Traditional and Novel Risk Factors for Incident Aortic Stenosis in Community-Dwelling Older Adults

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Abstract

Objectives: Calcific aortic stenosis (AS) is the most common valvular disease in older adults, yet its risk factors remain insufficiently studied in this population. Such studies are necessary to enhance understanding of mechanisms, disease management, and therapeutics.

Methods: The Cardiovascular Health Study is a population-based investigation of older adults that completed adjudication of incident AS over long-term follow-up. We evaluated traditional

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cardiovascular risk factors or disease, as well as novel risk factors from lipid, inflammatory and mineral-metabolism pathways, in relation to incident moderate or severe AS (including AS procedures) and clinically significant AS (severe AS, including procedures).

Results: Of 5,390 participants (age 72.9±5.6 years, 57.6% female, 12.5% Black), 287 developed moderate or severe AS, and 175 clinically significant AS, during median follow-up of 13.1 years. After full adjustment, age (HR=1.66 per SD [95% CI=1.45,1.91]), male sex (HR=1.41 [1.06,1.87]), diabetes (HR=1.53 [1.10,2.13]), coronary heart disease (CHD, HR=1.36, [1.01,1.84]), lipoprotein-associated phospholipase-A_2 (LpPLA$_2$) activity (HR=1.21 [1.07,1.37]) and sCD14 (HR=1.16 [1.01,1.34]) were associated with incident moderate/severe AS, while Black race demonstrated an inverse association (HR=0.40 [0.24, 0.65]), and creatinine-based estimated glomerular filtration rate (eGFR$_{cr}$) showed a U-shaped relationship. Findings were similar for clinically significant AS, although CHD and sCD14 fell short of significance, but interleukin-(IL) 6 showed a positive association.

Conclusion: This comprehensive evaluation of risk factors for long-term incidence of AS identified associations for diabetes and prevalent CHD, LpPLA$_2$ activity, sCD14 and IL-6, and eGFR$_{cr}$. These factors may hold clues to biology, preventive efforts, and potential therapeutics for those at highest risk.

Introduction

Calcific aortic stenosis (AS) is the most common valvular condition requiring hospitalization.[1] Calcific aortic valve disease (CAVD) chiefly affects older adults, whose cumulative frequency of moderate or severe AS reaches 6.0–7.0%.[2] Once symptomatic, untreated AS has a high mortality.[1] The only effective treatment is aortic valve replacement, which carries substantial risks and costs.[1]

Development of preventive medical therapies for AS rests on characterizing its determinants and mechanisms. Clinical and population studies have identified various risk factors for CAVD, including hypertension, dysglycemia, obesity, and smoking, as well as circulating LDL cholesterol (LDLc), lipoprotein (Lp)(a), creatinine, and high-sensitivity C-reactive protein (hsCRP).[3–8] Among these, blood pressure, body mass index (BMI), LDLc and Lp(a) have a potentially causal role.[9–12] Clinical trials of LDL-lowering therapies have been null,[3] however. Furthermore, based on documented links between mineral metabolism and CAVD, randomized trials have tested osteoporosis therapies[13] for aortic valve calcification (AVC), but results have been disappointing.

Available epidemiological evidence of CAVD determinants has partly come from imaging studies of AVC, which have often been cross-sectional.[3] Large-scale longitudinal studies have examined incident AS, but these have relied on administrative data for outcomes and, in some cases, risk factors, which can lead to misclassification.[3,7,8,11] Epidemiologic investigations have identified risk factors mostly in middle-aged cohorts, but determinants of AS incidence in elders remain insufficiently studied.

We recently adjudicated clinically meaningful AS over long-term follow-up in the Cardiovascular Health Study (CHS).[2] Here, we undertook a broad-based investigation of

traditional and novel risk factors for incident AS in this older cohort in order to define their relevance late in life and inform strategies for potential intervention.

Methods

Population

CHS is a prospective cohort study of community-dwelling adults 65. Eligible participants were sampled from Medicare-eligibility lists at four U.S. sites.[14] An initial cohort of 5,201 participants was enrolled in 1989–90, followed by an additional cohort of 687 Black participants in 1992–93. Follow-up involved semi-annual contacts through in-person examinations and/or telephone interviews.[14] All research centers received institutional review board approval. All participants gave informed consent.

Traditional Risk Factors

Traditional determinants included CVD or its risk factors. For the first cohort, these variables were taken from the 1989–90 visit, at which echocardiography was performed. For the second cohort, which did not undergo echocardiography until 1994–95, risk factors from the latter exam were used or, when missing, from previous years. History, physical, and laboratory assessments were standardized.[14] Hypertension was defined by blood pressure 140 mmHg (systolic), 90 mmHg (diastolic) or antihypertensive therapy; diabetes by glucose 126 mg/dL (fasting), 200 mg/dL (non-fasting) or hypoglycemic treatment. Estimated glomerular filtration rate was calculated using creatinine ($eGFR_{cr}$) or cystatin C ($eGFR_{cys}$) equations.[15] Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as fasting glucose (mmol/L)×fasting insulin (mU/L)/22.5. Coronary heart disease (CHD), stroke or transient ischemic attack (TIA), heart failure (HF), and peripheral arterial disease (PAD) were ascertained using reported methods.[14]

Novel Risk Factors

Novel determinants comprised biochemical markers from lipid, inflammatory, and mineral pathways previously measured in CHS for evaluation of other outcomes. Fasting blood was stored at −70–80°C at a core laboratory. All biomarkers were measured from 1989–90 specimens for the first cohort and 1992–93 specimens for the second cohort, with a few exceptions. Lp(a) was only available for the first cohort, while fetuin-A and klotho were measured in 1992–93 specimens for both cohorts. Lp(a) and lipoprotein-associated phospholipase-A_2 ($LpPLA_2$) mass and activity were determined as previously reported.[16] HsCRP, interleukin (IL)-6, soluble cluster of differentiation (sCD)14, sCD163, fetuin-A and klotho were measured by ELISA, as described elsewhere.[16–19]

Echocardiography

Standardized echocardiograms were performed in 1989–90 (first cohort) and 1994–95 (first and second cohorts), with interpretations completed at core reading centers. Methods for AS grading in CHS echocardiograms are detailed in the Supplemental Methods.

Incident AS

Procedures for adjudication of incident AS are described in the Supplemental Methods.[2] The primary outcome for the current analysis was probable/definite moderate or severe AS. The secondary outcome was probable/definite "clinically significant AS," defined as severe AS or procedural intervention for AS. Secondary analyses were also performed for possible/probable/definite moderate or severe AS, and clinically significant AS.

Statistical Analysis

Cox models were used to evaluate the relationship of risk factors with AS outcomes. Because the focus was on association rather than prediction, we applied cause-specific survival methods appropriate for the high competing risk of death in CHS.[2] Testing of the proportionality assumption with Schoenfeld residuals revealed no violations. Model 1 included age, sex and race. Model 2 (main model) additionally included education, BMI, smoking, hypertension, diabetes, LDLc, HDLc, triglycerides, prevalent CHD, stroke/TIA, HF, PAD and $eGFR_{cr}$. Secondary analyses examined waist circumference instead of BMI, and HOMA-IR in those without diabetes. Among novel risk factors, we evaluated individual markers in Models 1 and 2 above. In Model 3, we assessed the impact of concurrent adjustment for each novel biomarker class in the main model. We evaluated the functional form of associations using penalized cubic splines. These were approximately linear for all risk factors except $eGFR_{cr}$, which showed a U-shaped association that was modeled with linear and quadratic terms.

In exploratory analyses, we evaluated $eGFR_{cys}$; additionally adjusted for statins, oral glucocorticoids, and warfarin; censored follow-up at 10 years; and assessed interactions with age, sex, and race.

All analyses used STATA 12. Two-tailed $p<0.05$ defined statistical significance for main analyses, and $p<0.01$ for interaction analyses.

Participant and Public Involvement

Participants were not involved in the design of CHS.

Results

Descriptive Summary

Selection of the two study samples is described in Figure 1, and their characteristics given in Table 1. For the 1989–90/1994–95 baseline, 287 participants experienced incident probable/definite moderate or severe AS (345 participants possible/probable/definite moderate or severe AS) during median follow-up of 13.1 (maximum 25.0) years. There were 175 participants with incident probable/definite clinically significant AS (including possible, 234) during this period. For the 1992–93/1994–95 baseline, the corresponding numbers of probable/definite moderate or severe AS and clinically significant AS were 235 (including possible, 282) and 146 (including possible, 193), respectively, over median follow-up of 11.6 (maximum 22.1) years.

Traditional Risk Factors and AS

After minimal adjustment, several traditional risk factors were associated with onset of probable/definite moderate or severe AS, including age, male sex, adiposity, hypertension, dysglycemia, triglycerides, CHD, and HF (all positively), as well as Black race, HDLc (both inversely) and $eGFR_{cr}$ (U-shaped) (Table 2). Upon full adjustment (Model 2), relationships were generally attenuated. A few factors remained significantly associated with increased risk of moderate or severe AS, namely, age, male sex, diabetes and CHD, while Black race remained significantly associated with decreased risk (Table 2). The U-shaped association of $eGFR_{cr}$ with moderate or severe AS was also statistically significant (p=0.01), with a risk nadir at ~65.2 ml/min/1.73 m^2 (Figure 2). Using the nadir as reference, the HR for 30 ml/min/1.73 m^2 was 1.73 (95% CI=1.00, 3.00); for 60 ml/min/1.73 m^2, 1.01 (0.97, 1.06); and for 90 ml/min/1.73 m^2, 1.31 (1.05, 1.64).

For the secondary outcome, probable/definite clinically significant AS, findings were broadly consistent, except that the fully adjusted association for CHD was no longer significant (Table 2).

In contrast to $eGFR_{cr}$, the relationship of $eGFR_{cys}$ with incident probable/definite moderate or severe AS showed no departure from linearity. $eGFR_{cys}$ was significantly associated with lower incidence of the primary outcome in the minimally adjusted model (HR=0.83 per SD [95% CI=0.72, 0.95], p=0.01). After full adjustment, however, the association became non-significant (HR=0.88 per SD [0.75, 1.02], p=0.09).

In exploratory analyses assessing possible/probable/definite AS outcomes (Table S1), similar associations were seen for the same traditional risk factors as for probable/definite AS outcomes. There was also a significant relationship between hypertension and possible/probable/definite moderate or severe AS.

Novel Risk Factors and AS

In the minimally adjusted models examining novel lipid and mineral biomarkers, only $LpPLA_2$ activity was associated with incident probable/definite moderate or severe AS (Table 3). This relationship persisted after main-model adjustment, as well as simultaneous adjustment for $LpPLA_2$ mass and Lp(a). For inflammatory markers, IL-6, sCD14 and sCD163 showed significant positive associations with the primary outcome with minimal adjustment. These associations persisted for sCD14 and marginally for IL-6 after full adjustment for traditional risk factors but ceased to be significant for both after concurrent adjustment (Table 3). For the secondary outcome, $LpPLA_2$ activity and IL-6 were significantly associated with probable/definite clinically significant AS, but sCD14 was not (Table 3).

In additional analyses, $LpPLA_2$ activity and sCD14, though not IL-6, remained significantly associated with possible/probable/definite moderate or severe AS, but a significant association was also seen for sCD163 (Table S2). In the case of possible/probable/definite clinically significant AS, only $LpPLA_2$ activity and IL-6 again showed significant associations (Table S2).

Exploratory Analyses

Additional adjustment for statins, glucocorticoids and warfarin did not alter the findings. Censoring follow-up at 10 years yielded <½ the number of AS events (primary outcome, n=115; secondary outcome, n=69), but mostly showed a similar pattern of associations for traditional risk factors (Table S3). Yet, for both the primary and secondary outcome, there was attenuation of the risk estimates for diabetes, which became non-significant, but significant associations were detected for BMI. For novel risk factors, associations were not significant, with the exception of sCD14 and moderate or severe AS (Table S4).

There was no significant effect modification of risk factor associations with probable/ definite moderate or severe AS by age, sex, or race.

Discussion

Main Results

This investigation of risk factors for advanced AS in elders yielded the following findings: (i) older age, male sex, diabetes and prevalent CHD were positively associated with incident moderate or severe, as well as clinically significant, AS, while eGFR$_{cr}$ showed a U-shaped association, and Black race an inverse relationship with these outcomes after adjustment for demographic and clinical covariates; and (ii) the circulating lipid marker LpPLA$_2$ activity, and the inflammatory markers IL-6 and sCD14, were each independently associated with higher incidence of one or both of these AS outcomes (Figure 3). Exploratory analyses that considered possible as well as probable and definite cases of AS showed consistent findings, although they also identified positive associations for hypertension and sCD163 with moderate or severe AS.

Previous Studies

Multiple studies have evaluated the relationship of traditional or emerging CVD risk factors with AVC and incident AS outcomes.[3–11] These investigations have permitted identification of clinical and biological determinants of CAVD and leveraged Mendelian randomization analyses for causal inference, including in a large, predominantly male, multi-ethnic population.[7,10–12] Such genetic analyses have supported causal roles not just for obesity and hypertension, but also for LDLc, Lp(a), IL-6 and polyunsaturated fatty acids, identifying these as potential targets for AS therapeutics.[7,10–12] Despite important contributions, however, longitudinal studies of AS outcomes[3,5–9,11,12] have been subject to limitations, namely, uniform reliance on administrative diagnostic codes for AS, and, of relevance to observational studies, lack of baseline echocardiography for exclusion of prevalent disease and frequently incomplete consideration of risk factors.

To our knowledge, this is the first study to undertake a wide-ranging evaluation of traditional and novel risk factors for clinically adjudicated AS in elders. As we previously documented, age and male sex demonstrated positive, and Black race inverse, associations with incident AS, findings that align with prior reports.[2] Among traditional risk factors, only diabetes, CHD (both positively) and eGFR$_{cr}$ (U-shaped relationship) exhibited significant associations after main-model adjustment.

That diabetes emerged as a prominent risk factor for advanced AS is consistent with results from some,[5,8] though not all,[4,6] prior longitudinal studies. We did not detect a corresponding association for HOMA-IR, in contrast with an earlier report linking metabolic syndrome and AVC incidence in a younger population.[20] Our findings suggest that among elders the contribution resides with more severe metabolic dysregulation and hyperglycemia. Moreover, censoring follow-up at 10 years rendered the diabetes association with AS weaker and non-significant, suggesting that the disorder's consequences take time to become manifest. Contrariwise, BMI surfaced as a significant risk factor within this shortened follow-up, and waist circumference nearly so. Adiposity has been consistently implicated as a causal risk factor for AS,[7,11,12] but the observed weakening of the relationship during long-term follow-up could signify parallel contributions of weight loss and related inflammation to CAVD late in life.[14]

The findings on $eGFR_{cr}$ illuminate an important feature of CAVD risk factor assessment particular to older populations. Prior work in a middle-aged population associated serum creatinine with a monotonically increased risk of incident AS.[7] We now document that this association in elders is U-shaped instead. The inverse relationship observed in the lower range of $eGFR_{cr}$ is likely a true reflection of increased AS risk with worsening kidney function and its attendant oxidative stress, inflammation and mineral dysregulation.[21] But the positive relationship at the higher $eGFR_{cr}$ range could well reflect lower creatinine production in the setting of sarcopenia and its adverse implications for aging-related outcomes.[22]

The observed association of prevalent CHD with moderate or severe AS accords with well-recognized commonalities in atherosclerosis and CAVD pathogenesis.[1] That hypertension, LDLc and smoking did not exhibit significant associations with the primary outcome runs counter to findings in younger populations.[3] For hypertension, this could relate to a weakening of associations with aging-related weight loss or onset of HF. In the case of LDLc, a diminished role in the propagation phase, as contrasted with the initiation phase of CAVD, could account for the null association, as might aging-associated weight loss and LDLc's negative acute phase reactant properties.[14] For smoking, health factors prompting cessation versus continuation late in life might explain the lack of association in this older population.

Novel Factors

Histopathologic studies have implicated lipoprotein infiltration, inflammatory cell accumulation, heightened oxidative stress and fibrotic calcification as central to CAVD,[1] findings that have been bolstered by Mendelian randomization analyses.[12] We investigated several circulating markers from relevant lipid, mineral, and inflammatory pathways, of which only $LpPLA_2$ activity exhibited consistent associations with AS outcomes, while sCD14 and IL-6 were significantly or near-significantly related to the primary outcome.

$LpPLA_2$ is elevated in plasma from patients with CAVD,[23] as well as AS histologic specimens.[24] The enzyme contributes to fibrocalcific remodeling and mineralization by generating lysophosphatidylcholine, a powerful promoter of inflammation and apoptosis of valve interstitial cells.[23] $LpPLA_2$ is primarily bound to circulating lipoproteins but also

synthesized by aortic valve macrophages, possibly in response to oxidized LDL.[24] The current findings extend earlier analyses linking LpPLA$_2$ activity, though not mass, with faster echocardiographic progression of stenosis in mild, but not advanced, AS.[25] Mendelian randomization analyses did not support a causal role for LpPLA$_2$ in CAVD, however, much as was seen in CVD,[23] making it unlikely that LpPLA$_2$ could be directly targeted for CAVD therapeutics. But the present results indicate that the molecule's role as marker and pathogenic contributor deserves further investigation.

Unlike LpPLA$_2$ activity, Lp(a) was not associated with AS incidence. There is strong evidence supporting a causal role for Lp(a) in CAVD through its oxidized phospholipid cargo.[12] Yet a recent study associated Lp(a) to incidence of AVC, but not progression, raising the possibility that Lp(a) is more relevant to initiation than propagation of CAVD.[26] The implications for therapeutics will await completion of clinical trials evaluating Lp(a) lowering. It is also possible that Lp(a) may be buffered by other protective factors for survival to older age. Hence, causal associations reported for Lp(a) – as for other factors like LDLc – based on lifelong genetic exposure[12] may not hold for circulating levels of these biomarkers late in life. Whether resulting from survival bias or biology, in the case of Lp(a), or aging-related weight loss and comorbidities, in the case of LDLc or IL-6, our findings underscore the importance of defining risk factor associations specifically in older populations.

While inflammation has been implicated in CAVD, precise mechanisms remain unclear.[1] The association documented here for sCD14 and advanced AS may shed new light on the pathobiology. sCD14, the soluble form of a membrane glycoprotein expressed by myeloid and other cells, has been implicated in chronic lipopolysaccharide endotoxemia due to reduced intestinal barrier function.[27] Lipopolysaccharide upregulates sCD14, leading to immune activation,[28] which may explain sCD14's association with cardiovascular events.[18] Prior work from our group has linked sCD14 to echocardiographic AVC,[16] and the current association with advanced AS bolsters its potential role in CAVD.

IL-6, which showed a significant association with clinically significant AS, has been causally implicated in CAVD.[12] IL-6 levels, which are associated with risk of CVD, are also upregulated in AS specimens, where they promote calcification.[29] By contrast, hsCRP showed no relationship here, indicating its status as a weaker marker for AS in this older population.

Although bone and mineral dysregulation can contribute to CAVD, this study did not uncover associations of two corresponding markers, fetuin-A and klotho, with incident AS. While previous population-level data on klotho and CAVD are lacking, similar results were shown for fetuin-A and AVC in CHS[16] and MESA.[30] No or limited availability of additional mineral markers, including phosphate and fibroblast growth factor 23,[30] precluded their evaluation here.

Limitations

This observational study cannot demonstrate causality. Mendelian randomization analyses could be undertaken in consortia with more AS events. Given that our case-capture

methods relied on review of hospitalization records over a long follow-up period, cases of asymptomatic severe AS or those without access to care may not have been detected in our cohort. Yet participants' Medicare eligibility combined with their high rates of hospitalization and the natural history of CAVD likely rendered those cases rare. Similarly, pre-hospital death, clinical misattribution of symptoms or incomplete information may have led to missed cases or misclassification. We evaluated a large number of biomarkers, but selection was limited by prior availability in CHS. Because of strong prior probabilities based on prior literature, we did not correct for multiple comparisons; the present findings will require independent replication.

Conclusions

In this older cohort, assessment of traditional risk factors revealed diabetes and prevalent CHD to be positively, and $eGFR_{cr}$ bimodally, associated with incident AS. Evaluation of novel risk factors linked $LpPLA_2$ activity, sCD14 and IL-6 with increased risk of AS, implicating potentially specific lipid and inflammatory pathways in CAVD later in life. These findings underscore differences in risk profiles for elders, and the need to study older cohorts for identifying proper biomarkers for this disease in those at greatest risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key messages

What is already known about this subject?

Clinical and population studies have identified various risk factors for calcific aortic stenosis, including hypertension, dysglycemia, obesity, and smoking, as well as LDL cholesterol, lipoprotein (a), creatinine, and high-sensitivity C-reactive protein. Among these, blood pressure, body mass index, LDL cholesterol and lipoprotein (a) have a potentially causal role.

What does this study add?

In older adults, assessment of traditional risk factors revealed diabetes and prevalent CHD to be positively, and eGFR$_{cr}$ bimodally, associated with incidence of adjudicated, clinically meaningful aortic stenosis over 25 years of follow-up. Concurrent evaluation of novel risk factors newly showed that circulating lipoprotein-associated phospholipase-A$_2$ activity, sCD14 and interleukin-6 were prospectively associated with an increased risk of aortic stenosis, implicating potentially specific lipid and inflammatory pathways in the development of CAVD later in life.

How might this impact on clinical practice?

These findings illustrate differences in risk profiles for CAVD in elders, highlighting the need for longitudinal study of older cohorts to properly identify circulating biomarkers and putative therapeutic targets for this disease in those at greatest risk.
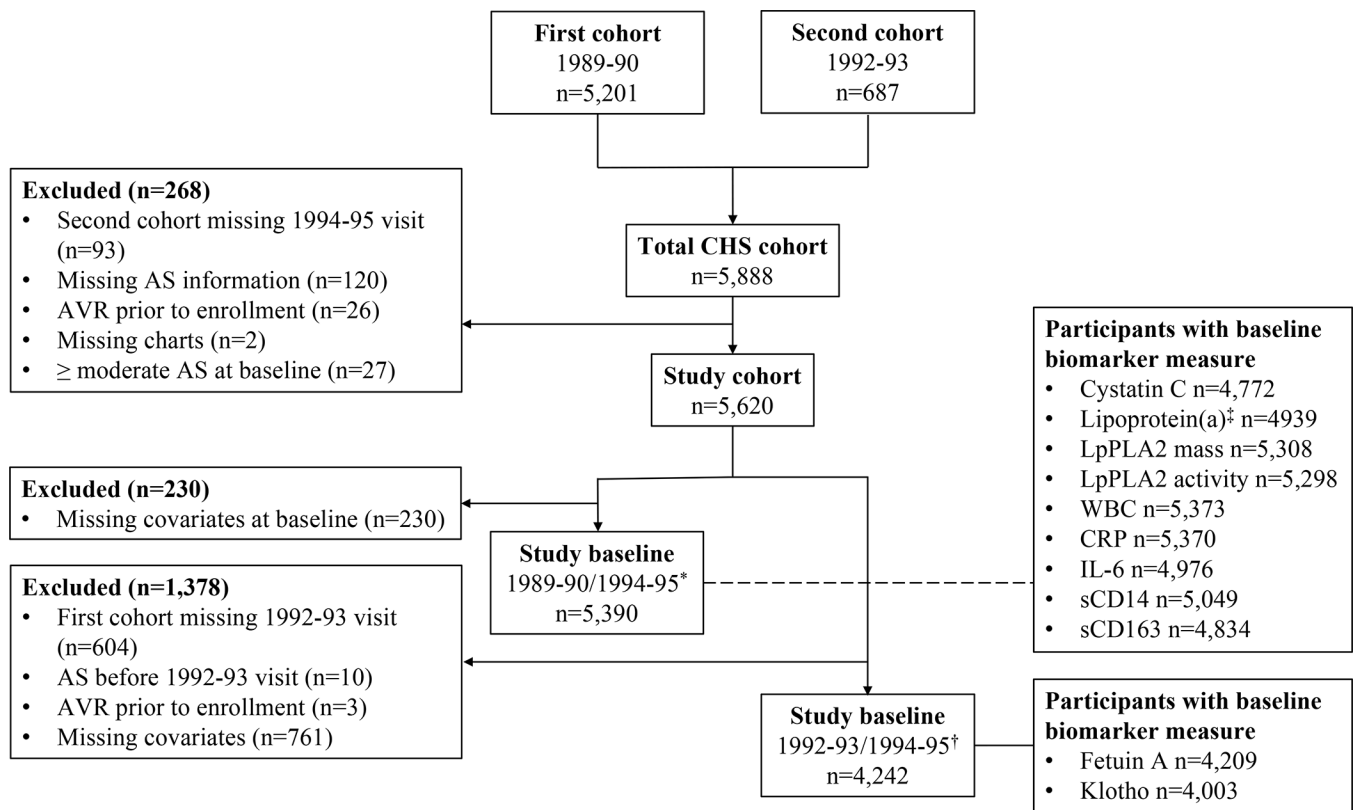
Figure 1.

Flow chart of the study.

* 1989–90 for the first cohort, 1994–95 for the second cohort.

† 1992–93 for the first cohort, 1994–95 for the second cohort.

‡ For the first cohort only.

Figure 2.
Penalized cubic spline plots of estimated glomerular filtration rate (eGFR) by creatinine and (A) incident probable/definite moderate/severe aortic stenosis, (B) probable/definite clinically significant aortic stenosis.

Figure 3.
Graphic figure summarizing the key findings of the study.

Table 1.

Baseline Characteristics

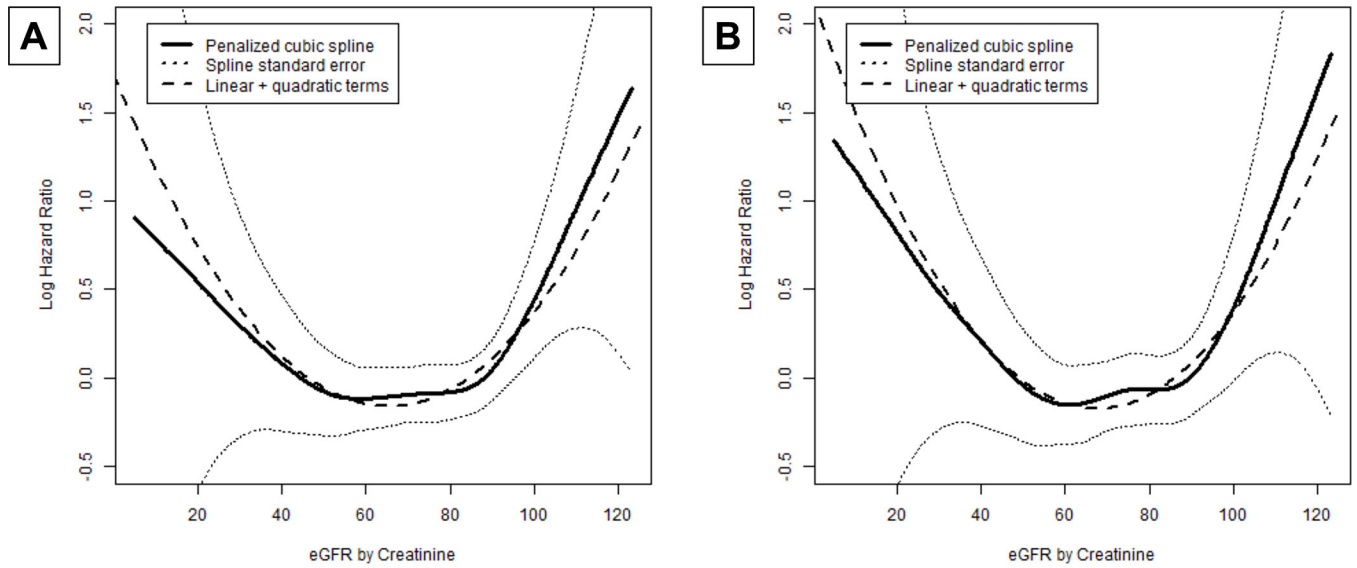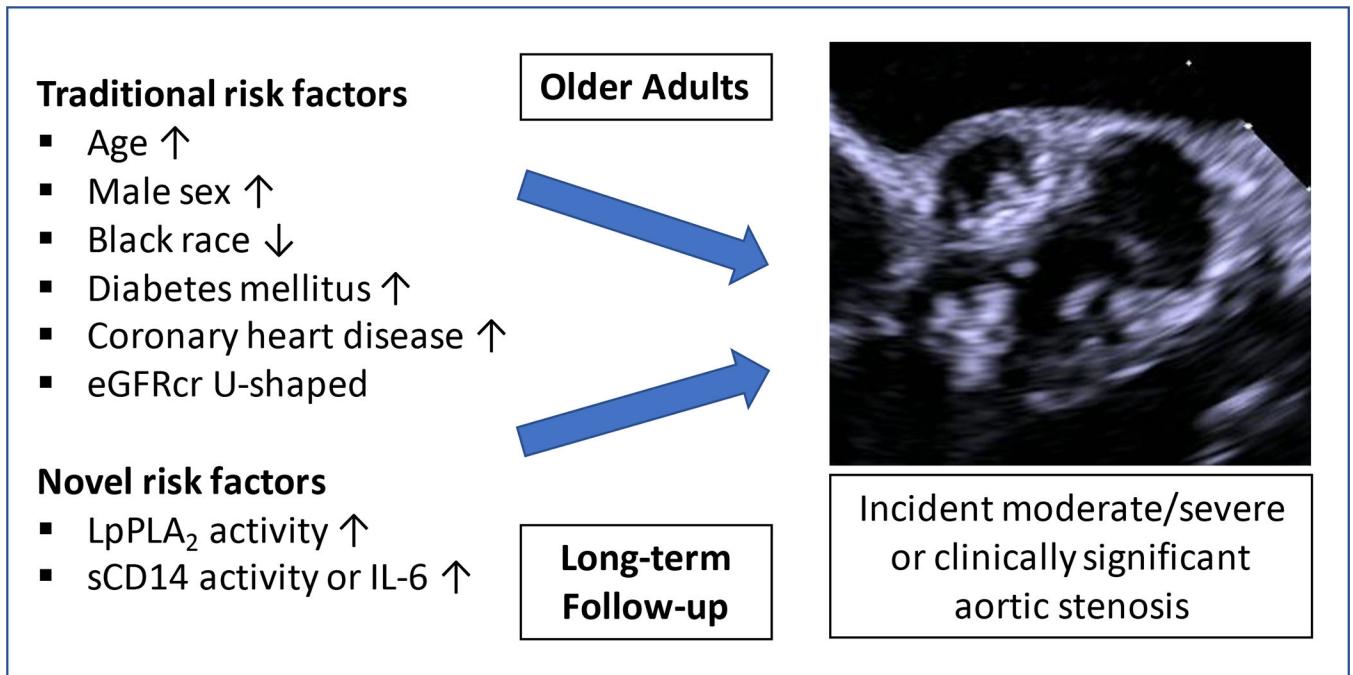| Variable	1989–90/1994–95 Baseline (n=5390)	1992–93/1994–95 Baseline (n=4242)
Age, years	72.9 (5.6)	75.1 (5.2)
Male sex, n (%)	2288 (42.4)	1784 (42.1)
Black race, n (%)	675 (12.5)	610 (14.4)
BMI, kg/m^2	26.6 (4.6)	26.7 (4.6)
Waist circumference, cm	94.17 (12.98)	N/A
Education, < high school, n (%)	1531 (28.4)	1080 (25.5)
HOMA-IR [*]	3.43 (2.37)	N/A
Current smoker, n (%)	631 (11.7)	406 (9.6)
Ever smoker, n (%)	2916 (54.1)	2332 (55.0)
LDLc, mg/dL	130 (36)	127 (34)
HDLc, mg/dL	54 (16)	53 (14)
Triglycerides, mg/dL	135 (60)	138 (65)
eGFR$_{cr}$, ml/min/1.73 m^2	72 (18)	71 (17)
eGFR$_{cys}$, ml/min/1.73 m^2	72 (19)	66 (18)
Hypertension, n (%)	3123 (57.9)	2370 (55.9)
Diabetes, n (%)	824 (15.3)	704 (16.6)
Coronary heart disease, n (%)	1037 (19.2)	900 (21.2)
Stroke/TIA, n (%)	307 (5.7)	304 (7.2)
Heart failure, n (%)	236 (4.4)	236 (5.6)
Peripheral arterial disease, n (%)	138 (2.6)	125 (2.9)
Statin use, n (%)	116 (2.2)	199 (4.7)
Oral steroid use, n (%)	111 (2.1)	84 (2.0)
Warfarin use n (%)	72 (1.3)	95 (2.2)
Lp(a), μg/mL	54.3 (56.0)	NA
LpPLA$_2$ Mass, ng/mL	343.6 (117.3)	NA
LpPLA$_2$ activity, nmol/min/mL	39.6 (13.0)	NA
Fetuin-A, g/L	NA	0.5 (0.1)
Klotho, pg/mL	NA	900.0 (529.3)
CRP, g/L	4.7 (8.1)	NA
IL-6, pg/mL	2.2 (1.9)	NA
WBC, ×10^3/μL	6.3 (2.1)	NA
sCD14, ng/mL	1641 (356)	NA
sCD163, ng/mL	788 (220)	NA

[*] Among participants free of diabetes.

Abbreviations: BMI = body mass index; CRP = C-reactive protein; eGFR$_{cr}$ = creatinine-based estimated glomerular filtration rate; eGFR$_{cys}$ = cystatin C-based estimated glomerular filtration rate; HDLc = high density lipoprotein cholesterol; HOMA-IR = homeostasis model assessment of insulin resistance; IL-6 = interleukin-6; LDLc = low density lipoprotein cholesterol; Lp(a) = lipoprotein(a); LpPLA$_2$ = lipoprotein-associated phospholipase-A2; sCD14 = soluble CD14; sCD163 = soluble CD163; TIA = transient ischemic attack; WBC = white blood cell count.

Table 2.

Associations of Traditional Risk Factors with Incidence of Probable/Definite Moderate or Severe Aortic Stenosis, as well as Probable/Definite Clinically Significant Aortic Stenosis

Variable	Moderate/severe AS				Clinically significant AS			
	Model 1		Model 2		Model 1		Model 2	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
Age (per SD)	1.63 (1.44,1.85)	<0.01	1.66 (1.45,1.91)	<0.01	1.45 (1.23,1.72)	<0.01	1.48 (1.23,1.78)	<0.01
Black race	0.50 (0.31,0.82)	0.01	0.40 (0.24,0.65)	<0.01	0.43 (0.22,0.84)	0.01	0.31 (0.16,0.63)	<0.01
Male sex	1.52 (1.20,1.92)	<0.01	1.41 (1.06,1.87)	0.02	1.63 (1.21,2.20)	<0.01	1.67 (1.17,2.39)	<0.01
Education <HS	1.24 (0.96,1.61)	0.11	1.15 (0.89,1.50)	0.29	1.23 (0.88,1.72)	0.23	1.13 (0.80,1.58)	0.49
BMI (per SD)	1.20 (1.06,1.35)	<0.01	1.10 (0.97,1.26)	0.14	1.19 (1.02,1.39)	0.03	1.09 (0.92,1.29)	0.34
Waist circumference (per SD) *	1.19 (1.05,1.35)	0.01	1.10 (0.96,1.25)	0.18	1.16 (0.99,1.36)	0.07	1.05 (0.88,1.25)	0.60
Hypertension	1.31 (1.03,1.66)	0.03	1.17 (0.92,1.50)	0.20	1.47 (1.08,1.99)	0.01	1.31 (0.95,1.79)	0.10
HOMA-IR (per SD) †	1.11 (1.02,1.21)	0.01	1.07 (0.94,1.22)	0.28	1.10 (0.97,1.24)	0.15	1.04 (0.86,1.27)	0.67
Diabetes	1.82 (1.33,2.50)	<0.01	1.53 (1.10,2.13)	0.01	2.11 (1.44,3.10)	<0.01	1.79 (1.19,2.69)	<0.01
Current smoking	0.75 (0.46,1.22)	0.24	0.69 (0.41,1.15)	0.15	1.10 (0.64,1.87)	0.74	1.08 (0.61,1.91)	0.79
Ever smoking	1.18 (0.93,1.50)	0.18	1.26 (0.98,1.62)	0.08	1.12 (0.82,1.52)	0.49	1.10 (0.80,1.53)	0.56
LDLc (per SD)	1.05 (0.93,1.18)	0.40	1.06 (0.94,1.19)	0.35	1.12 (0.96,1.30)	0.15	1.13 (0.97,1.31)	0.11
HDLc (per SD)	0.84 (0.73,0.96)	0.01	0.93 (0.79,1.09)	0.37	0.83 (0.70,1.00)	0.04	0.98 (0.80,1.20)	0.85
Triglycerides (per SD)	1.14 (1.02,1.27)	0.02	1.03 (0.90,1.17)	0.65	1.19 (1.03,1.36)	0.01	1.08 (0.92,1.27)	0.35
Coronary heart disease	1.55 (1.16,2.07)	<0.01	1.36 (1.01,1.84)	0.04	1.62 (1.13,2.34)	0.01	1.39 (0.95,2.04)	0.09
Stroke/TIA	1.37 (0.78,2.40)	0.27	1.14 (0.64,2.01)	0.66	1.06 (0.47,2.40)	0.89	0.83 (0.36,1.89)	0.65
Heart failure	2.17 (1.21,3.90)	0.01	1.54 (0.84,2.84)	0.16	2.54 (1.24,5.21)	0.01	1.83 (0.86,3.86)	0.11
Peripheral arterial disease	1.67 (0.74,3.78)	0.21	1.32 (0.58,3.01)	0.51	2.29 (0.93,5.63)	0.07	1.72 (0.69,4.30)	0.24
eGFR$_{cr}$ (per SD)	0.29 (0.13,0.62)	<0.01	0.36 (0.16,0.78)	0.01	0.21 (0.08,0.56)	<0.01	0.29 (0.11,0.78)	0.03
eGFR$_{cr}$ (per SD) squared	1.18 (1.07,1.29)		1.15 (1.04,1.27)		1.22 (1.08,1.37)		1.17 (1.04,1.33)	

*
Included in Model 2 in place of BMI.

†
Among participants free of diabetes.

Model 1. Includes age, sex and race and other traditional risk factors individually.

Model 2 (Main Model). Includes age, sex, race, education, BMI, hypertension, diabetes, smoking, LDLc, HDLc, triglycerides, coronary heart disease, stroke/TIA, heart failure, peripheral arterial disease and eGFR$_{cr}$.

Abbreviations: BMI = body mass index; eGFR$_{cr}$ = creatinine-based estimated glomerular filtration rate; HDLc = high density lipoprotein cholesterol; HOMA-IR = homeostasis model assessment of insulin resistance; HS = high school; LDLc = low density lipoprotein cholesterol; TIA = transient ischemic attack.

Table 3.

Associations of Novel Risk Factors with Incidence of Probable/Definite Moderate or Severe Aortic Stenosis and Probable/Definite Clinically Significant Aortic Stenosis

Variables	Model 1		Model 2		Model 3	
	HR* (95% CI)	p	HR* (95% CI)	p	HR* (95% CI)	p
Probable/Definite Moderate or Severe AS						
Lipid Markers						
Lp(a)	1.02 (0.89,1.17)	0.78	1.03 (0.90,1.18)	0.70	1.04 (0.90,1.20)	0.59
LpPLA$_2$ Mass	1.10 (0.99,1.23)	0.09	1.08 (0.96,1.21)	0.19	1.00 (0.87,1.14)	0.95
LpPLA$_2$ Activity	1.22 (1.10,1.35)	<0.01	1.21 (1.07,1.37)	<0.01	1.21 (1.06,1.39)	0.01
Mineral Markers						
Fetuin-A	1.04 (0.91,1.18)	0.61	0.99 (0.86,1.13)	0.89	0.99 (0.86,1.13)	0.84
Klotho	1.00 (0.87,1.15)	0.99	1.00 (0.87,1.15)	1.00	1.00 (0.87,1.15)	1.00
Inflammatory Markers						
hsCRP	1.06 (0.95,1.19)	0.30	1.00 (0.87,1.14)	1.00	0.96 (0.80,1.14)	0.62
IL–6	1.11 (1.03,1.20)	0.01	1.09 (1.00,1.20)	0.06	1.08 (0.98,1.20)	0.13
WBC	1.11 (1.00,1.23)	0.05	1.06 (0.93,1.20)	0.37	1.06 (0.92,1.22)	0.42
sCD14	1.18 (1.04,1.34)	0.01	1.16 (1.01,1.34)	0.03	1.15 (0.98,1.34)	0.08
sCD163	1.20 (1.06,1.36)	<0.01	1.10 (0.97,1.26)	0.15	1.07 (0.93,1.22)	0.36
Probable/Definite Clinically Significant AS						
Lipid Markers						
Lp(a)	1.00 (0.84,1.20)	0.99	1.00 (0.84,1.20)	0.98	1.00 (0.83,1.21)	>0.99
LpPLA$_2$ Mass	1.11 (0.97,1.28)	0.14	1.06 (0.91,1.23)	0.43	0.98 (0.83,1.15)	0.79
LpPLA$_2$ Activity	1.26 (1.11,1.43)	<0.01	1.20 (1.03,1.40)	0.02	1.21 (1.02,1.44)	0.03
Mineral Markers						
Fetuin-A	1.11 (0.94,1.32)	0.22	1.02 (0.86,1.22)	0.78	1.02 (0.85,1.21)	0.84
Klotho	1.05 (0.91,1.21)	0.49	1.04 (0.90,1.20)	0.58	1.04 (0.90,1.20)	0.58
Inflammatory Markers						
hsCRP	1.11 (0.98,1.24)	0.09	1.06 (0.92,1.21)	0.44	1.07 (0.92,1.25)	0.37

Variables	Model 1		Model 2		Model 3	
	HR* (95% CI)	p	HR* (95% CI)	p	HR* (95% CI)	p
IL-6	1.14 (1.04,1.24)	<0.01	1.12 (1.01,1.25)	0.04	1.10 (0.97,1.25)	0.13
WBC	1.16 (1.04,1.30)	0.01	1.11 (0.96,1.29)	0.15	1.11 (0.94,1.31)	0.20
sCD14	1.10 (0.92,1.31)	0.28	1.05 (0.87,1.26)	0.64	0.98 (0.80,1.21)	0.88
sCD163	1.24 (1.06,1.46)	0.01	1.14 (0.96,1.35)	0.13	1.11 (0.94,1.33)	0.22

*
Per SD increment in each biomarker.

Model 1. Adjusted for age, sex and race and individual novel risk factors.

Model 2 (Main Model). Adjusted for age, sex, race, education, BMI, hypertension, diabetes, smoking, LDLc, HDLc, triglycerides, coronary heart disease, stroke/TIA, heart failure, peripheral arterial disease and eGFR$_{cr}$.

Model 3. *Lipids:* Model 2 variables, with concurrent inclusion of LpPLA2 mass, LpPLA2 activity and Lp(a) (in first cohort only). ***Mineral Markers:*** Model 2 variables, with concurrent inclusion of fetuin-A and klotho. ***Inflammatory Markers:*** Model 2 variables, with concurrent inclusion of hsCRP, IL–6, WBC, sCD14, and sCD163.

Abbreviations: hsCRP = high-sensitivity C-reactive protein; IL–6 = interleukin-6; Lp(a) = lipoprotein(a); LpPLA2 = lipoprotein- associated phospholipase A2; sCD14 = soluble CD14; sCD163 = soluble CD163; WBC = white blood cell count.