopausal women [24] and menopause engendered the augmentation of arterial stiffness in an age-dependent manner [25–27]. Indeed, post-menopausal women, compared with pre-menopausal women, had lower IgM concentration (1.17 vs. 1.37 g/L; $P < 0.001$) but higher baPWV

Table 3 Associations of brachial ankle pulse wave velocity with serum immunoglobulin-M (IgM) concentration and conventional risk factors by sex

	Brachial ankle pulse wave velocity (m/s)			
	Men ($n = 407$)		Women ($n = 623$)	
	$\beta \pm$ SE	P	$\beta \pm$ SE	P
Age (+ 10 years)	1.45 ± 0.11	< 0.0001	1.38 ± 0.08	< 0.0001
Mean arterial pressure (+ 10 mm Hg)	0.93 ± 0.11	< 0.0001	0.82 ± 0.07	< 0.0001
Heart rate (+ 10 beats/minute)	0.32 ± 0.09	0.0008	0.33 ± 0.07	< 0.0001
Body mass index (+ 10 kg/m^2)	0.27 ± 0.13	0.03	0.21 ± 0.11	0.08
Diabetes mellitus (yes vs. no)	-	> 0.10	1.02 ± 0.39	0.009
Use of antihypertensive drugs (yes vs. no)	-	> 0.10	0.44 ± 0.22	0.04
IgM[a] (+ 1 g/L, Log)	-	> 0.10	−0.82 ± 0.31	0.009

Values are regression coefficient (β) ± standard error (SE). The analysis was adjusted for age, body mass index, mean arterial pressure, heart rate, current smoking (not in women because of small numbers), and alcohol intake, the use of antihypertensive and antihyperglycemic drugs, the presence of hypertension and diabetes, plasma glucose, serum total and high-density lipoprotein cholesterol. The variables are listed in an order of the size of the absolute value of the regression coefficients in men. For definitions of hypertension, diabetes mellitus, see Methods

[a]The regression coefficient was computed for 1 unit increase in the logarithmically transformed IgM (equals ten times increases in IgM)

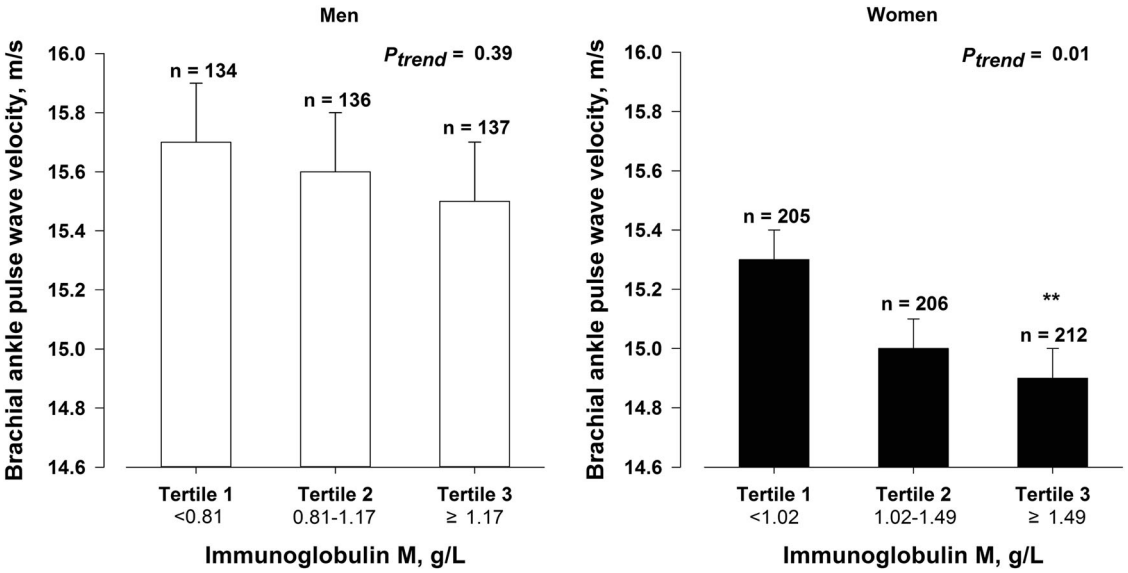

Fig. 1 Relationship of serum immunoglobulin-M (IgM) concentration with brachial ankle pulse wave velocity (baPWV) in men (left panel) and women (right panel) by IgM subgroup. Open (men) and closed bars (women) indicate adjusted mean value of baPWV per tertile of IgM. The analysis was adjusted for age, mean arterial pressure, heart rate, body mass index, current smoking (not in women because of small numbers), and alcohol intake, the use of antihypertensive and antihyperglycemic drugs, the presence of hypertension and diabetes, plasma glucose, serum total, and high-density lipoprotein cholesterol. The P-value for trend and the number of subjects per subgroup are given for men and women separately. $^{**}P = 0.01$ vs. tertile 1

(16.0 vs. 13.4 m/s; $P < 0.001$) in our study. We therefore speculate that menopause status could partially explain the sex-specific association between IgM with baPWV.

Another interesting finding of the current study is a negative correlation between serum IgM and alcohol intake in general population, which is consistent with the results obtained by McMillan et al. [28]. and Nissinen et al. [29]. Nevertheless, our finding did not accord with a study performed by Gonzalez-Quintela et al. [30] in which alcohol consumption was not associated with significant changes in serum IgM. The disparities in association of alcohol intake and IgM between our finding and the results of a previous study [30] might be explained by the difference in the sample size. In 124 heavy drinkers and 137 abstainer

Table 4 Associations of serum immunoglobulin-M (IgM) concentration with arterial stiffness by sex

	Serum IgM[a] (+ 1 g/L, Log)			
	Men ($n = 407$)		Women ($n = 623$)	
	Odds ratio (95% CI)	*P*	Odds ratio (95% CI)	*P*
Arterial stiffness				
Crude model	0.96 (0.36–2.53)	0.93	0.17 (0.07–0.37)	< 0.001
Adjusted model	0.66 (0.17–2.62)	0.55	0.26 (0.08–0.82)	0.02

In the adjusted model, odds ratio (95% CI) were adjusted for age, sex, body mass index, mean arterial pressure, heart rate, current smoking (not in women because of small numbers), and alcohol intake, the use of antihypertensive and antihyperglycemic drugs, the presence of hypertension and diabetes, plasma glucose, serum total and high-density lipoprotein cholesterol. For definitions of arterial stiffness, see Methods

[a]The odds ratio and 95% CI was computed for 1 unit increase in the logarithmically transformed IgM (equals ten times increases in IgM)

controls, Gonzalez-Quintela et al. [30] reported similar levels of IgM (1.12 g/L in men vs. 1.47 g/L in women) as our study. However, in this previous study, serum IgM level was not significantly correlated with alcohol intake. This previous study apparently has insufficient power to show significant association of the size observed in our study because drinkers tended to have lower IgM concentration than abstainers (1.24 vs. 1.37 g/L) in their study.

The main strength of our current study is a relative large population study, which enable us to find the sex-specific differences because of sufficient sample size. A major limitation of our study is the cross-sectional nature of the design, which does not allow us to draw any casual inference. Another limitation of this study is that we only performed measurement of baPWV but not carotid femoral PWV in current study. The latter is considered as the golden standard for assessing arterial stiffness. Nonetheless, baPWV has been reported previously to be closely correlated with carotid femoral PWV [31]. Future studies are necessary to investigate the association of cfPWV and serum IgM. Finally, the studied subjects were aged at least 30 years, which are not fully representative of general population. Future studies including subjects aged between 18 and 30 years are warranted to further explore the relationship between serum IgM and arterial stiffness.

In summary, our study demonstrates serum IgM is negatively associated with baPWV and accordingly associated with a lower risk of arterial stiffness in Chinese women. One of the potential clinical implications of our study is that prospective observational and interventional studies are needed to study the modulation of IgM production in arterial stiffness and cardiovascular disease prevention.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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