Aortic arch calcification and risk of all-cause mortality and cardiovascular disease: The Guangzhou Biobank Cohort Study

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Summary

Background There were no reports on the associations of aortic arch calcification (AAC) measured by chest X-ray with all-cause mortality and cardiovascular disease (CVD) in older general population. Moreover, previous studies of hemodialysis patients showed that AAC was correlated with left ventricular hypertrophy (LVH) and predicted CVD jointly. Whether the effects remained in the general population is unknown. We examined the associations of AAC with all-cause mortality and CVD in general population and the risk associated with the coexistence of AAC and LVH.

Methods Presence and severity (grades 0-2) of AAC were measured by chest X-ray, and LVH was identified by 12-lead electrocardiogram in 27,166 Chinese aged 50+ years free of CVD from Guangzhou Biobank Cohort Study. Multivariate Cox regressions were used to examine associations of AAC and LVH with outcomes.

Findings During an average follow-up of 14.3 years, 5,350 deaths and 4,012 CVD occurred. Compared to those without AAC at baseline, those with AAC had higher risks of all-cause mortality (HR 1.24, 95% CI 1.17-1.31) and CVD (HR 1.22, 95% CI 1.14-1.30), with dose-response relationship (P ≤ 0.001). Furthermore, those with coexistence of AAC and LVH had higher risks of all-cause mortality (HR 1.72, 95% CI 1.37-2.15) and CVD (HR 1.80, 95% CI 1.40-2.32) than those without AAC and LVH.

Interpretation As chest X-ray has been performed commonly for health screening and in hospital patients when first admitted, AAC measured by chest X-ray can be further applied to assist cardiovascular risk stratification in the community and clinical settings.

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Introduction

Cardiovascular disease (CVD) is a major cause of disability and premature death in the world.1 The age-standardized CVD mortality has been declining in high-income countries over the past few decades, whereas declining trends are not clear in low- and middle-income countries (LMICs),2 highlighting the need of identifying neglected CVD risk factors especially in LMICs.

Vascular calcification is a common pathological manifestation of atherosclerosis, vascular damage and chronic kidney disease.3 Calcification in coronary
artery,4 abdominal aorta,5 thoracic aorta6–8 and multisite extra-coronary arteries9,10 has been associated with higher risks of death and CVD in the general population, but evidence on the association of aortic arch calcification (AAC) is limited.6,8,11 Most previous studies on AAC were conducted in patients with end-stage renal disease and they consistently showed a higher risk of CVD related to AAC.12–21 We found only one prospective population-based cohort study in the United States (US) on 116,309 participants with 28 years of follow-up.22 This study showed that AAC measured by chest radiograph at checkup in 1964–1973 was associated with a higher risk of nonfatal and fatal coronary heart disease (CHD) in both sexes and ischemic stroke in women.23 Our paper from the Guangzhou Biobank Cohort Study (GBCS) showed that the baseline prevalence of AAC in middle-aged to older Chinese appeared to be higher than that of similar age groups in the US study.24 However, whether the US results more than 20 years ago can be generalized to contemporary Asian and other populations is unclear.

Computed tomography (CT) is the gold standard for measuring vascular calcification. The Rotterdam Study showed that AAC volume measured by CT was associated with both cardiovascular and non-cardiovascular mortality, independent of cardiovascular risk factors and calcification elsewhere.25–27 However, the high cost and ionizing radiation have limited the use of CT in large epidemiologic studies. AAC grades on chest X-ray was positively associated with coronary artery calcification score determined by CT.28–30 However, whether the presence of AAC in chest X-ray predicts risks of all-cause mortality and CVD remains to be examined.

Moreover, in dialysis patients, vascular calcification was a predictor of left ventricular hypertrophy (LVH),31 and the latter was associated with higher risks of all-cause mortality and CVD.32–34 Whether the coexistence of AAC and LVH increases the risks of all-cause mortality and CVD remains to be examined. Therefore, we examined the associations of AAC measured by chest X-ray with all-cause mortality and CVD (nonfatal and fatal) in the general population using data from the GBCS. We also hypothesized that participants with coexistence of AAC and LVH had higher risks of all-cause mortality and CVD than those with only one of the two risk factors.

Methods

Study population
Details of GBCS and AAC studies have been reported previously.35–37 Briefly, GBCS is a 3-way collaboration among the Guangzhou Twelfth People’s Hospital and the Universities of Hong Kong and Birmingham. All participants were recruited from “The Guangzhou Health and Happiness Association for the Respectable Elders” (GHHARE), a community social and welfare organization. GHHARE included about 7% of Guangzhou residents aged 50 years or older, with branches in all districts of Guangzhou, the capital city of Guangdong Province in southern China. All information was collected by full-time trained nurses and technicians. Fasting blood samples were drawn using a vacutainer tube, and biochemical parameters were measured in the hospital laboratory. Face-to-face interviews were done using a computer-assisted standardized structured questionnaire. The Guangzhou Medical Ethics Committee of the Chinese Medical Association approved the study. All participants gave written informed consent before participation.

Exposure
Both presence and severity of AAC were assessed by plain chest X-ray examination using a Toshiba KSO-15R machine. The chest X-ray films were taken when the participants were in the standing posteroanterior position and with deep inspiration breath-hold. All chest X-ray films were reviewed independently by two experienced radiologists who were blinded to the participants’ identities and information on exposures and disease
history. As shown in our previous paper, the rate of agreement on diagnosis for the two radiologists was 85% and Kappa coefficient was 0.68 (P < 0.001), showing a moderate agreement.21 Details of the assessment of AAC in the GBCS have been described elsewhere.28 The length of calcification plaque was used to assess the severity of AAC. In participants with plaques at more than one location, the radiologists added the lengths of the differently located calcification plaques to get the total length. The severity of AAC was classified into 3 calcification grades (grade 0 indicated no AAC, grade 1 was defined as length of calcification plaque < 10.0 mm and grade 2 was defined as length of calcification plaque ≥ 10.0 mm).29

Outcomes
Outcomes included all-cause mortality and the development of nonfatal or fatal CVD. Causes of death and CVD were coded according to the 10th revisions of the International Classification of Diseases (ICD-10) by trained clinical coding officers in each hospital. CVD was defined as any hospital admission or death from ischemic heart disease (IHD) (ICD-10: I20-125), stroke (ICD-10: I60-169), peripheral artery disease (ICD-10: I73) and heart failure (ICD-10: I50). When a participant had multiple CVD events, the first event was designated as the incident event. Information on underlying causes of deaths up to April 2021 was mostly obtained via record linkage with the Death Registry Department of the Guangzhou Centre for Disease Control and Prevention (GZCDC). Incidence information on CVD up to December 2018 was collected from the hospitalization data of the Guangzhou Social Insurance Bureau and GZCDC. Vital status of all participants was ascertained from three separate sources. When the death certificates were not issued by medical institutions (and hence might have quality issue with the coding), the causes of death were verified by the GZCDC as part of their quality assurance programme by cross-checking past medical history and conducting verbal autopsy. Eleven verbal autopsy meetings were conducted in the Guangzhou Twelfth People’s Hospital to verify the deaths with uncertain causes. A physician panel including five chief physicians from various disciplines reviewed all available medical records of the same individuals and physicians from various disciplines reviewed all available medical records of the same individuals and assigned in a standard manner a cause of death, with assistance of an epidemiologist in the last meeting for unsettled cases.30-32 Details of the follow-up methods in GBCS have been reported elsewhere.33-35

Potential confounders
Potential confounders considered included baseline demographic characteristics, lifestyle factors (smoking and alcohol use), family and personal medical history, anthropometrics (weight and height), and clinical parameters (systolic and diastolic blood pressure (BP), fasting plasma glucose, lipids and inflammatory markers). Body mass index (BMI) was calculated as weight in kilogram divided by square of the height in meters (kg/m²). Physical activity was measured by a validated Chinese version of International Physical Activity Questionnaire (IPAQ) (validated by us34) and classified into inactive, moderately active and physically active. BPs were measured in the seated position in triplicate using a digital BP monitor. Hypertension was defined as systolic and/or diastolic BP ≥ 140/90mmHg, or being on treatment with medication for hypertension. Biochemical parameters including fasting plasma glucose, lipids (low- (LDL-), high-density lipoprotein (HDL-) cholesterol, triglycerides (TG)) and uric acid (UA) were measured using a biochemical auto-analyzer in the clinical laboratory of hospital. The estimated glomerular filtration rate (eGFR), lower values indicating poor kidney function, was calculated by the Chronic Kidney Disease Epidemiology Collaboration equation using serum cystatin C equations as we previously reported.35 All participants received blood test, but only 9,115 participants recruited in 2003-2004 (the first recruitment phase) measured eGFR and UA.

Effect modifiers
Sex, age, smoking status, diabetes and LVH were considered as effect modifiers. Diabetes was defined by fasting glucose ≥ 7.0 mmol/l, use of anti-diabetes medications, or self-reported physician-diagnosed diabetes. LVH was measured by electrocardiogram (ECG). Details of ECG measurement were reported in one of our previous studies.36 Briefly, ECG was performed in the supine position after resting for 5 min. The ECG recordings were evenly distributed to two qualified physicians in the Guangzhou Twelfth People’s Hospital, interpreted independently and blinded to other information. Any uncertainties in interpretation of ECG were resolved through discussion. LVH was defined as the ECG pattern meeting the Cornell voltage criteria [SV3 + RaVL > 28 mm for men, > 20 mm for women]37 or Sokolow−Lyon indices [SV1 + RV5 > 35 mm and RaVL > 11 mm].38

Statistical analysis
Chi-square tests or analysis of variance (ANOVA) were used to compare participants’ baseline characteristics by the presence of AAC. Possible confounding factors with a P-value less than 0.05 were adjusted in the multivariable regression models. The Cox proportional hazards regression was used to calculate crude and adjusted hazard ratios (HRs) as well as 95% confidence intervals (CIs). The Cox proportional assumption was checked by visual inspection of plots of log (−log S) against time using “stphplot” command in STATA, where S was the estimated survival function. Follow-up time for each participant was calculated from the date of baseline enrollment to the date of diagnosis of CVD, death, or
the end of the study on April 19, 2021, whichever came first. Cumulative survival curves were generated by the Kaplan-Meier method, and between-group survival was compared by the log-rank test. We conducted likelihood ratio tests for comparison the fitness of models with and without including interaction terms between AAC and some potential effect modifiers (sex, age, smoking status, diabetes and LVH). In sensitivity analyses, we excluded deaths within the first 3 years of follow-up to avoid reverse causation (where severe AAC at baseline was the result of poor health status, rather than the cause, of the underlying pathology). In addition, we also performed competing risk survival analyses for all-cause mortality and CVD. As the proportion of missing values was less than 3% for all included variables, we used complete-case analysis in the current study. All statistical analyses were done using STATA/MP 16.0 and all tests were two-sided with significance level of 0.05.

Role of the funding source
The Guangzhou Biobank Cohort Study was funded by the Natural Science Foundation of China (No. 81941019), the Major Infectious Disease Prevention and Control of the National Science and Technology Major Project (2018ZX10715004), the National Key R&D Program of China (2017YFC0907100), Natural Science Foundation of Guangdong (2018A030313140), the Guangzhou Science and Technology Bureau (201704030132), the University of Hong Kong Foundation for Educational Development and Research (SN/1f/HKUF-DC; C20400.28505200), the Health Medical Research Fund (HMRF/13143241) in Hong Kong and the University of Birmingham, UK. The funders had no role in study design, data collection, data analyses, interpretation, writing of the report.

Results
30,430 participants aged 50+ years were recruited at baseline from November 2003 to January 2008. Of them, 3,264 were excluded, and of them, 318 were lost to follow-up with unknown vital status, 237 had incomplete information on chest radiography, or 2,709 had a self-reported history of CVD (IHD, stroke, angina, myocardial infarction (MI), peripheral vascular disease, heart failure and congenital heart disease), giving 27,166 participants in the present analyses. During an average follow-up of 14.3 (standard deviation (SD)=3.1) years, 5,350 deaths occurred and 4,012 developed CVD.

Table 1 shows that at baseline, compared to participants without AAC, more those with AAC were men, older, had lower education and personal annual income, lower prevalence of other job, ever drinking and active physical activity, and higher prevalence of ever smoking, family history of CVD, and chronic diseases (hypertension, diabetes, LVH) (all P from < 0.001 to 0.04).

Moreover, those with AAC at baseline also had lower BMIs, higher levels of other vascular risk factors (waist circumference, systolic and diastolic blood pressure, LDL-cholesterol, fasting glucose and white blood cell count (WBC)), lower eGFR and higher UA (all P from < 0.001 to 0.02).

Table 2 shows that after adjusting for sex, age, education, occupation, personal annual income, physical activity, alcohol use, smoking status, diabetes, family history of CVD, BMI, hypertension, LDL-cholesterol and WBC, the presence of AAC was associated with higher risks of all-cause mortality (HR 1.24, 95% CI 1.17-1.31), CVD (1.22, 1.14-1.30), IHD (1.31, 1.17-1.46), MI (1.40, 1.19-1.65), IHD and ischemic stroke (1.20, 1.11-1.29), stroke (1.14, 1.04-1.24) and hemorrhagic stroke (1.35, 1.09-1.69). Using AAC grade as an indicator for AAC severity, participants with severe AAC (grade 2) had even higher risks of all-cause mortality, CVD, IHD, MI, IHD and ischemic stroke, stroke, and hemorrhagic stroke. Non-significant association of presence AAC with ischemic stroke was found (1.02, 0.98-1.06, P=0.35), although the HR for severe AAC was marginally significant (1.05, 1.00-1.10, P=0.04).

Table 2 also shows that in 9,115 participants, further adjustment for eGFR and UA did not substantially change the associations of AAC with all-cause mortality, CVD, IHD, MI, IHD and ischemic stroke. However, the associations of AAC with stroke (including hemorrhagic and ischemic stroke) were attenuated to become non-significant after adjustment for eGFR and UA. In sensitivity analyses we found similar results, suggesting that the potential issue of reverse causation (Table 2) and competing risk between all-cause mortality and CVD (Supplementary Table 1) were less likely reasons for the observed associations.

Kaplan-Meier analyses show significant dose-response associations of AAC severity with higher risks of all-cause mortality, CVD, IHD and stroke (all P < 0.001) (Figure 1). We found no evidence that the associations varied by sex, age (<62/≥62 years), smoking status (never/ever) or diabetes (yes/no) (all P values for interactions ≥ 0.10) (Supplementary Table 2). As significant interactions between AAC and LVH on IHD and ischemic stroke (P for interaction =0.03), ischemic stroke (P for interaction =0.01) were found (Supplementary Table 2), analyses were further broken down by AAC and LVH. Table 3 shows that compared to those without AAC and LVH, participants with only LVH were not associated with all-cause mortality, CVD and specific events (all P values > 0.05), whereas those with AAC only had significantly higher risks, and those with the coexistence of AAC and LVH had the highest risks. The HR (95% CI) in those with the coexistence of AAC and LVH was 1.72 (1.37-2.15) for all-cause mortality, 1.80 (1.40-2.32) for CVD, 1.89 (1.27-2.81) for IHD, 1.76 (1.32-2.35) for IHD and ischemic stroke, 1.76 (1.29-2.40) for stroke, 3.33 (1.82-6.07) for hemorrhagic stroke and
both AAC and LVH had the highest risks of all-cause mortality, CVD, IHD and stroke (Figure 2).

Table 1: Baseline characteristics by the presence of aortic arch calcification (AAC) of 27,166 participants in Guangzhou Biobank Cohort Study recruited from 2003 to 2008.

| Variables                                      | Presence of AAC | P-value |
|------------------------------------------------|-----------------|---------|
| Number of participants (%)                    | 18,001 (66.26)  | 9,165 (33.74) | -       |
| Sex, % men                                     | 27.24           | 28.94   | 0.003   |
| Age, years                                     | 59.93 ± 6.46    | 65.45 ± 6.82 | < 0.001 |
| Education, %                                   | 8.66            | 4.86    | < 0.001 |
| Primary or below                               | 38.87           | 51.16   |
| Middle school                                  | 52.47           | 40.37   |
| College or above                               |                |         |
| Occupation, %                                   |                | < 0.001 |
| Manual                                         | 61.68           | 61.82   |
| Non-manual                                     | 22.57           | 24.33   |
| Other                                          | 15.75           | 13.85   |
| Personal annual income, % RMB/year             |                | < 0.001 |
| <10,000                                        | 32.68           | 35.64   |
| 10,000-14,999                                  | 42.75           | 42.73   |
| ≥15,000                                        | 19.30           | 16.97   |
| Not reported                                   | 5.27            | 4.67    |
| Smoking, %                                     |                | < 0.001 |
| Never                                          | 82.32           | 77.61   |
| Former                                         | 8.01            | 10.90   |
| Current                                        | 9.67            | 11.48   |
| Alcohol use, %                                  |                | 0.04    |
| Never                                          | 71.61           | 73.10   |
| Former                                         | 3.49            | 3.35    |
| Current                                        | 24.90           | 25.55   |
| Physical activity, %                           |                | < 0.001 |
| Inactive                                       | 8.81            | 7.44    |
| Moderate                                       | 39.90           | 42.66   |
| Active                                         | 51.29           | 49.90   |
| Family history of CVD, % yes                   | 7.97            | 9.21    | < 0.001 |
| Hypertension, %                                | 26.93           | 38.21   | < 0.001 |
| Diabetes, %                                    | 10.76           | 15.10   | < 0.001 |
| Left ventricular hypertrophy, % yes            | 1.58            | 2.49    | < 0.001 |
| Body mass index, kg/m²                         | 23.76 ± 3.26    | 23.63 ± 3.40 | 0.001   |
| Waist circumference, cm                        | 78.3 ± 9.0      | 79.2 ± 9.0 | < 0.001 |
| Systolic blood pressure, mmHg                  | 127.7 ± 21.4    | 134.5 ± 22.7 | < 0.001 |
| Diastolic blood pressure, mmHg                 | 73.3 ± 11.2     | 73.9 ± 11.3 | < 0.001 |
| Fasting glucose, mmol/l                        | 5.68 ± 1.64     | 5.84 ± 1.71 | < 0.001 |
| LDL-cholesterol, mmol/l                        | 3.26 ± 0.70     | 3.28 ± 0.71 | 0.02    |
| HDL-cholesterol, mmol/l                        | 1.66 ± 0.41     | 1.66 ± 0.41 | 0.13    |
| Triglycerides, mmol/l                          | 1.36 (0.99-1.94)| 1.38 (0.99-1.98)| 0.14    |
| White blood cell count, × 10⁹/l                | 6.10 (5.20-7.20)| 6.20 (5.30-7.30) | < 0.001 |
| eGFR, ml/min per 1.73 m²                       | 74.88 (64.81-85.97)| 71.84 (61.74-83.31) | < 0.001 |
| Uric acid, μmol/l                              | 332.5 (282.0-392.0)| 340.0 (289.0-402.0) | < 0.001 |

AAC: aortic arch calcification; CVD: cardiovascular disease; LDL: low-density lipoprotein; HDL: high-density lipoprotein; eGFR: estimated glomerular filtration rate.

Discussion
This is the first study showing a significant dose-response association of AAC measured by chest X-ray response association of AAC measured by chest X-ray...
### Table 2: Rates and adjusted HRs (95% CIs) of all-cause mortality, cardiovascular disease and specific events for presence and severity of aortic arch calcification (AAC) in Guangzhou Biobank Cohort Study from 2003 to 2008 and followed up until April 2021.

1 Participants recruited from 2003 to 2008 and followed up until April 2021. HRs were adjusted for sex, age, education, occupation, personal annual income, physical activity, alcohol use, smoking status, diabetes, family history of cardiovascular disease, body mass index, hypertension, low-density lipoprotein cholesterol and white blood cell count.

2 Participants recruited from 2003 to 2004 and followed up until April 2021. HRs were additionally adjusted for eGFR and UA.

3 Crude HRs (95% CI) are presented in Supplementary Table 3. Grade 0: without AAC; Grade 1: length of AAC < 10 mm; Grade 2: length of AAC ≥ 10 mm. HR, hazard ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate; UA, uric acid; IHD, ischemic heart disease.

| Grade | All-cause mortality | Cardiovascular disease | IHD | Myocardial infarction | IHD + ischemic stroke | Stroke | Hemorrhagic stroke | Ischemic stroke |
|-------|---------------------|------------------------|-----|-----------------------|-----------------------|--------|-------------------|---------------|
| 0     | 2,674 (10.25)       | 2,110 (8.37)           | 757 | 319                   | 1,715 (6.77)          | 1,403  | 182 (0.70)        | 1,008 (3.87) |
| 1     | 962 (17.46)         | 698 (13.29)            | 275 | 121                   | 548 (10.36)           | 434 (8.13)| 69 (1.26)         | 288 (5.24)   |
| 2     | 1,714 (23.78)       | 1,204 (17.65)          | 507 | 223                   | 942 (13.66)           | 747 (10.76)| 125 (1.74)        | 479 (6.77)   |
|       |                     |                        |     |                       |                       |        |                   |               |
|       |                     |                        |     |                       |                       |        |                   |               |
|       |                     |                        |     |                       |                       |        |                   |               |
|       |                     |                        |     |                       |                       |        |                   |               |

| Presence of AAC |
|-----------------|
| HR (95% CI)     |
| Grade 1+2       |

| Number of deaths/events (Rate, per 1,000 person-years) | Severity of AAC | Presence of AAC |
|-------------------------------------------------------|-----------------|-----------------|
| Grade 0 | Grade 1 | Grade 2 | Grade 1 | Grade 2 | P for trend | Grade 1+2 |
|----------|---------|---------|---------|---------|-------------|-----------|
| 1.41 (0.96-1.62)** | 1.70 (1.22-2.39)*** | <0.001 | 1.24 (1.17-1.31)*** |
| 1.16 (0.96-1.26)*** | 1.26 (1.17-1.36)*** | <0.001 | 1.22 (1.14-1.30)*** |
| 1.21 (1.05-1.40)** | 1.38 (1.22-1.55)** | <0.001 | 1.31 (1.17-1.46)** |
| 1.28 (1.03-1.56)** | 1.49 (1.24-1.80)** | <0.001 | 1.40 (1.19-1.65)** |
| 1.14 (1.03-1.25)** | 1.24 (1.14-1.35)** | <0.001 | 1.20 (1.11-1.29)** |
| 1.08 (0.96-1.12) | 1.18 (1.07-1.30)** | <0.001 | 1.14 (1.04-1.24)** |
| 1.25 (0.94-1.67) | 1.43 (1.12-1.84)** | <0.001 | 1.35 (1.09-1.69)** |
| 0.98 (0.93-1.10) | 1.05 (0.90-1.18)* | <0.06 | 0.92 (0.98-1.06) |

Adjusted for eGFR and UA (N=9,115)

| Study from 2003 to 2008 and followed up until April 2021. |
Figure 1. Kaplan-Meier analyses for associations of AAC grade (0-2) with all-cause mortality, CVD, IHD and stroke.

Note: grade 0: without AAC; grade 1: length of AAC < 10.0 mm; grade 2: length of AAC ≥ 10.0 mm.

AAC, aortic arch calcification; CVD, cardiovascular disease; IHD, ischemic heart disease.
## Articles

### Guangzhou Biobank Cohort Study from 2003 to 2008 and followed up until April 2021.

HRs were adjusted for sex, age, education, occupation, personal annual income, physical activity, alcohol use, smoking status, diabetes, family history of cardiovascular disease, body mass index, hypertension, low-density lipoprotein cholesterol and white blood cell count.

### Table 3

Rates and adjusted HRs (95% CIs) of all-cause mortality, cardiovascular disease and specific events for AAC and LVH in Guangzhou Biobank Cohort Study from 2003 to 2008 and followed up until April 2021.

Without LVH & AAC

| Event                        | Crude model | Adjusted model |
|------------------------------|-------------|----------------|
| Without LVH & AAC           | 2,013 (8.29)| 1.00           | 1.00           |
| LVH only                     | 41 (11.55)  | 1.43 (1.05-1.95)* | 1.04 (0.76-1.43)|
| AAC only                     | 738 (6.22)  | 2.16 (1.95-2.39)*** | 1.31 (1.17-1.46)***|
| Both LVH and AAC             | 26 (9.83)   | 3.58 (2.42-5.30)*** | 1.89 (1.27-2.81)***|

**P for trend**

| Event                        | Crude model | Adjusted model |
|------------------------------|-------------|----------------|
| Without LVH & AAC           | 1,340 (5.46)| 1.00           | 1.00           |
| LVH only                     | 28 (7.85)   | 1.19 (0.82-1.73) | 0.87 (0.59-1.28) |
| AAC only                     | 325 (2.70)  | 2.28 (1.95-2.67)*** | 1.37 (1.15-1.62)***|
| Both LVH and AAC             | 10 (3.71)   | 3.33 (1.77-6.26)*** | 1.61 (0.85-3.05)***|

**P for trend**

| Event                        | Crude model | Adjusted model |
|------------------------------|-------------|----------------|
| Without LVH & AAC           | 1,646 (6.74)| 1.00           | 1.00           |
| LVH only                     | 17 (4.71)   | 2.34 (1.24-4.39) | 1.38 (0.71-2.69) |
| AAC only                     | 1,101 (45.1)| 3.28 (1.95-5.44)*** | 1.86 (1.09-3.18)***|
| Both LVH and AAC             | 103 (19.12) | 3.06 (2.30-4.06)*** | 1.76 (1.32-2.35)***|

**P for trend**

Stroke

| Event                        | Crude model | Adjusted model |
|------------------------------|-------------|----------------|
| Without LVH & AAC           | 1,340 (5.46)| 1.00           | 1.00           |
| LVH only                     | 25 (6.92)   | 1.29 (0.87-1.91) | 0.96 (0.64-1.44) |
| AAC only                     | 1,119 (45.1)| 1.79 (1.45-2.26)*** | 1.12 (1.03-2.23)***|
| Both LVH and AAC             | 49 (19.12)  | 3.19 (2.34-4.33)*** | 1.76 (1.29-2.40)***|

**P for trend**

Hemorrhagic stroke

| Event                        | Crude model | Adjusted model |
|------------------------------|-------------|----------------|
| Without LVH & AAC           | 169 (6.67)  | 1.00           | 1.00           |
| LVH only                     | 8 (2.18)    | 3.26 (1.60-6.63)*** | 2.06 (0.96-4.42) |
| AAC only                     | 178 (4.81)  | 2.23 (1.60-2.75)*** | 1.33 (1.01-1.67)***|
| Both LVH and AAC             | 12 (4.47)   | 6.93 (3.86-12.45)*** | 3.33 (1.82-6.07)***|

**P for trend**

Ischemic stroke

| Event                        | Crude model | Adjusted model |
|------------------------------|-------------|----------------|
| Without LVH & AAC           | 973 (3.88)  | 1.00           | 1.00           |
| LVH only                     | 12 (3.27)   | 1.38 (0.78-2.45) | 1.01 (0.56-1.83) |
| AAC only                     | 723 (5.99)  | 1.41 (1.28-1.56)*** | 1.07 (0.96-1.18) |
| Both LVH and AAC             | 26 (9.70)   | 4.12 (2.79-6.08)*** | 2.76 (1.86-4.10)***|

**P for trend**

*HRs were adjusted for sex, age, education, occupation, personal annual income, physical activity, alcohol use, smoking status, diabetes, family history of cardiovascular disease, body mass index, hypertension, low-density lipoprotein cholesterol and white blood cell count.

HR, hazard ratio; CI, confidence interval; IHD: Ischemic heart disease; AAC: aortic arch calcification; LVH: left ventricular hypertrophy.

**P < 0.05; ***P < 0.01; ****P < 0.001.
Figure 2. Kaplan-Meier analyses for associations of the presence of AAC with all-cause mortality, CVD, IHD and stroke in participants with and without LVH.

CVD, cardiovascular disease; IHD, ischemic heart disease; AAC, aortic arch calcification; LVH, left ventricular hypertrophy.
with higher risks of all-cause mortality and CVD (nonfatal and fatal), and risk further increased with the coexistence of AAC and LVH than having either factor alone, after adjustment of multiple risk factors, and further adjustment of eGFR and UA.

Most previous studies on AAC were based on hemodialysis patients and consistently showed a higher risk of vascular events and mortality related to the presence of AAC. However, extrapolating the results to the general population may over- or underestimate the association. A meta-analysis of 8 studies showed that dialysis patients with AAC had a higher risk of all-cause mortality and 2.3-fold risk of cardiovascular mortality than those without AAC and most of the results in this meta-analysis were adjusted for diabetes. Vascular calcification could occur in the intima or in the media, secondary to metabolic diseases such as chronic kidney disease and diabetes, and these metabolic diseases may also lead to a higher risk of mortality. Results without adjusting for these factors may be biased by confounding. Regarding the association of AAC with CVD in the general population, we found only one US prospective paper in 2000 showing that both men and women with AAC in plain chest X-ray, versus without, had 2.2%–2.7% higher risks of CHD. However, the outcomes of this study did not include all-cause mortality and this study did not adjust for important confounding factors such as kidney function. In our study, the association of AAC with stroke attenuated slightly to non-significant after adjusting for eGFR and UA, suggesting the association could be partly explained by poor kidney function. The significant associations with all-cause mortality, CVD, IHD, MI, IHD and ischemic stroke remained after adjustment for multiple confounding factors, providing evidence that AAC is an independent risk factor for all-cause mortality and CVD.

In dialysis patients, more severe AAC, assessed by calcification plaque or AAC score, has been associated with higher risks of all-cause and cardiovascular mortality. The above meta-analysis on dialysis patients showed that the pooled HR for cardiovascular and all-cause mortality was 2.31 (95% CI 1.57–3.40) and 1.45 (95% CI 1.08–1.96), respectively, for grade 2/3 AAC. In our study, although the association of severity of AAC with all-cause mortality was comparable with this meta-analysis, our estimated CVD risk was lower. This discrepancy could be partly due to our enrollment of relatively healthy people, and/or adjustment of more factors, as the crude estimates were higher and comparable. It could also be due to under-diagnosis of AAC using chest X-ray, as some participants with very mild calcification plaque might not be diagnosed in chest X-ray and misclassified as normal. The results on severity showed a dose-response pattern, which suggests the association between AAC and all-cause mortality or CVD could be causal. Further investigations on risk or protective factors of development and progression of AAC are warranted.

LVH is a significant risk factor for cardiovascular morbidity and mortality, which is highly prevalent in hypertensive patients. Some previous studies showed that AAC and LVH were correlated and significantly predicted CVD independently and jointly in hemodialysis patients. We found a significant interaction between AAC and LVH. In patients without AAC, no association of LVH with the risks of all-cause mortality and CVD was found. Participants with the coexistence of AAC and LVH had up to 2.3 times higher risks of all-cause mortality and CVD than those without AAC or LVH after adjusting for hypertension, suggesting AAC might provide additional predictive value to the existing CVD risk profile. Patients with LVH are more vulnerable to adverse events associated with aortic stiffness secondary to vascular calcification. Furthermore, LVH may increase the risk of ischemic injuries on the heart, brain and peripheral arteries, and the adverse effect could be exacerbated when vascular calcification or related vascular dysfunction involved these organs. Thus, our results underline the need for more attention and timely intervention to patients with coexistence of AAC and LVH.

Our study had some limitations. First, GBCS participants were recruited from the GHHARE, which represented a relatively healthy group of older people in Guangzhou. Those who had severe AAC could have developed CVD and could not participate. Survivor bias could not be completely ruled out. In addition, some diseases, such as peripheral artery disease, do not merit admission on diagnosis. The non-admitted events might not be captured and the CVD incidence could be an underestimation. Therefore, the HRs could be conservative. Second, our participants may not accurately represent the general population because of an overrepresentation of women. However, within sex and age-group, the participants had fairly similar levels of chronic diseases to nationally representative samples of urban Chinese. In addition, we found no interaction between AAC and sex (Supplementary Table 2, P values from 0.11 to 0.85), and the results were also adjusted for sex to minimize its potential confounding effect. Thus, the unbalanced sex ratio might not be a major concern in this study. Third, the diagnosis of AAC was based on chest X-ray and LVH based on 12-lead ECG, which is less accurate than CT and echocardiography, respectively, and could lead to underestimation of the prevalence (i.e., the prevalence of LVH was relatively low in the current study). However, chest X-ray and 12-lead ECG are cheap and routinely used in health examinations in China and many other LMICs. The detection is convenient and non-invasive, and can be easily used in large epidemiological studies. Fourth, our sample size may be insufficient for examining some
specific outcomes such as hemorrhagic or ischemic stroke, or for subgroup analyses in those with LVH. Fifth, in our study, participants had lower BMI than those without AAC, which was consistent with the US study. A possible explanation is that the chest wall thickness increases with higher BMI, affecting the detection rate of the AAC assessed by chest X-ray. Finally, while we could not exclude residual confounding, we adjusted for most of the confounders (n = 14), including many confounders that were not adjusted in previous studies.

In conclusion, we have first shown that AAC measured by chest X-ray was an independent risk factor for all-cause mortality and CVD in the general population with dose-response relationship, and the risk further increased with coexistence of LVH. As chest X-ray radiography has been performed commonly for health screening and in hospital patients when first admitted in China and elsewhere, and using chest radiographs for AAC has no additional imaging and minimal additional reading overhead and is convenient, our findings suggest the further utility of the chest radiograph, when it is already done, to assist cardiovascular risk stratification in the community and clinical settings.

Declaration of interests
All authors declare no competing interests.

Contributors
WBT, WSB, CQJ, XYL, YLJ, THL, KKC and LX have substantial contributions to conception and design, acquisition of funding, data and interpretation of data; WBT and LX analyzed the data, WBT, LX and THL drafted the article, WBT, LX and THL revised it critically for important intellectual content, LX was responsible for the decision to submit the manuscript, and all authors contributed to final approval of the paper.

Data sharing statement
The datasets analyzed during the current study are not publicly available due to the protection of the privacy of participants, but are available from the corresponding author on reasonable request.

Supplementary materials
Supplementary material associated with this article can be found in the online version at doi:10.1016/j.lanwpc.2022.100460.

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