


# BMJ Open Gender discrepancy in the predictive effect of aortic root diameter on incidence of cardiovascular events among rural Northeast Chinese

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## ABSTRACT

**Objectives** The possible predictive effect of echocardiographic aortic root diameter (ARD) on the incidence of cardiovascular events (CVEs) in a large, general population is limited. In addition, there is a lack of data about rural participants. We intend to figure out the possible relationship between ARD and the incidence of CVEs among the general population from rural China.

**Design** Population-based cohort study.

**Setting** Rural areas in Liaoning Province, Northeast China.

**Participants** At baseline, 9810 participants (mean age 53±10, 49.1% male) were enrolled in the Northeast China Rural Cardiovascular Health Study between 2012 and 2017.

**Main outcome measures** Cardiac ultrasonography, lifestyle, medical history, laboratory testing, blood pressure, weight and height. ARD measurement was conducted at the level of the sinuses of Valsalva. Furthermore, the ARD was indexed to height or body surface area.

**Results** During a median follow-up of 4.66 years, 550 non-fatal or fatal CVEs were recorded. Adjusting for blood pressure, age, total cholesterol, fasting blood glucose, estimated glomerular filtration rate, current smoking and drinking, previous cardiovascular diseases and antihypertensive treatment; ARD/height (HR per 1-unit increase=1.781, 95% CI: 1.160 to 2.736, p=0.008) was associated with an increased risk of CVEs in men only. The combination of left ventricular hypertrophy (LVH) and aortic dilation was an independent and powerful predictor for cardiovascular prognosis compared with aortic dilation alone in men but not in women.

**Conclusions** Our study enrolls a large sample of rural Chinese residents, and first confirms that ARD/height has a predictive effect on the incidence of CVEs among rural Chinese residents. The combination of LVH and aortic dilation is synergistic, which increases its predictive effect on CVEs in men only, suggesting that aortic dilatation predicts cardiovascular prognosis better than LVH does in men but not in women.

## INTRODUCTION

Aortic dilation has a close relationship with aortic rupture and dissection, which are clinically lethal conditions.<sup>1</sup> Previously, it was

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ The present study focuses on the possible predictive effect of aortic root diameter (ARD) in cardiovascular events among rural general Northeast Chinese population in whom no study has been conducted to address these issues.
- ⇒ The present study did not measure ARD in multiple levels due to the large sample size which might introduce bias.
- ⇒ The observational design of the present study does not allow for conclusions about the cause of aortic dilation.
- ⇒ This study used questionnaires to get data from participants; therefore, some data obtained were participants' subjective perceptions.

assumed that aortic root (AR) dilation was prevalent only among patients with Marfan syndrome.<sup>2</sup> However, until recently, there is cumulative evidence confirming that, even among patients with only leptosomic features, the rate of aortic dilation is similar to patients with Marfan syndrome.<sup>3</sup> In addition, aortic dilatation is common among patients with congenital ventricular septal defect, tetralogy of Fallot and chronic kidney disease.<sup>4-6</sup> Furthermore, 10 patients with mitochondrial cytopathy also presented with aortic dilation, which had not been previously reported as being associated with mitochondrial disease.<sup>7</sup> Aortic extension might be due to cystic medial necrosis. However, the aetiology and pathogenesis of this process is complex and still poorly understood. There are some factors that might be responsible for it, such as ageing, hypertension, atherosclerosis, smoking, valvular diseases, trauma, inflammation, family history and specific genetic disorders.<sup>8,9</sup> In the Danish Cardiovascular Multicenter Screening Trial, the overall prevalence of ascending aortic dilation was 4.0%, which was close to two times more

than descending aortic dilation.<sup>10</sup> In various types of thoracic aortic dilation, many studies have reported that the most prevalent lesion was ascending aortic dilation.<sup>11</sup> In the Corinthia study, the incidence of AR dilation was 2.4%, and it confirmed the association between alcohol consumption and the incidence of AR dilation.<sup>12</sup>

Left ventricular hypertrophy (LVH) is characterised by an increase in left ventricular (LV) mass, which is due to an increase in wall thickness or LV cavity enlargement or both.<sup>13</sup> There are various clinical conditions that can result in LVH, including essential hypertension, renal artery stenosis, athletic heart with physiological LVH, aortic valve stenosis and coarctation of the aorta.<sup>14</sup> Previous studies have confirmed that LVH is present in 15%–20% of the general population and is more prevalent among blacks, older subjects, the obese and in subjects with hypertension.<sup>15</sup> In addition, there is no significant difference in the prevalence of LVH between men and women.<sup>15</sup> LVH is responsible for causing systolic or diastolic dysfunction and end-stage heart failure. Furthermore, eccentric hypertrophy can significantly increase myocardial oxygen demand, causing angina or ischaemia.<sup>16</sup> A previous study has found that patients with aortic dissection presented with greater LV mass indexes compared with normal subjects and concluded that LV mass is independently associated with the aortic arch, and LVH may be a risk factor for aortic enlargement.<sup>17</sup> Cuspidi and colleagues claimed that aortic root diameter (ARD), in addition to LV mass, could refine cardiovascular risk stratification in the general population.<sup>18</sup>

However, as far as we know, there is a lack of data about ARD and its association with the incidence of cardiovascular events (CVEs) in the general Chinese population, especially in rural areas. In addition, whether there is a synergistic effect of ARD and LVH on prediction of CVEs among the general population remains controversial. Therefore, we aim to evaluate whether the value of ARD is effective in the prediction of the incidence of CVEs in rural Chinese populations, which might help to better understand and control the risk of CVEs; to this purpose, we analysed data obtained in the Northeast China Rural Cardiovascular Health Study (NCRCHS), a population study performed in rural China.

## MATERIALS AND METHODS

### Study design and participants

A community-based prospective study named the NCRCHS was carried out in rural China.<sup>19</sup> In brief, we enrolled 11 956 participants (older than 35 years old). The Ethics Committee of China Medical University approved the present study (Shenyang, China AF-SDP-07-1, 0-01).

During 2012–2013, we collected detailed information on the participants, including socioeconomic characters, body circumference measurements, blood pressures and blood tests. In the follow-up study, participants were invited to attend another physical

examination during 2015–2017. Among all the participants, 1256 participants were excluded because of lacking contact information, and 86.6% of participants finished at least one follow-up visit, with a median follow-up 4.66 years at the end of the study. Overall, 9810 out of 10 349 participants who did not have significant cardiac valve disease were enrolled in the present study, including more than one valve with regurgitation, any degree of valvular stenosis or prosthesis.

### Baseline data

Self-reported history of stroke, coronary heart disease and chronic heart failure at baseline was recorded and confirmed by the medical records. Participants were requested to wear light weight clothing and to take off their shoes when measuring weight and height. Waist circumference was measured as previously described.<sup>13</sup> Obesity was defined using a body mass index (BMI) criteria with the cut-off of  $\geq 28 \text{ kg/m}^2$  ( $\text{BMI} = \text{weight (kg)} / \text{height (m)}^2$ ).<sup>20</sup> Blood pressure measurements followed the standard criteria using an automatic electronic sphygmomanometer (HEM-907; Omron, Tokyo, Japan). Hypertension was defined as a systolic blood pressure (SBP)  $\geq 140 \text{ mm Hg}$  and/or diastolic blood pressure (DBP)  $\geq 90 \text{ mm Hg}$  and/or use of antihypertensive medications.<sup>21</sup> After fasting at least 12 hours, blood samples were collected from participants by trained nurses. Fasting plasma glucose (FPG), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and total cholesterol (TC) were analysed enzymatically. We used the Chronic Kidney Disease Epidemiology Collaboration equation to calculate the estimated glomerular filtration rate (eGFR).<sup>22</sup>

### Echocardiography

Cardiac echocardiography was conducted following standardised procedures.<sup>23</sup> Per the recommendations of the American Society of Echocardiography (ASE), M-mode measurements were performed at the end diastolic and end systolic dimensions. Frames that showed optimal visualisation of interfaces and exhibited simultaneous visualisation of the LV internal diameter, posterior wall and septum were used to calculate. LV mass was estimated by the corrected ASE method and indexed to body surface area (BSA) or height in order to normalise.<sup>24</sup> LVH was defined as a LV mass index equal to or higher than  $115 \text{ g/m}^2$  in men and  $99 \text{ g/m}^2$  in women.<sup>25</sup> At the level of the sinuses of Valsalva, we used M-mode tracings to measure the ARD value, with the maximal distance between the leading edges of the anterior and posterior AR wall at end diastole.<sup>26</sup>

### Follow-up

During the median follow-up of 4.66 years, an incident CVE was defined as a composite of new onset stroke or CHD (Coronary heart disease) during the follow-up period. The specific incidences of stroke and CHD were

also determined. For all participants reporting possible diagnoses or deaths, all available clinical information was collected, including medical records and death certificates.

The end-point assessment committee was responsible for reviewing and adjusting all materials independently. The WHO Multinational Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) criteria was used to define stroke,<sup>27 28</sup> as instantly developing signs of global or a focal disturbance of cerebral function, continuing for more than 24 hours (unless interrupted by surgery or death) with no definite non-vascular causes. Stroke cases with a diagnosis of subarachnoid haemorrhage or intracerebral haemorrhage were defined as haemorrhagic stroke, whereas stroke cases with a diagnosis of thrombosis or embolism were defined as ischaemic stroke. Transient ischaemic attacks and chronic cerebral vascular disease were excluded. CHD was defined as a diagnosis of hospitalised angina, hospitalised myocardial infarction, CHD death or any revascularisation procedure.<sup>29</sup>

### Cross-sectional analysis

Sex-specific upper limits of normality (mean $\pm$ 1.96 SD) for absolute ARD, index to BSA or height were derived from 931 healthy participants, excluding hypertension, obesity, diabetes, dyslipidaemia and cardiovascular diseases. Values were presented as the means $\pm$ SDs or as percentages. T-tests, analysis of variance, non-parametric tests or  $\chi^2$ -tests were used to evaluate the differences among categories as appropriate. The strength of linear correlation between variables was tested by Pearson's correlation coefficient. A multiple linear regression model with stepwise selection was used to identify variables independently associated with the ARD. Clinical variables considered were age, sex, SBP, DBP, serum glucose, TC and TG. Variables were selected by stepwise selection ( $\alpha=0.05$ ); p values  $<0.05$  were considered statistically significant.

### Follow-up analysis

We compared absolute ARD values, ARD/BSA and ARD/height in patients with and without incident CVEs (include non-fatal and fatal cases). HRs of CVEs were evaluated by Cox's proportional hazard model. HR was calculated per unit increment of ARD (ie, 1 cm, 1 cm/BSA and 1 cm/height). Age, previous cardiac diseases (including angina, myocardial infarction, atrial fibrillation, other kinds of arrhythmia, heart failure and others), antihypertensive treatment, current smoking and drinking, SBP, DBP, TC, FPG and eGFR were all adjusted. Finally, subjects with neither LVH nor AR dilatation (ie, LV mass index  $<115/99\text{ g/m}^2$  and ARD  $<2.4\text{ cm}/2.7\text{ cm}$ ) were considered to be references, with the rest of the groups including subjects with isolated LVH, isolated AR dilatation or both of these conditions. Kaplan-Meier estimates were adopted to compute the cumulative incidence of CVEs for each group, and the log-rank test was conducted to compare the differences in estimates. SPSS

V.17.0 software (Chicago, Illinois, USA) was used to calculate all the statistical analyses, and p values  $<0.05$  were considered to be statistically significant.

### Patient and public involvement

There was no patient or public involvement in the design of this study

### RESULTS

Out of the 10 349 participants in the present study, 9810 (mean age  $53\pm 10$  years old, 49.1% male) had echocardiographic data at baseline examination and were used for the present study (table 1).

### Normality values of ARD

Sex-specific upper limits of normality (mean $\pm$ 1.96) for absolute ARD, ARD indexed to BSA and to height derived from 931 participants (424 females and 507 males) after excluding participants with hypertension, obesity, diabetes, dyslipidaemia and cardiovascular diseases were the following: 2.40 cm, 1.66 cm/m<sup>2</sup>, and 1.53 cm/m, respectively, in women and 2.70 cm, 1.71 cm/m<sup>2</sup>, and 1.66 cm/m, respectively, in men. According to these values, the prevalence of aortic dilatation in the whole study sample (n=9810) varied from 4.2% (AR/BSA) to 13.3% (ARD). Women had a significantly higher rate of aortic dilatation compared with men (AR/BSA: 5.1% vs 3.1%; ARD: 15.1% vs 11.1%; ARD/height: 13.5% vs 6.0%, all p $<0.001$ ).

Table 2 shows data about the absolute ARD, ARD/BSA and ARD/height in participants with or without metabolic disorders. The values of ARD and ARD/height increased with elevated WC and TG in both sexes whereas ARD/BSA decreased. Similarly, ARD and ARD/height were higher among the impaired fasting glucose and high LDL groups in both women and men, while ARD/BSA decreased in men but not in women. ARD/BSA significantly decreased with high TC among men and women. With regard to low HDL-C, men had higher ARD and lower ARD/BSA values, whereas women had lower ARD/BSA values only.

### Correlation analyses

Table 3 shows that absolute ARD was positively correlated with all indexes while ARD/BSA did not correlate with heart rate, LDL-C and FPG. ARD/height did not correlate with heart rate only among women. Among men, absolute and indexed ARD values were not correlated with heart rate. In addition, ARD did not correlate with TC, LDL-C and eGFR, while ARD/BSA did not correlate with LV mass. ARD/height did not correlate with TC, HDL-C and uric acid (UA). After multiple regression analyses, age, BMI, mean DBP, heart rate, FPG and LV mass/BSA were still significantly associated with absolute ARD among women, whereas among men, age, BMI, mean DBP, TC, LV mass/BSA, TG and HDL-C were still significantly associated. Age, LV mass/BSA, BMI, and eGFR were

**Table 1** Clinical characteristics of the subjects at the baseline

Variables	Women (n=5286)	Men (n=4524)	Total (n=9810)
Age (years)	53.31±10.23	54.14±10.63	53.69±10.42
BMI (kg/m <sup>2</sup> )	24.89±3.84	24.77±3.51	24.83±3.69
BSA (m <sup>2</sup> )	1.57±0.15	1.74±0.16*	1.65±0.18
WC (cm)	81.06±9.76	83.72±9.65*	82.29±9.80
Height (m)	1.56±0.06	1.66±0.06*	1.61±0.08
SBP (mm Hg)	140.37±24.01	143.87±22.46*	141.98±23.37
DBP (mm Hg)	80.62±11.44	83.90±11.77*	82.14±11.71
Heart rate (bpm)	79.98±13.10	76.41±13.06*	78.33±13.20
TC (mmol/L)	5.31±1.13	5.19±1.04*	5.25±1.09
TG (mmol/L)	1.58±1.28	1.63±1.62	1.60±1.44
LDL-C (mmol/L)	2.99±0.86	2.91±0.81*	2.96±0.83
HDL-C (mmol/L)	1.42±0.35	1.42±0.43	1.42±0.39
FPG (mmol/L)	5.86±1.58	5.94±1.64*	5.89±1.61
UA (mmol/L)	252.67±66.68	330.15±80.96*	288.32±83.11
eGFR (ml/min/1.73 m <sup>2</sup> )	92.68±16.05	94.64±14.49*	93.58±15.38
ARD (cm)	2.14±0.32	2.37±0.28*	2.25±0.32
ARD/BSA (cm/m <sup>2</sup> )	1.37±0.22	1.37±0.19	1.37±0.21
ARD/height (cm/m)	1.38±0.21	1.42±0.17*	1.40±0.20
RWT	0.38±0.25	0.38±0.25	0.38±0.25
LV mass (g)	125.15±37.95	154.88±42.56*	138.86±42.79
LV mass/BSA (g/m <sup>2</sup> )	79.91±23.09	89.09±23.53*	84.14±23.73
LV mass/height <sup>2.7</sup> (g/m <sup>2.7</sup> )	38.19±12.15	39.38±11.56*	38.74±11.90
IVSTd (cm)	0.85±0.13	0.91±0.16*	0.88±0.15
LVPWTd (cm)	0.84±0.22	0.89±0.15*	0.86±0.19
LVEDD (cm)	4.54±0.41	4.90±0.43*	4.70±0.46
EF (%)	62.70±3.84	62.93±3.89*	62.81±3.87
Antihypertensive drugs (%)	892 (70.5)	550 (63.5)*	1442 (67.6)
Previous CV events (%)	1059 (20.0)	500 (11.1)*	1559 (15.9)
Current smoking (%)	858 (16.2)	2620 (57.9)*	3478 (35.5)
Current drinking (%)	153 (2.9)	2066 (45.7)*	2219 (22.6)
Diabetes (%)	616 (11.7)	479 (10.6)	1095 (11.2)
Dyslipidaemia (%)	4255 (80.5)	3198 (70.7)*	7453 (76.0)

Data are shown as means±SD, percentages or absolute numbers. RWT was defined by the ratio of posterior wall and IVS thickness to LVIDd. \*P<0.05 versus women.

ARD, aortic root diameter; BSA, body surface area; DBP, diastolic blood pressure; EF, ejection fraction; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; IVSTd, interventricular septum thickness in diastole; LDL-C, low-density lipoprotein cholesterol; LVEDD, left ventricular end-diastolic diameter; LVIDd, left ventricular internal diameter in diastole; LVPWTd, Left ventricular posterior wall thickness in diastole; RWT, relative wall thickness; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride; UA, uric acid; WC, Waist circumference.

predictors of ARD/BSA among women, while age, BMI, mean SBP, LV mass/BSA, eGFR and HDL-C were predictors among men. Age, BMI, heart rate and LV mass/BSA were the predictors of ARD/height among women, while age, BMI, mean SBP, TC, LV mass/BSA, TG, eGFR and HDL-C were the predictors among men. Interestingly, in all models, LV mass/BSA was the most important factor independently associated with ARD, ARD/BSA

and ARD/height after age and body size measurements. [Table 4](#) shows the multivariate analysis between ARD parameters and different variables. Sex, age and BMI were significantly associated with all ARD parameters. In general subjects, DBP, heart rate, TC, TG, HDL-C, FPG, UA, relative wall thickness and LV mass were significantly associated with ARD. Similarly, there were apparent associations between SBP, HDL-C, eGFR, LV mass and ARD/

**Table 2** Parameters of ARD in subjects with normal or abnormal metabolic disorders

	Women			Men		
	Normal BP	High BP	P value	Normal BP	High BP	P value
ARD	2.11±0.30	2.18±0.33	<0.001	2.33±0.26	2.40±0.29	<0.001
ARD/height	1.35±0.20	1.41±0.22	<0.001	1.40±0.16	1.45±0.18	<0.001
ARD/BSA	1.37±0.22	1.38±0.23	0.003	1.36±0.17	1.38±0.20	0.004
	Normal WC	Elevated WC	P value	Normal WC	Elevated WC	P value
ARD	2.09±0.34	2.18±0.29	<0.001	2.34±0.29	2.43±0.26	<0.001
ARD/height	1.35±0.23	1.40±0.19	<0.001	1.41±0.18	1.45±0.16	<0.001
ARD/BSA	1.42±0.25	1.34±0.20	<0.001	1.40±0.19	1.29±0.15	<0.001
	Normal FPG	IFG	P value	Normal FPG	IFG	P value
ARD	2.13±0.32	2.15±0.31	0.006	2.36±0.26	2.38±0.30	0.027
ARD/height	1.37±0.21	1.39±0.21	<0.001	1.42±0.16	1.43±0.18	0.033
ARD/BSA	1.38±0.23	1.37±0.22	0.685	1.37±0.18	1.36±0.20	0.048
	Normal HDL	Low HDL-C	P value	Normal HDL	Low HDL-C	P value
ARD	2.13±0.32	2.15±0.31	0.071	2.36±0.29	2.39±0.26	0.022
ARD/height	1.38±0.21	1.38±0.21	0.447	1.42±0.18	1.43±0.16	0.258
ARD/BSA	1.39±0.23	1.35±0.21	<0.001	1.38±0.19	1.33±0.17	<0.001
	Normal TG	Hypertriglycerides	P value	Normal TG	Hypertriglycerides	P value
ARD	2.12±0.29	2.18±0.37	<0.001	2.35±0.30	2.40±0.25	<0.001
ARD/height	1.37±0.19	1.40±0.25	<0.001	1.42±0.18	1.44±0.15	0.001
ARD/BSA	1.38±0.21	1.36±0.26	0.030	1.38±0.20	1.33±0.16	<0.001
	Normal TC	High TC	P value	Normal TC	High TC	P value
ARD	2.37±0.27	2.37±0.29	0.677	2.37±0.27	2.37±0.29	0.677
ARD/height	1.42±0.17	1.43±0.18	0.499	1.42±0.17	1.43±0.18	0.499
ARD/BSA	1.38±0.17	1.36±0.19	0.010	1.38±0.19	1.36±0.19	0.010
	Normal LDL	High LDL-C	P value	Normal LDL	High LDL-C	P value
ARD	2.13±0.29	2.16±0.36	0.005	2.36±0.26	2.38±0.32	0.008
ARD/height	1.37±0.19	1.40±0.24	<0.001	1.42±0.16	1.44±0.19	0.003
ARD/BSA	1.37±0.21	1.38±0.25	0.612	1.37±0.18	1.35±0.20	<0.001

Data are shown as means±SD.

ARD, aortic root diameter; BP, blood pressure; BSA, body surface area; HDL-C, high-density lipoprotein cholesterol; IFG, impaired fasting glucose; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol.

BSA. In addition, HDL-C, eGFR and LV mass significantly correlated with ARD/height in the general population. Furthermore, sex discrepancies existed in these associations, which are also shown in [table 4](#).

### Prognostic significance of baseline ARD

A total of 550 CVEs (non-fatal or fatal) were recorded (203 coronary heart diseases, 83 myocardial infarctions and 365 strokes). Out of the 550 events, 73 due to coronary heart diseases, 54 due to myocardial infarction and 120 due to strokes were fatal (44.9%). The first event for every participant was considered in the counting of total events.

The association between the ARD at the baseline evaluation and incidence of CVEs was investigated by comparing ARD values in subjects with and without incident CVEs;

by calculating the risk of CVEs related per 1-unit increase in ARD in both unadjusted and adjusted Cox models; and by assessing the risk of CVEs in subjects divided into four groups: LVH (-) and ARD (-) (reference group), LVH (+) and ARD (-), LVH (-) and ARD (+), and LVH (+) and ARD (+).

Women who had CVEs had greater ARD/BSA and ARD/height but not absolute ARD (ARD/BSA=1.41±0.18 cm/m<sup>2</sup>, ARD/height=1.41±0.15 cm/m) compared with their counterparts without CVEs (ARD/BSA=1.37±0.23 cm/m<sup>2</sup>, p=0.016; ARD/height=1.37±0.21 cm/m, p=0.009) during follow-up. Men who had CVEs had significantly higher ARD values (absolute ARD: 2.42±0.41 cm, ARD/BSA=1.41±0.28 cm/m<sup>2</sup>, ARD/height=1.48±0.25 cm/m) than those without CVEs (absolute ARD: 2.36±0.27 cm,

**Table 3** Correlation between ARD parameters and metabolic variables

	ARD (cm)				ARD/BSA (cm/m <sup>2</sup> )				ARD/height (cm/m)			
	Women		Men		Women		Men		Women		Men	
	r	P value	r	P value	r	P value	r	P value	r	P value	r	P value
Age (years)	0.136	<0.001	0.061	<0.001	0.280	<0.001	0.269	<0.001	0.244	<0.001	0.160	<0.001
BMI (kg/m <sup>2</sup> )	0.248	<0.001	0.201	<0.001	-0.365	<0.001	-0.387	<0.001	0.247	<0.001	0.190	<0.001
SBP (mm Hg)	0.150	<0.001	0.156	<0.001	0.044	0.002	0.057	<0.001	0.204	<0.001	0.184	<0.001
DBP (mm Hg)	0.120	<0.001	0.131	<0.001	-0.048	<0.001	-0.036	0.016	0.125	<0.001	0.117	<0.001
Heart rate (bpm)	-0.050	<0.001	-0.014	0.362	0.024	0.075	0.007	0.655	-0.016	0.234	-0.001	0.921
TC (mmol/L)	0.053	<0.001	-0.001	0.945	0.041	0.003	-0.050	0.001	0.100	<0.001	0.011	0.463
TG (mmol/L)	0.108	<0.001	0.091	<0.001	-0.050	<0.001	-0.155	<0.001	0.131	<0.001	0.067	<0.001
LDL-C (mmol/L)	0.047	0.001	0.028	0.063	-0.020	0.147	-0.096	<0.001	0.090	<0.001	0.038	0.012
HDL-C (mmol/L)	-0.071	<0.001	-0.041	0.006	0.101	<0.001	0.178	<0.001	-0.044	0.002	-0.007	0.633
FPG (mmol/L)	0.080	<0.001	0.046	0.002	-0.009	0.527	-0.037	0.012	0.096	<0.001	0.051	0.001
UA (mmol/L)	0.119	<0.001	0.050	0.001	-0.035	0.012	-0.153	<0.001	0.118	<0.001	0.005	0.716
eGFR (ml/min/1.73 m <sup>2</sup> )	-0.094	<0.001	-0.004	0.781	-0.146	<0.001	-0.046	0.002	-0.125	<0.001	-0.041	0.007
RWT	0.067	<0.001	0.036	0.014	0.105	<0.001	0.064	<0.001	0.124	<0.001	0.077	<0.001
LV mass (g)	0.291	<0.001	0.273	<0.001	-0.042	0.002	-0.017	0.251	0.256	<0.001	0.233	<0.001
LV mass/BSA (g/m <sup>2</sup> )	0.194	<0.001	0.189	<0.001	0.210	<0.001	0.219	<0.001	0.266	<0.001	0.250	<0.001
LV mass/height <sup>2.7</sup> (g/m <sup>2.7</sup> )	0.228	<0.001	0.239	<0.001	0.140	<0.001	0.151	<0.001	0.356	<0.001	0.318	<0.001

ARD, aortic root diameter; BMI, body mass index; BP, blood pressure; BSA, body surface area; DBP, diastolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LV, left ventricular; RWT, relative wall thickness; SBP, systolic blood pressure; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride; UA, uric acid.

**Table 4** Multivariate analysis between ARD parameters and different variables

	ARD (cm)			ARD/BSA (cm/m <sup>2</sup> )			ARD/height (cm/m)		
	Total	Women	Men	Total	Women	Men	Total	Women	Men
Gender	0.272			-0.058			0.063		
Age (years)	0.075	0.090	0.075	0.225	0.238	0.217	0.177	0.187	0.177
BMI (kg/m <sup>2</sup> )	0.103	0.122	0.098	-0.292	-0.272	-0.321	0.158	0.162	0.159
SBP (mm Hg)	-0.004	-0.025	0.029	0.035	0.015	0.060	0.025	0.005	0.056
DBP (mm Hg)	0.042	0.046	0.038	-0.010	0.000	-0.021	0.009	0.016	-0.001
Heart rate (bpm)	-0.041	-0.066	-0.011	0.003	-0.019	0.035	-0.016	-0.038	0.017
TC (mmol/L)	-0.063	-0.021	-0.135	-0.018	0.005	-0.060	-0.040	-0.005	-0.098
TG (mmol/L)	0.038	0.009	0.078	0.014	-0.005	0.034	0.025	0.001	0.055
LDL-C (mmol/L)	0.024	-0.007	0.074	-0.016	-0.032	0.008	0.003	-0.022	0.041
HDL-C (mmol/L)	0.037	0.016	0.067	0.050	0.031	0.073	0.046	0.023	0.076
FPG (mmol/L)	0.026	0.032	0.019	0.006	0.007	0.001	0.015	0.018	0.009
UA (mmol/L)	0.024	0.023	0.020	-0.001	0.010	-0.020	0.008	0.015	-0.007
eGFR (ml/min/1.73 m <sup>2</sup> )	0.018	0.005	0.049	0.053	0.043	0.075	0.042	0.031	0.069
RWT	-0.021	-0.009	-0.036	-0.005	0.002	-0.013	-0.011	-0.002	-0.022
LV mass (g)	0.142	0.108	0.181	0.066	0.038	0.090	0.100	0.065	0.131

RWT was defined by the ratio of posterior wall and interventricular septum thickness to LVIDd.

ARD, aortic root diameter; BP, blood pressure; BSA, body surface area; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LV, left ventricular; RWT, relative wall thickness; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride; UA, uric acid.

$p=0.001$ ;  $ARD/BSA=1.37\pm 0.18\text{ cm/m}^2$ ,  $p<0.001$ ;  $ARD/\text{height}=1.42\pm 0.17\text{ cm/m}$ ,  $p<0.001$ ).

Table 5 shows relative HRs for the risk of CVEs associated with per 1-unit increase in absolute ARD, ARD/BSA and ARD/height. After adjusting for age, previous cardiac diseases, antihypertensive treatment, current smoking and drinking, SBP, DBP, TC, FPG, eGFR, ARD/height (HR: 1.781, 95% CI: 1.160 to 2.736,  $p=0.008$ ) predicted an increased risk of CVEs among men but not among women.

Figure 1 reports the incidence rates of CVEs in subjects divided into four groups according to the status of LVH and AR dilatation. After full adjustment, men with AR

dilatation and without LVH were significantly higher than those without AR dilatation or LVH (reference group) (HR: 1.487, 95% CI: 1.000 to 2.212,  $p=0.050$ ). Furthermore, compared with the reference group, the adjusted risk of subjects with LVH and AR dilatation was even higher than those with isolated AR dilatation (HR: 1.950, 95% CI: 1.168 to 3.256,  $p=0.011$ ), while among women, LVH but not AR dilatation was associated with a higher incidence of CVEs. Figure 2 is the Kaplan-Meier cardiovascular disease survival curves for the four groups among men and women. Kaplan-Meier analysis showed that there were significant differences in the survival rates among these groups (log-rank testing,  $p<0.01$ ) in both women

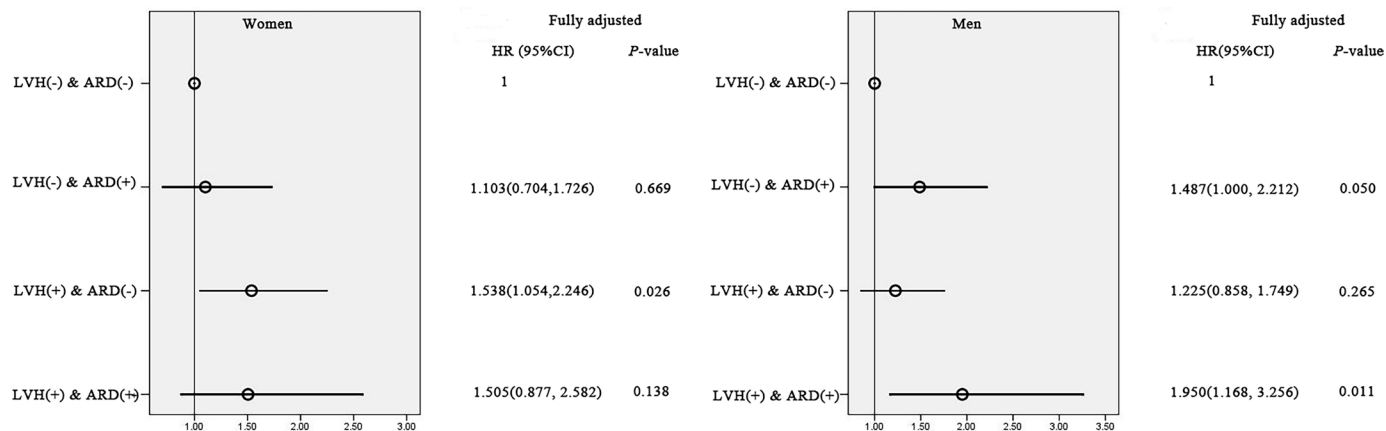
**Table 5** Relative hazard rates relating increments of one unit measurement of ARD parameters to the incidence of cardiovascular events

		Women			Men				
		HR	95% CI	P value	HR	95% CI	P value		
Model 1	ARD (cm)	1.237	0.935	1.637	0.137	1.575	1.228	2.019	<0.001
Model 2	ARD (cm)*	0.991	0.950	1.033	0.991	1.330	0.966	1.832	0.081
Model 1	ARD/BSA (cm/m <sup>2</sup> )	1.558	1.099	2.209	0.013	2.202	1.549	3.128	<0.001
Model 2	ARD/BSA (cm/m <sup>2</sup> )	1.066	0.538	2.106	0.824	1.502	0.966	2.336	0.071
Model 1	ARD/height (cm/m)	1.597	1.124	2.270	0.009	2.603	1.876	3.612	<0.001
Model 2	ARD/height (cm/m)	0.980	0.454	2.113	0.980	1.781	1.160	2.736	0.008

Model 1: unadjusted; Model 2: adjusted for age, previous cardiac diseases, antihypertensive treatment, current smoking and drinking, systolic blood pressure, diastolic blood pressure, total cholesterol, fasting plasma glucose and estimated glomerular filtration rate.

\*Additionally adjusted for BMI in the Model 2.

ARD, aortic root diameter; BMI, body mass index; BSA, body surface area.



**Figure 1** Adjusted for age, previous cardiac diseases, antihypertensive treatment, current smoking and drinking, systolic blood pressure, diastolic blood pressure, total cholesterol, fasting plasma glucose and estimated glomerular filtration rate relative HR and 95% CIs of fatal and non-fatal cardiovascular events in participants divided into four groups according to the presence/absence of LVH and ARD. Participants without LVH and ARD represent the reference group. ARD, aortic root dilation; LVH, left ventricular hypertrophy.

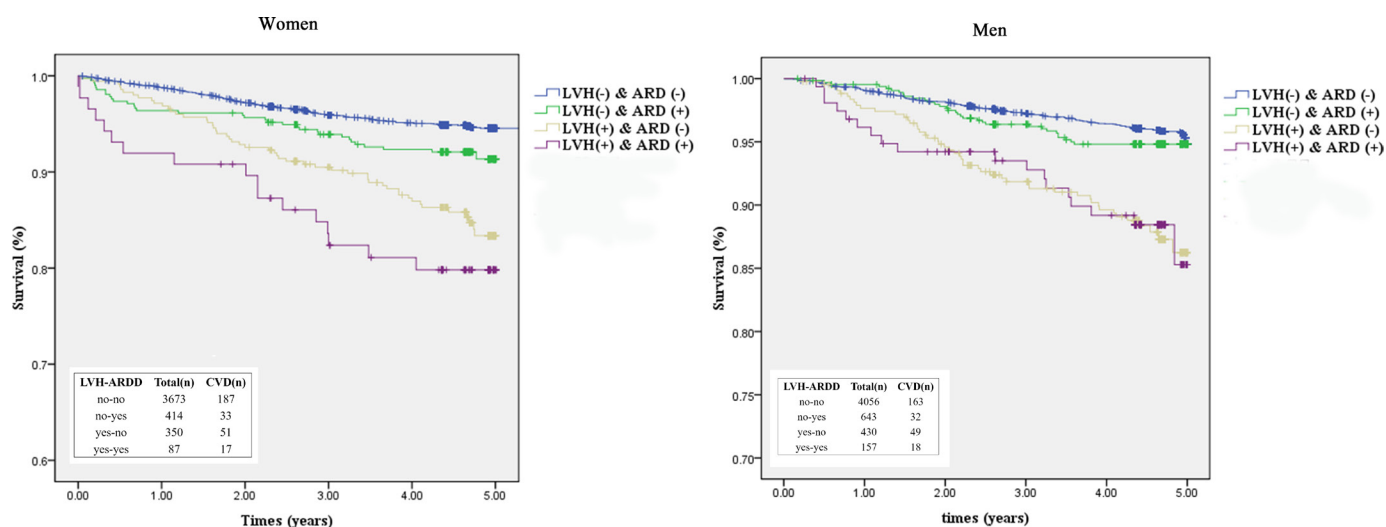
and men. Among women, log-rank testing showed that the survival rate was significantly lower in the LVH (+) and ARD (-) group ( $p < 0.01$ ) and LVH (+) and ARD (+) group ( $p < 0.01$ ) compared with the LVH (-) and ARD (-) group. There were no significant differences between the LVH (-) and ARD (+) and LVH (-) and ARD (-) groups ( $p = 0.278$ ). For men, when compared with the LVH (-) and ARD (-) group, the other three groups all showed a significant decrease survival rates (all  $p < 0.05$ ).

## DISCUSSION

The present study enrolled a large sample from the general population of rural China and for the first time, reported the existence of sex discrepancies with regard to the predictive effect of ARD and its indexes of the incidence of cardiovascular diseases. It showed that ARD/height (but not ARD and ARD/BSA) was associated with the incidence of non-fatal and fatal CVEs among

rural Chinese men only. After adjusting for possible confounders, ARD indexed to height was a significant predictor of incident CVEs. It is worth noting that AR dilation (but not LVH) was significantly correlated with CVEs among rural Chinese men, whereas LVH was associated with a higher rate of CVEs among women. However, the combination of LVH and AR dilation was a stronger predictor of cardiovascular outcomes than that entailed by LVH or AR dilation alone among men.

The evaluation of aortic diameters has great effect on the clinical estimation and management of diseases of the aorta.<sup>1</sup> However, until recently, there was still a lack of normal range of aortic diameters in the general population due to the different measurement sites, race and composition of analysed studies.<sup>1-30</sup> Vríz *et al* conducted a study aiming to figure out the average value of ARD in a wide age range of healthy subjects.<sup>31</sup> It reported that men had a significantly higher value of ARD compared



**Figure 2** Cardiovascular disease survival curves in the four groups according to the presence/absence of LVH and ARD. ARD, aortic root dilation; LVH, left ventricular hypertrophy.



with women in all age groups, and as age increased, the average value of ARD increased in both men and women.<sup>31</sup> In addition, it concluded that blood pressure had a close relationship with ARD. In our study, except for blood pressure, we evaluated many other metabolic disorders aiming to figure out the possible association between them. Data from our study revealed that ARD was relatively higher in abnormal metabolic disorders, except in high TC among both sexes and low HDL-C among women. It suggested the possibility that, in addition to hypertension, other metabolic disorders might play a role in altering ARD. We further explored the possible relationship between ARD, ARD indexes and other metabolic parameters, such as blood pressure, lipids, glucose, UA and kidney function. We figured out that ARD was associated with all the parameters studied among women but not TC, LDL-C and kidney function among men.

Cumulative evidence indicated the importance of ARD on cardiovascular diseases. Recently, Katchunga reported the prevalence of AR dilatation was 3.5% among Congolese and confirmed that ARD had a close relationship with LV mass, LV diastolic diameter and E/A ratio.<sup>32</sup> Similarly, Anders Sahlén claimed that larger AR size was an independent determinant of lower global afterload and larger stroke volume.<sup>33</sup> One review enrolled a total of eight studies including 10 791 patients with hypertension and concluded that aortic dilatation was a common phenotype in patients with hypertension (total: 9.1%; 12.7% for men; 4.5% for women), with men exhibiting a markedly higher susceptibility.<sup>34</sup> However, in our study, the rate of aortic dilatation was higher in women compared with men. It might be due to the difference in the selection of participants. In our study, we enrolled the general population rather than patients with hypertension. There were also many previous studies that have confirmed the predictive effect of ARD on CVEs. In the Cardiovascular Health Study, which enrolled 3993 elderly without cardiovascular diseases at baseline, the ARD at baseline had a significant relationship with a higher incidence of stroke and cardiovascular mortality over one decade of follow-up.<sup>35</sup> Likewise, in our study, we found that ARD/height was an effective predictor of the onset of CVEs. Most of the previous studies which intended to estimate the possible predictive effect of ARD on CVEs or CV mortality enrolled only elderly or middle-aged general population. As for our study, our contribution extends to an aged  $\geq 35$  years general population sample. Previous studies held the conclusion that echocardiographic assessment of ARD may contribute to stratify the risk of CVEs in elderly or middle-aged participants who suffered from greater likelihood of aortic dilatation due to age-dependent underlying structural changes in the aortic wall. Nevertheless, our study added a new prospect that echocardiographic assessment of ARD can be used to assess the stratification of CVEs in younger healthy individuals from the general population equally. Besides, a novel contribution of the present study is that ARD/height but not absolute ARD and ARD/BSA was

effective predictor of CVEs among male but not female. This gender discrepancy of ARD predicting CVEs was not mentioned previously. This emphasises that ARD index to height was a significant predictor of CVEs among rural male residents. Hence, a relatively more frequent follow-up should be recommended by physician once rural male residents were diagnosed with ARD. As we evaluate the cardiovascular risk factors, increased ARD index to height should be considered as well. However, this gender discrepancy was also coincident with the previous study, which enrolled subjects with hypertension, claiming that men had a markedly higher susceptibility.<sup>34</sup> Why ARD was predictive of CVEs in men but not in women is not known. There were some possible factors that might be relevant about this phenomenon. First, as previously reported, aortic remodelling increases with increasing age and aged-associated advancement of ARD is well-established in epidemiological studies.<sup>36–38</sup> As shown in our study, the mean age in men was significantly higher than that of women, resulting in relatively higher value of ARD in men. Second, many previous studies have found that men had a significantly larger ARD compared with women, regardless of age, race or which body size adjustment was used.<sup>35,39</sup> The larger value of ARD in men might result in a more significant relationship between ARD value and CVEs while estimating. Third, the Cardiovascular Health Study also reported that the highest quintile of ARD was found to be a significant but modest predictor of congestive heart failure with LV systolic dysfunction in men (overall HR 1.47) but not in women. They considered that this might be due to the relatively higher prevalence of CHF with LV systolic dysfunction among men. Similarly, in our study, ARD being able to predict CVEs among men but not among women might be associated with the relatively lower risk for cardiovascular diseases among women in general.<sup>40</sup> Therefore, it suggested that more emphasis should be put on rural Chinese men who have a relatively higher value of ARD or aortic dilation.

Except for aortic dilation, there are many cardiac ultrasound indexes related to cardiovascular diseases, such as LVMI (left ventricular mass index), which is used to estimate LVH. It is very clear that both greater LVMI and LV concentric or eccentric hypertrophy are associated with higher mortality and adverse cardiovascular disease outcome.<sup>41,42</sup> Many previous studies found out an independent association of increased LV mass with aortic dilatation in different clinical settings, like patients with hypertension, patients with acute thoracic dissection and elderly individuals.<sup>17,35,43</sup> The Framingham Heart Study reported that as a continuous variable, the predictive value of ARD lost its statistical significance as LV mass index was adjusted in the multivariable model. However, if subjects were subdivided into four groups according to the presence/absence of LVH or AR dilatation, the fully adjusted risk of CVEs was markedly greater in those combination of LVH and aortic dilatation compared with their counterparts with LVH alone. In order to further confirm this association among rural Chinese, we further



ran this analysis and added a new piece of information over previous evidence by revealing that the overall risk is significantly increased when residents have both LV structure alterations together with aortic dilatation as compared with isolated alterations of LV structure. In addition, our study first time announced that the combination predictive effect of LVH and aortic dilatation on CVEs was only significant among men but not women rural residents. More emphasis should be put on men who have both LVH and aortic dilatation since they had significantly higher risk factors to get CVEs.

There have already been many studies intended to estimate the relationship between ARD, cardiovascular diseases and risk factors. The results from the Framingham Heart Study claimed that, after adjustment for clinical risk factors, a greater ARD at baseline, as well as an increase in ARD over 8 years, was correlated with the risk of incident heart failure.<sup>41</sup> However, after adjustment for LVM, this association was no longer significant.<sup>41</sup> In addition, the Jackson Heart Study, which enrolled only blacks, reported that a greater ARD increased the risk of CVEs in a community-based cohort of blacks.<sup>44</sup> Similarly, in our study, we confirmed that ARD and its index was significantly associated with CVEs in men, whereas after adjustment of BMI, only ARD/height was still effective in predicting CVEs. The greater difference between our study and the Framingham Heart Study was that the previous study only estimated the incidence of heart failure. Both of the previous two studies did not underestimate this relationship according to sex. Furthermore, they only estimated the predictive effect of ARD but no other ARD-related indexes, which might also be effective parameters in predicting cardiovascular diseases and risk factors.

There are some limitations of the present study. First, due to the large sample, we did not measure ARD in multiple levels, such as the annulus, supra-aortic ridge and ascending aorta, which might have introduced bias. The observational design of the present study does not allow for conclusions about the cause of aortic dilatation. In addition, the association between ARD and metabolic disorders, such as dyslipidaemia, high fasting glucose and kidney function, was based on a single blood test that might have bias. Furthermore, a low incidence of cardiovascular events (<10% over a 4.66-year follow-up period) was observed among rural Northeast China which might explain the limited strength of correlation between ARD and CVEs.

## CONCLUSIONS

The present study enrolled a large study sample of general rural residents in China and for the first time, presented that sex discrepancies existed in the association between ARD, ARD indexes and future risk of CVEs. Among rural Chinese men, ARD plays an important role in predicting subclinical organ damage for better assessing prognosis and prevention strategies. In addition, the combination of

LVH and aortic dilatation in our study presented a stronger predictive effect on cardiovascular outcomes than aortic dilatation alone.

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