Atrial Cardiomyopathy and Longitudinal Outcomes in the UK Biobank

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A thesis

Submitted in partial fulfillment of the

Requirements for the degree of

Master of Science

University of Washington

2025

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Program Authorized to Offer Degree:

Epidemiology

University of Washington

Abstract

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Background: Atrial cardiopathy often precedes atrial fibrillation (AF) and has emerged as an independent risk factor for cardiovascular outcomes. Previous studies assessing atrial function in relation to clinical outcomes have been small, and the importance of right-sided function is largely unknown.
Methods: In 51,693 UK Biobank participants with no previous history of AF, we assessed left and right atrial volumes and ejection fraction from cardiac magnetic resonance imaging (CMR) using deep learning segmentation. We evaluated associations with new-onset AF, ischemic stroke, heart failure, and dementia and conducted a genome-wide association study of each atrial measure. Potential causal associations with downstream outcomes were evaluated using Mendelian randomization.
Results: During a median follow-up time of 4.0 (IQR 2.9-5.4) years, 964 (1.9%) developed AF, 266 (0.5%) developed ischemic stroke, 365 (0.7%) developed heart failure, and 72 (0.1%) developed dementia. After adjustment for clinical risk factors, left and right atrial measures were independently associated with risk of new-onset AF, ischemic stroke, and heart failure, with stronger associations in women. Left atrial minimal volume was also associated with increased risk of dementia. We identified 51 genetic loci associated with left and right atrial measures ($p < 5 \times 10^{-8}$), including 27 novel trait-locus associations, many of which do not overlap with established AF loci. Genetic correlations showed that both chambers had similar correlations with AF but varying correlations with blood pressure, body mass

index, and type II diabetes. In Mendelian randomization analyses, left atrial measures had direct causal effects on AF, ischemic stroke, and cardioembolic stroke, though stroke associations were no longer significant after accounting for AF variants.

Conclusion: In this largest assessment of atrial structure and function to date, both left and right atrial cardiopathy were associated with clinical outcomes attributed to AF. We identified several novel genetic loci for left and right atrial traits and observed unique genetic correlations between left and right atrial traits and cardiovascular phenotypes, providing insight into chamber-specific remodeling. Several of these measures are likely to be causal determinants of cardiovascular complications previously attributed to AF, which may be mediated by intercurrent AF. These findings highlight atrial cardiopathy's potential as a screening tool to identify individuals at high risk for cardiovascular complications.

Introduction

Atrial fibrillation (AF), the most common cardiac arrhythmia, affects over 59 million people worldwide and is a significant risk factor for heart failure, ischemic stroke, dementia, and mortality.[1-3] Treating AF with anticoagulation can reduce the risk of ischemic stroke by two-thirds.[4] Still, many patients with AF remain untreated, and emerging evidence suggests that some of the morbidity and mortality attributed to AF may result from underlying structural and contractile abnormalities of the cardiac atria, referred to as atrial cardiopathy.[5,6] Recent studies have found that sensitive measures of impaired left atrial function from echocardiography and cardiac magnetic resonance imaging (CMR) are stronger independent risk factors for AF, ischemic stroke, vascular brain injury, and dementia than electrocardiographic measures reflecting left atrial structure.[7-10] In the absence of randomized controlled trials of interventions targeting atrial cardiopathy, it remains unclear whether these relationships are causal.

Most prior research on atrial cardiopathy has focused on the left atrium despite evidence of the right atrium's critical role in AF.[6,7,9,11] As the lowest-pressure cardiac chamber, the right atrium is highly susceptible to hemodynamic changes, potentially allowing for earlier identification of cardiac dysfunction.[12] Recent epidemiologic studies have reported that structural changes in the right atrium are associated with an increased risk of AF, even after adjusting for left atrial parameters.[13] Similar findings have been reported in clinical settings, where right atrial measures were superior to left atrial measures in predicting AF recurrence.[14] However, little is known about the potential impact of right atrial structure and function on other cardiovascular diseases, including ischemic stroke and heart failure.

To advance our understanding of the role of both left- and right-sided atrial cardiopathy in the development of clinical complications, we applied deep learning image segmentation analyses to CMR performed on nearly 60,000 participants of the UK Biobank (UKBB) Imaging Study and evaluated associations with longitudinal clinical outcomes. To explore the biology underlying these potential casual relationships, we used these data to perform the largest genome-wide association study (GWAS) of atrial

function to date, evaluated genetic correlations between phenotypes, and assessed for evidence of causal associations with Mendelian randomization.

Methods

Study Cohort

The UKBB is a prospective cohort study that recruited approximately 500,000 participants aged 40 to 69 from the United Kingdom between 2006 and 2010.[15] The baseline assessment included comprehensive questionnaires, blood and urine collection for biochemical measurements, anthropometry, and interviews.[15] All UKBB participants underwent whole-genome genotyping through the UKBB Whole-Genome Sequencing Consortium.[16] All participants provided electronic informed consent at the UKBB assessment centers. The UKBB received ethics approval from the North West Multi-Centre Research Ethics Committee. This study was conducted under application #40713. The results are reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.

CMR Parameters

The UKBB Imaging Study began in 2014 and included magnetic resonance imaging of the brain, abdomen, and heart.[17] The CMR protocol consists of a 20-minute scan performed using a 1.5 Tesla scanner.[18] We applied a fully convolutional network to CMR scans conducted during the first imaging visit available as of October 8, 2023, to obtain volume and function measures. Exposures of interest were left atrial minimal volume ($LAVI_{min}$) and left atrial maximal volume ($LAVI_{max}$) indexed to body surface area, left atrial ejection fraction (LAEF), right atrial minimal volume ($RAVI_{min}$) and right atrial maximal volume

($RAVI_{max}$) indexed to body surface area, and right atrial ejection fraction (RAEF). The CMR and quality control protocol are described in Supplemental Methods 1.

Covariates

All covariates were assessed at the time of the imaging visit, with the exception of the Townsend index and biochemical measures.[18-20] The Townsend index was assessed at the baseline visit, and the biochemical measures were taken from the visit closest to the imaging visit. Blood samples were collected from participants during the center examination and processed at a central processing laboratory.[21] High-density lipoprotein (HDL), total cholesterol, and C-reactive protein (CRP) were assayed in all participants.[22] PR interval and P-wave duration measurements were obtained from the imaging visit electrocardiogram.

Genetic Data

488,377 participants in the UKBB have been genotyped for over 800,000 variants using DNA extracted from blood samples collected at the baseline examination.[23] Genotypes were directly called using the UK Biobank Axiom (Affymetrix, Santa Clara, California) and UK Applied Biosystems Array. Imputation was carried out using the Haplotype Reference Consortium, UK10K reference panel, and 1000 Genomes Project reference panel.[23]

Outcomes

Longitudinal follow-up for health outcomes was performed through linkages with national databases on hospitalizations, primary care records, and death records. Incident AF events and dementia were identified from self-report and diagnosis codes, while ischemic stroke and heart failure were identified solely from diagnosis codes (Supplemental Methods 2). Participants diagnosed with AF before the imaging visit and the presence of a pacemaker were excluded from analyses (Figure 1).

Additionally, participants whose imaging visits occurred after the UKBB data censoring dates were excluded. The follow-up for this study extended through 2022.

Statistical Analyses

Cox proportional hazard models were used to test the association of atrial measures as continuous variables with incident outcomes, excluding individuals with prevalent disease at baseline and adjusting for established risk factors for each outcome. Incident AF models adjusted for age, sex, ethnicity, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), antihypertensive medications use, current smoking, diabetes, history of heart failure, and history of myocardial infarction. Incident ischemic stroke models adjusted for age, sex, ethnicity, BMI, SBP, antihypertensive medication use, total cholesterol, HDL cholesterol, current smoking, and diabetes. Incident heart failure models adjusted for age, sex, ethnicity, BMI, SBP, antihypertensive medication use, total cholesterol, HDL cholesterol, left ventricular ejection fraction, diabetes, and history of myocardial infarction. Incident dementia models adjusted for age, sex, ethnicity, BMI, SBP, antihypertensive medication use, diabetes, Townsend index, and presence of APOE4 allele. We used multiple imputation methods with chained equations to account for missing clinical variables.[24] To explore non-linear associations, we evaluated each atrial measure as quintiles, adjusting for the same potential confounding variables described above.

Secondary analyses for incident AF, heart failure, and ischemic stroke additionally adjusted for Townsend index, CRP levels, and electrocardiographic measures of atrial cardiopathy (P-wave duration and PR interval). Additional secondary adjustment variables for incident dementia included history of ischemic stroke, heart failure, and myocardial infarction. Sensitivity analyses adjusted for intercurrent AF that occurred after baseline as a time-varying covariate. Effect modification by sex and age was evaluated in fully adjusted models. Separate Cox models were fit for each sex and age subgroup for each outcome.

To explore the genetic determinants behind these relationships, we conducted a discovery GWAS for each atrial trait, performed genetic correlation analyses, and evaluated causal relationships

using Mendelian randomization (Supplemental Methods 3). All statistical analysis was performed using R Statistical Software version 4.0.1 (R Group for Statistical Computing).

Results

Left and right atrial measures

After excluding participants with prevalent AF, a pacemaker, or lacking follow-up, 51,693 passed CMR quality control and were included in analyses (Figure 1). The mean age was 65, 48% were men, and 24% used hypertension medications (Table 1). The population was relatively healthy and free of cardiovascular disease; only 0.4% had heart failure. For the vast majority of participants, left atrial measures fell within sex-specific normal reference ranges (Supplemental Table 1). $LAVI_{min}$ was highly correlated with $LAVI_{max}$ and LAEF ($|r| > 0.75$), while $LAVI_{max}$ was weakly correlated with LAEF ($r = -0.36$) (Figure 1). Similarly, $RAVI_{min}$ was correlated strongly with $RAVI_{max}$ and RAEF, while $RAVI_{max}$ correlated poorly with RAEF ($r = -0.12$). Left-sided measures correlated poorly with right-sided measures ($|r| < 0.3$).

Clinical Associations

During a median follow-up time of four years (IQR, 2.9-5.4), 964 (1.9%) participants developed AF, 266 (0.5%) participants developed ischemic stroke, 365 (0.7%) developed heart failure, and 72 (0.1%) developed dementia. In primary analyses adjusting for established clinical risk factors, both left- and right-sided atrial measures were significantly associated with new-onset AF, ischemic stroke, and heart failure (Table 2). For instance, each SD increase in $LAVI_{min}$ was associated with a 55% higher risk of AF (95% CI, 48-62%). Right-sided measures were less strongly associated but still met criteria for statistical significance; each SD increase in $RAVI_{min}$ was associated with a 39% higher risk of AF (95% CI, 31-47%). Only $LAVI_{min}$ was associated with risk of incident dementia; each SD unit increase in $LAVI_{min}$ was associated with a 19% increased risk of dementia (95% CI, 3-38%). These associations remained relatively unchanged with adjustment for secondary adjustment parameters and intercurrent AF (Supplemental Tables 2-3).

There was evidence of significant effect modification by sex and age, where atrial measures were all more strongly associated with AF and heart failure in women than in men, and $LAVI_{max}$ was more strongly associated with AF in participants aged 65 and older (Supplemental Tables 4-7). When categorizing atrial measures into quintiles, there was a pronounced threshold effect, where the highest-risk quintile of each left atrial measure was associated with more than a 3-times increased risk of AF and 2-times increased risk of heart failure compared with the reference quintile (Figure 2).

Discovery of independent genomic loci for atrial traits

Up to 55,881 participants were included in the atrial structure and function parameter GWAS, and we tested 11,628,826 variants with minor allele frequency > 0.005. Heritability analyses observed modest genetic contributions to atrial traits (Supplemental Table 8). We identified 51 significant variants ($p<5\times10^{-8}$) associated with atrial structure and function traits, of which several were within 500kb of previously identified AF loci (Table 3, Supplemental Table 9).[25] Only two loci overlapped between left and right atrial traits. Additionally, 24 loci were within 500kb of previous loci identified in left and right atrial GWASs, and 13 overlapped with established AF risk factor loci (Supplemental Tables 10-11).[26-29] Post-GWAS annotation revealed several candidate genes mapped to these loci (Supplemental Table 12).

Genetic correlations

There was a high degree of genetic correlation between $LAVI_{min}$ and $LAVI_{max}$ (r=0.94), $LAVI_{min}$ and LAEF (r=-0.79), and $RAVI_{min}$ and $RAVI_{max}$ (r=0.93) (Supplemental Figure 2, Supplemental Table 13). We observed several significant genetic correlations with cardiovascular outcomes and risk factors, with both shared and distinct patterns for left and right atrial traits (Supplemental Figure 3, Supplemental Figure 14). Both left and right atrial volumes were positively correlated with AF but had varying associations with cardiometabolic risk factors.

Mendelian Randomization

Mendelian randomization identified causal effects of $LAVI_{max}$ and LAEF on new-onset AF, ischemic stroke, and cardioembolic stroke (Supplemental Table 15). The strongest association was observed between LAEF and cardioembolic stroke (β=-0.8, $p=2.48\times10^{-3}$). No causal associations were observed between right atrial measures and clinical outcomes. In multivariable Mendelian randomization analyses accounting for the effect of AF, there was no significant evidence of an independent (direct) effect of left atrial measures on stroke (Supplemental Table 16).

Discussion:

In this largest and most comprehensive evaluation of atrial cardiopathy, both left and right atrial structure and function measures from CMR were associated with new-onset AF, heart failure, and ischemic stroke after adjustment for established risk factors. Despite a small number of events, $LAVI_{min}$ was also associated with new-onset dementia. These associations were robust to adjustment for additional potential risk factors, and many of the associations were substantially stronger in women. Our GWAS of these traits identified 27 novel loci, several of which do not overlap with prior AF loci. These results were used as genetic instruments in Mendelian randomization analyses, which established a strong causal relationship between left atrial measures and new-onset AF, ischemic stroke, and cardioembolic stroke, the hallmark complication of AF and atrial cardiopathy.

Prior research has established the association between atrial cardiopathy and increased risks of AF, ischemic stroke, and heart failure.[30-33] In the Multi-Ethnic Study of Atherosclerosis, higher $LAVI_{max}$, lower LAEF, and lower peak left atrial strain were independently associated with an increased risk of AF.[8] Similar independent associations have been reported between reduced LAEF and the risk of ischemic stroke.[7] Previous releases of the UKBB imaging data have also been analyzed by others, with smaller sample sizes and a fraction of the cardiovascular events reported here.[19,27] Our analyses corroborated previously reported findings linking left atrial volumes with new-onset AF, heart failure, and ischemic stroke while also reporting novel associations with dementia, right atrial measures, and effect modification of associations by sex. Additionally, we identified several novel genetic loci in our larger sample of participants.

In contrast to previous studies,[34,35] we observed significant sex differences in our atrial measures-outcome associations: women had a 17% higher risk of AF and an 18% higher risk of heart failure per increase in $LAVI_{min}$. These findings align with recent studies reporting that women have higher degrees of atrial fibrosis than men and that women with AF and LA enlargement have a higher risk of cardiovascular mortality.[36,37] Additional research has shown that women consistently have higher levels of atrial fibrosis across nearly all age groups, further suggesting biological differences in atrial remodeling between men and women.[38] These findings emphasize the importance of sex-specific approaches for cardiovascular risk stratification.[39-41]

In the largest GWAS of left and right atrial measures to date, we identified 51 (27 novel) significant genetic associations. Prior GWAS using echocardiographic measures of atrial structure and function did not find any loci significantly associated with left atrial structure or function.[42,43] In contrast, recent studies using UKBB CMR measures have identified several loci associated with atrial structure and function, which may be due to higher quality of CMR imaging of the cardiac atria and greater variability in image acquisition with echocardiography.[26-28] Many of these loci overlap with our findings, with gene regions mapped to cardiomyopathy, AF risk factors, and within 500kb of the largest AF GWAS, suggesting a shared genetic basis between atrial structure, AF risk factors, and AF. For example, *LINC01438* is in close proximity to *PITX2*, a gene expressed in the left atrium that has been well-studied for its role in AF.[44]

LD score regression identified several genetic correlations with AF risk factors that differed for left and right atrial traits. Left atrial volumes were positively correlated with SBP, while right atrial volumes were negatively correlated with SBP, DBP, BMI, and type II diabetes. This corroborates previous findings from the UKBB, where participants with diabetes had lower values of right atrial structure and function in age and sex-adjusted models but no significant difference in left atrial measures.[45] These chamber-specific differences reflect the complex relationship between traditional cardiovascular risk factors and atrial traits, which may be influenced by distinct biological pathways in response to metabolic stress and the unique embryological origins of each atrium. Additionally, it is possible that cardiometabolic conditions have direct atrial myocardial involvement, and these differential chamber patterns capture

early signs of cardiac dysfunction. Further studies are needed to explore these chamber-specific remodeling mechanisms.

Our MR analyses build upon previously reported causal relationships between left atrial traits and disease risk while revealing novel insights into the atrial cardiopathy paradigm.[26] While previous analyses did not fully account for indirect pathways,[27] our analysis accounted for the effect of blood pressure, which can impact both AF and atrial measures, and applied Multivariable MR to account for potential pleiotropy through the AF in the atrial measures-stroke relationship. In our forward MR, we initially observed causal associations between left atrial measures, AF, and cardioembolic stroke, as well as a novel causal association with ischemic stroke. However, stroke associations were significantly attenuated after accounting for the effect of AF, suggesting the relationship between left atrial cardiopathy and stroke may be mediated through AF. These findings challenge the hypothesis that atrial cardiopathy and its associated endothelial dysfunction directly promote thromboembolic events independent of AF.[46,47] In contrast to left atrial traits, we did not find evidence of a causal relationship between right atrial traits and adverse cardiovascular outcomes despite strong epidemiologic associations between right atrial measures and outcomes. These results suggest that right atrial remodeling may reflect broader hemodynamic stress, while left atrial remodeling may be a more relevant therapeutic target. However, additional studies with greater statistical power are needed to confirm these findings.

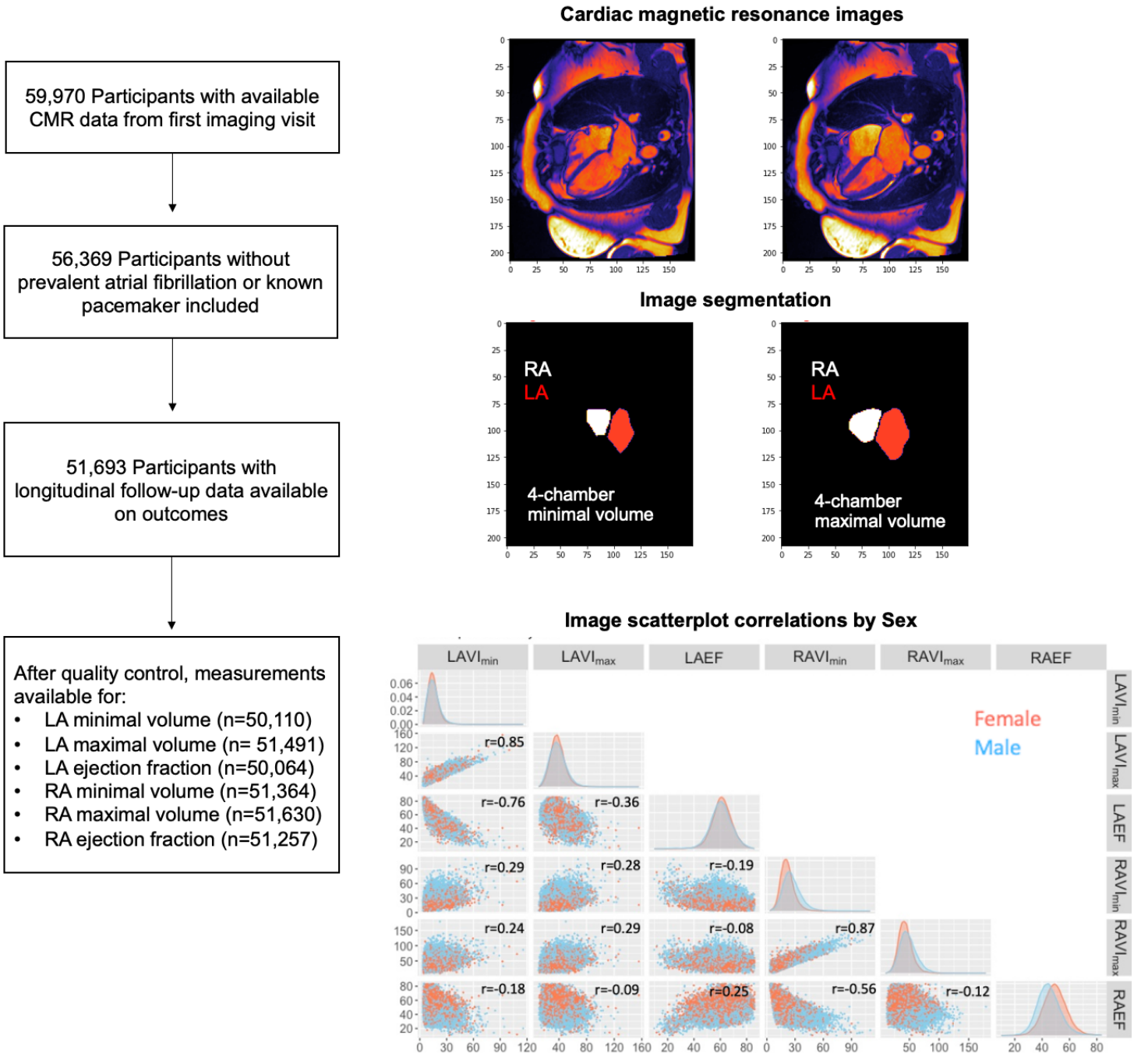
The strengths of this study include the large sample size, high-quality CMR imaging, and longitudinal follow-up for cardiovascular events identified from U.K. national electronic health data, which enabled a comprehensive epidemiologic and genetic evaluation of atrial cardiopathy. This approach enabled us to conduct a well-powered MR analysis of left and right atrial function measures based on all currently available CMR imaging that accounted for horizontal pleiotropy and the potential mediating role of AF. While previous MR analyses have relied on conventional sensitivity analyses that cannot fully account for pleiotropy, we used knowledge about measures associated with confounders and atrial measures to exclude pleiotropic variants in our analyses.[48] There are also important limitations. First, the vast majority of UKBB participants self-identify as White, and our GWAS included only European

ancestry individuals to avoid population stratification as a source of bias, which may limit the generalizability of both our epidemiologic and genetic study results to other racial groups.[49,50] Second, the number of events observed for ischemic stroke and dementia was small, and our median follow-up time of four years may have limited our power to identify associations with atrial traits due to small event counts and the natural history of slowly developing conditions such as dementia. Third, our genetic instrument threshold was less stringent ($p<10^{-6}$) than conventional GWAS significant thresholds but allows for exploring potential associations that can guide future validation. Finally, this study uses CMR at a single imaging visit and does not allow us to assess how changes in these measures impact longitudinal outcomes.

Conclusion: In this analysis of over 50,000 participants with CMR measures, we observed that accurate and reproducible measures of atrial cardiopathy were associated with an increased risk of AF, ischemic stroke, heart failure, and dementia, particularly in women and independent of established clinical risk factors. Through genetic analyses, we identified several novel loci and observed both common and chamber-specific patterns of remodeling that may inform the development of future therapeutic targets. Future research is needed to translate these clinical insights to a general screening population using practicable, low-cost methods for detecting left and right atrial cardiopathy.

Figures and Tables

Figure 1: Study Flowchart



Legend: After exclusion, data from 51,693 participants was available for analysis.

Table 1: Baseline Characteristics

Variables	Mean (SD) or N (%)	Missing, n
Age (years), mean (SD)	65 (7.7)	0
Male sex, N (%)	24,584 (48)	0
Ethnicity, N (%)		
European	49,938 (97)	116
British African	353 (0.7)	
East Asian	253 (0.5)	
South Asian	500 (1.0)	
Mixed	533 (1.0)	
Height (cm), mean (SD)	169 (9.2)	44
Weight (kg), mean (SD)	76 (15)	98
BMI (kg/m^2), mean (SD)	27 (4.4)	139
SBP (mmHg), mean (SD)	140 (19)	4839
DBP (mmHg), mean (SD)	79 (10)	4839
Antihypertensive Medications, N (%)	12,222 (24)	365
Total Cholesterol (mmol/L), mean (SD)	5.7 (1.1)	2842
HDL levels (mmol/L), mean (SD)	1.5 (0.4)	6674
Townsend Index, mean (SD)	-1.9 (2.7)	48
CRP levels (mg/L), mean (SD)	2.0 (3.6)	2931
Ventricular Rate, mean (SD)	62 (11)	6272
PR Interval (ms), mean (SD)	165 (27)	8162
P Wave Duration (ms), mean (SD)	98 (16)	8125
LVEF (%), mean (SD)	60 (6.3)	27
Current Smoking, N (%)	1,739 (3.4)	313
Diabetes, N (%)	2,802 (5.4)	453
History of HF, N (%)	191 (0.4)	0
History of MI, N (%)	1,110 (2.1)	0
APOE4 Allele Presence, N (%)	13,886 (27)	1404

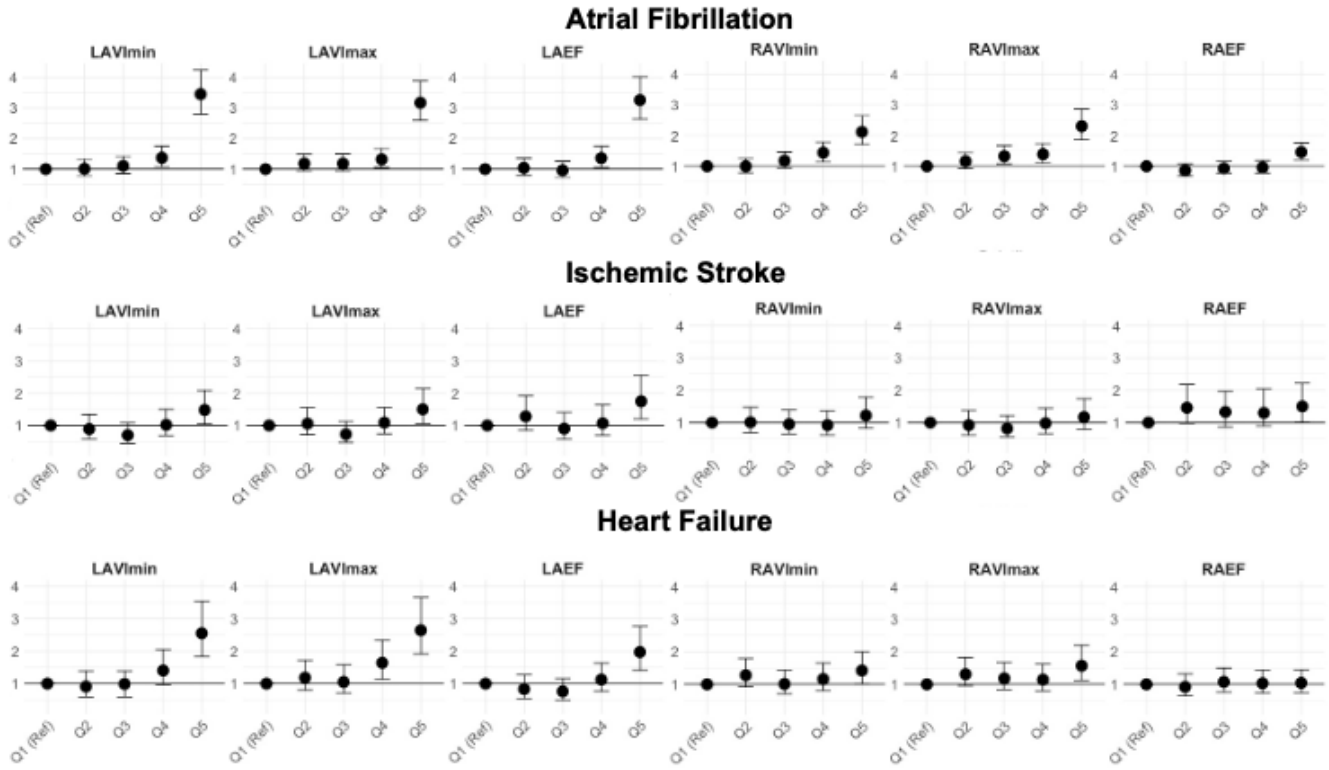
Baseline characteristics among 51,683 participants in analytic sample.

Table 2: Associations of Atrial Function and Structure with Outcomes

	Atrial Fibrillation	**Ischemic Stroke**	**Heart Failure**	**Dementia**
Variable	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
$LAVI_{min}$ (mL/m^2)	**1.55(1.48-1.62)**	**1.28(1.16-1.38)**	**1.23(1.15-1.32)**	**1.19(1.03-1.38)**
$LAVI_{max}$ (mL/m^2)	**1.60(1.52-1.68)**	**1.19(1.05-1.35)**	**1.35(1.25-1.46)**	1.21(0.99-1.48)
LAEF (%)	**0.55(0.52-0.59)**	**0.75(0.66-0.85)**	**0.76(0.69-0.84)**	0.85(0.68-1.05)
$RAVI_{min}$ (mL/m^2)	**1.39(1.31-1.47)**	**1.18(1.02-1.36)**	**1.22(1.10-1.35)**	1.03(0.85-1.26)
$RAVI_{max}$ (mL/m^2)	**1.34(1.26-1.42)**	1.11(0.96-1.27)	**1.22(1.09-1.35)**	0.98(0.80-1.21)
RAEF (%)	**0.81(0.74-0.88)**	0.87(0.76-1.00)	0.93(0.83-1.03)	0.93(0.72-1.19)

Hazard ratios are reported per standard deviation increase atrial measure. Significant associations are bolded.

Figure 2: Associations of Atrial Function and Structure with Atrial Fibrillation, Ischemic Stroke, and Heart Failure by Quintiles.



The highest quintile values of left atrial volume and right atrial volume measures were compared to a reference of the lowest quintile. The lowest quintile values of left atrial ejection fraction and right atrial ejection fraction were compared to a reference of the highest quintile. Hazard ratios are on the x-axis, and quintiles (Q1-Q5) are on the y-axis.

Table 3: Genetic loci for Left and Right atrial measures.

Trait	RSID	chr	position	Coded Allele	Other Allele	CAF	Beta	SE	P	Gene
LAVImin	**rs147436345***	1	51664488	T	TTTTATTTATTTATTTATTTA	0.99	-0.19	0.034	3.60E-08	*LINC01562*
LAVImin	rs9685833*	4	111682944	G	A	0.20	0.05	0.008	2.44E-09	*LINC01438*
LAVImin	rs35216833	8	97223162	C	T	0.46	0.04	0.006	9.76E-09	*UQCRB*
LAVImin	rs9664170	10	92692047	T	A	0.42	-0.04	0.006	1.88E-09	*RNU6-740P*
LAVImin	**rs28456**	11	61589481	A	G	0.69	0.04	0.007	8.64E-11	*FADS1*
LAVImin	**rs2585035**	15	65496475	T	G	0.37	0.04	0.006	1.45E-08	*CILP*
LAVImin	rs3810333	19	46318691	T	C	0.61	0.04	0.007	3.04E-08	*SYMPK*
LAVImin	rs133902*	22	26164079	C	T	0.56	-0.04	0.006	2.79E-11	*MYO18B*
LAVImax	**rs72858515***	1	10704547	A	T	0.96	0.10	0.016	1.17E-10	*CASZ1*
LAVImax	4:111697815_TG_T*	4	111697815	TG	T	0.80	-0.04	0.008	3.14E-08	*LINC01438*
LAVImax	rs12656497	5	32831939	T	C	0.40	-0.03	0.006	4.19E-08	*NPR3*
LAVImax	**rs12190287**	6	134214525	C	G	0.63	-0.04	0.006	6.15E-10	*TCF21*
LAVImax	**rs17681427**	8	8462368	A	G	0.83	0.05	0.008	3.42E-08	*RN7SL178P*
LAVImax	**rs34389718**	8	9065525	A	G	0.61	0.04	0.006	7.11E-09	*AC022784.1*
LAVImax	**rs3808604**	8	10698227	A	T	0.69	0.04	0.007	6.77E-09	*AC011008.1*
LAVImax	**rs2645457***	8	11614112	T	G	0.42	0.04	0.006	1.85E-09	*GATA4*
LAVImax	**rs28456**	11	61589481	A	G	0.69	0.04	0.007	3.16E-11	*FADS1*
LAVImax	**rs78341827***	15	73401141	C	G	0.96	-0.09	0.016	3.12E-08	*NEO1*
LAVImax	rs133873*	22	26156505	T	A	0.77	-0.04	0.007	4.08E-08	*MYO18B*
LAEF	rs10801991*	1	116309438	T	G	0.66	-0.05	0.006	8.18E-13	*CASQ2*
LAEF	rs35487382*	9	97585788	A	G	0.58	0.03	0.006	4.65E-08	*AOPEP*
LAEF	rs10748555	10	92682060	C	A	0.49	-0.03	0.006	1.51E-08	*RNU6-740P*
LAEF	rs2681038	15	65497849	A	G	0.37	-0.04	0.006	4.27E-10	*CILP*
LAEF	rs10421891	19	46315809	A	G	0.64	0.04	0.006	9.64E-11	*RSPH6A*
LAEF	rs133885*	22	26159289	G	A	0.55	0.05	0.006	1.73E-15	*MYO18B*
RAVImin	rs12465459*	2	179672711	T	C	0.34	-0.05	0.006	5.75E-13	*TTN*
RAVImin	**rs6441111**	3	156821808	C	T	0.52	-0.03	0.006	9.76E-09	*LINC00880*
RAVImin	rs4868243*	5	172643118	G	A	0.84	-0.05	0.008	4.65E-11	*RPL7AP33*
RAVImin	rs12210733*	6	118653075	G	A	0.95	0.10	0.013	9.09E-13	*SLC35F1*

RAVImin	**rs798560**	7	2758309	A	G	0.71	0.04	0.007	2.45E-08	*AMZ1*
RAVImin	**rs12542381**	8	10427495	C	G	0.77	0.04	0.007	9.14E-09	*PRSS55*
RAVImin	rs112852637	8	32413240	T	C	0.53	-0.04	0.006	1.11E-12	*NRG1*
RAVImin	**rs11786896**	8	145018354	C	T	0.95	-0.09	0.014	4.65E-10	*PLEC*
RAVImin	**rs34005679***	10	112458010	T	TC	0.45	-0.04	0.006	2.23E-09	*RBM20*
RAVImin	**rs138893640**	12	101498230	C	T	0.99	0.19	0.035	4.75E-08	*ANO4*
RAVImin	rs4766734*	12	115155121	T	A	0.65	0.04	0.006	6.33E-12	*AC026765.3*
RAVImin	**15:98260531_TC_T**	15	98260531	TC	T	0.57	0.04	0.006	3.11E-11	*LINC00923*
RAVImin	**rs851058**	17	41837719	G	A	0.57	-0.03	0.006	2.29E-08	*SOST*
RAVImin	**19:38721268_AAAGAG_A**	19	38721268	AAAGAG	A	0.47	0.03	0.006	2.74E-08	*DPF1*
RAVImin	rs56096557	19	46310895	A	C	0.65	-0.04	0.006	1.54E-11	*RSPH6A*
RAVImax	rs12465459*	2	179672711	T	C	0.34	-0.04	0.006	2.49E-09	*TTN*
RAVImax	**rs2277923***	5	172662024	T	C	0.70	-0.04	0.007	2.31E-09	*NKX2-5*
RAVImax	**rs3951016***	6	118559658	T	A	0.53	0.04	0.006	5.12E-10	*SLC35F1*
RAVImax	rs150386926	8	32412419	A	AGACT	0.56	-0.04	0.006	1.62E-09	*NRG1*
RAVImax	**rs138893640**	12	101498230	C	T	0.99	0.19	0.035	2.11E-08	*ANO4*
RAVImax	**12:115162091_GTGTGCCCC_G***	12	115162091	GTGTGCCCC	G	0.62	0.04	0.006	1.10E-08	*AC026765.3*
RAVImax	**rs17631783**	17	61687600	C	T	0.74	-0.04	0.007	8.57E-10	*AC046185.2*
RAEF	**rs146170154***	6	36646768	C	CTA	0.80	-0.04	0.008	4.77E-09	*CDKN1A*
RAEF	**rs770537744***	10	112573688	CAG	C	0.89	0.06	0.010	3.70E-09	*RBM20*
RAEF	rs412768*	14	23866713	A	G	0.69	0.05	0.006	4.25E-15	*MYH6*
RAEF	rs2854300	19	46274392	G	C	0.96	-0.08	0.015	8.42E-09	*DMPK*

Variants with $p < 5 \times 10^{-8}$ from the right and left atrial GWAS are shown. The index variants are identified for each locus by iteratively taking the variant with the lowest p-value and excluding other variants within a 500kb window. The nearest genes were annotated using GENCODE v26. Loci associated with atrial fibrillation from prior GWAS within 500kb of our results are indicated via asterisk *. Novel loci (not within 500kb of previously reported studies) identified in association with left and right atrial structure and function are in bold. Beta indicates the regression coefficient. Abbreviations: chr, chromosome; position, hg19 position; CAF, coded allele frequency in the UK Biobank cohort; SE, standard error of effect size.

SUPPLEMENTAL MATERIAL

Supplemental Tables 1-8 and Figures 1-3

Supplemental Tables 9-16 are attached separately.

Supplement Methods 1. CMR Protocol and Quality Control of the Atrial Measures.

In the UK Biobank Imaging Study CMR Protocol, cardiac volume and function parameters were obtained through three long-axis cines and complex short-axis stacks of balanced, steady-state free precession cines.[42] The first 5,065 CMR scans were manually reviewed and annotated in two laboratories located in Oxford and London.[18] Bai et al. developed a fully automated, quality-controlled pipeline to facilitate the large-scale derivation of measures of cardiac structure and function from CMR images.[51] The pipeline was trained using a dataset of manually annotated CMR images, which were then converted into NIfTI format for storage. The dataset was split into training, validation, and test cohorts, and a fully convolutional network was employed to learn the CMR image features through a series of convolutions, ultimately leading to automated image segmentation.[52] The accuracy of these automated methods has been evaluated quantitatively by various technical metrics (Dice metric, contour distance metrics, and Hausdorff distance) and qualitatively by clinical experts.[51] This algorithm is publicly available to the research community and has been used in published studies.[53]

We applied this fully convolutional network to all CMR scans conducted during the first imaging visit available as of October 8, 2023, to obtain left atrial minimal volume, left atrial maximal volume, right atrial minimal volume, and right atrial maximal volume. Images from the first visit CMR studies were acquired from April 2014 to May 2023. Left atrial volumes were indexed to body surface area to obtain left atrial indexed minimal volume ($LAVI_{min}$) and left atrial indexed maximal volume ($LAVI_{max}$). Right atrial volumes were indexed to body surface area to obtain right atrial indexed minimal volume ($RAVI_{min}$) and right atrial indexed maximal volume ($RAVI_{max}$). Left atrial ejection fraction (LAEF) and right atrial ejection fraction (RAEF) were calculated through the following formula: [(maximal volume – minimal volume/maximal volume) *(100)]. We then manually reviewed images when estimated measurements were biologically implausible and identified threshold values for these measurements that were excluded from further analyses.

Since it is not feasible to manually review over 50,000 CMR images, quality control (QC) efforts were focused on assessing the outliers to improve the reliability of the automated measurements. QC metrics were focused on LA and RA traits: LA minimal volume, LA maximal volume, LA ejection fraction, RA minimal volume, RA maximal volume, and RA ejection fraction. To start, the 10 highest and 10 lowest measurements for each trait were visually inspected to ensure quality. The segmented atria passed through the QC metric if the structure was clearly visible at the frame that the measurement was obtained, there was no evidence of image fragmentation interfering with the measurement, and there was no incorrect registration of another structure (i.e., the aorta) occurring in place of the atria. This process was performed in 1-mL or 1-percentile increments. After a multidisciplinary discussion weighing the risks and benefits of over- or under-exclusion, we set the QC metric at 50% of the values in each increment that passes QC. Based on this rigorous protocol, we established thresholds for inclusion in our study: LA minimal volume > 8 mL, LA maximal volume > 24 mL, RA minimal volume > 7 mL, and RA maximal volume > 23 mL.

Next, we used the QC-approved volumetric measurements to re-calculate atrial ejection fractions according to this formula: [(maximal volume – minimal volume) / (maximal volume)] * 100 and applied the same QC protocol to the resulting ejection fraction values. This resulted in the inclusion of LA ejection fraction ≤86% and RA ejection fraction ≤83.5%. To validate our QC process, we then randomly sampled 50 measurements for each trait and visually inspected each image to verify accuracy. This validation process revealed >95% accuracy for the randomly sampled RA and LA values, which can be used in future analyses.

Supplemental Methods 2. Outcomes Measures.

Outcome events were identified through self-report at nurse interviews (all in-center visits) and/or hospital admission codes, death register cause of death codes, and UK Biobank first occurrence data. The UK Biobank first occurrence data utilizes the first 3-characters of the ICD-10 codes and includes primary care, hospitalization, death, and self-report sources. All-cause dementia events were identified using the UK Biobank's algorithmically defined outcomes.[54]

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Atrial Fibrillation	**Self-report codes:** 1471, 1483 **ICD-9 codes:** 427.3 **ICD-10 code**: I48 **First occurrence code:** I48
Ischemic Stroke	**ICD-9 codes:** 433, 434, 436 **ICD-10 codes:** I63, I64
Heart Failure	**ICD-9 codes:** 428 **ICD-10 codes**: I50, I110, I1130 **First occurrence code**: I50
Dementia	**Self-report codes:** 1263 **ICD-9 codes**: 290.2,2 90.3, 290.4, 291.2, 294.1, 331.0, 331.1, 333.2, 331.5 **ICD-10 codes:** A81.0, F00, F00.0, F00.1, F00.2, F00.9, F01, F01.0, F01.1, F01.2, F01.3, F01.8, F01.9, F02, F02.0, F02.1, F02.2, F02.3, F02.4, F02.8, F03, F05.1, F10.6, G30, G30.1, G30.8, G30.9, G31.0, F31.8

Supplemental Methods 3. Genetic analyses and Mendelian randomization methodology

Genome-Wide Association Studies (GWAS)

We conducted discovery GWAS for each atrial trait: $LAVI_{min}$, $LAVI_{max}$, LAEF, $RAVI_{min}$, $RAVI_{max}$, and RAEF. Individuals with prevalent AF or who were outliers for heterozygosity were excluded from analyses. Analyses were performed using a linear mixed model to account for relatedness using the GENESIS package.[55] To improve statistical power and control for Type I errors with a non-normal phenotype distribution, we implemented a fully adjusted two-stage procedure for rank normalization when fitting the null model.[56] The residuals from a regression model adjusted for age at the imaging visit sex, ten principal components of ancestry, UK BiLEVE or UK Biobank Axiom array, and imaging center were rank-normalized. In a second step, those transformed residuals were fit in a null model, adjusting for the same fixed effects and a sparse genetic relationship matrix (GRM). The GRM was constructed from the KING kinship coefficients limited to third-degree relatives from the UK Biobank.[23] The resulting null model was used to perform genome-wide score tests of genetic association for all individual variants with minor allele frequency > 0.005. All GWAS were also repeated only in individuals of European ancestry for use in additional genetics analyses. We used genomic control factor lambda and the regression intercept from LD score regression (LDSC) v1.0.1 to assess inflation due to population stratification or polygenicity.[57,58] We estimated the trait heritability (h^2) using the LDSC regression slope.

To allow us to evaluate the genetic correlation of atrial traits with left ventricular traits, we performed GWAS of left ventricular mass (LVM) and left ventricular ejection fraction (LVEF), as derived from the Bai et al. segmentation method.[51] LVM was indexed to body surface area (LVMi). Analyses were restricted to individuals of European ancestry and variants with a minor allele frequency > 0.005. GWAS analyses used the methods described above, adjusting for age at imaging visit sex, ten principal components of ancestry, UK BiLEVE or UK Biobank Axiom array, and imaging center.

For each GWAS, we identified index variants for each locus by iteratively taking the variant with the lowest p-value and excluding other variants within a 500 kilobase (kb) window. The nearest genes were annotated using GENCODE v26.[59]

Genetic Trait Correlations

We used LD score regression to estimate genetic correlations between atrial traits and related outcomes and risk factors using default settings, which leaves the intercept unconstrained. GWASs were restricted to individuals of European ancestry and limited to variants with minor allele frequencies > 0.01. Outcome trait GWASs used the largest available European ancestry meta-analyses for AF[25], ischemic and cardioembolic stroke[60], heart failure[61], Alzheimer's dementia[62], and type II diabetes.[63] Correlation for related traits and risk factors included body mass index[64], blood pressure[65], and PR interval.[66] Correlations with LVM and LVEF used GWAS we performed in the UK Biobank. To account for multiple testing, we defined significance using a false discovery rate (FDR) of 0.05 as calculated by the Benjamin-Hochberg method.

Overlap with Atrial Fibrillation GWAS and prior GWAS

Using the 142 independent genome-wide significant loci for AF reported by Neilson et al.,[25] we identified index variants from our GWAS of each atrial trait within 500kb of these AF variants. We also compared our findings with prior GWAS of atrial structure and function measures derived from prior CMR image analysis pipelines on smaller samples of UK Biobank participants.[26-28,67]

Druggability

The Functional Mapping and Annotation (FUMA) SNP2GENE platform was employed to annotate genome-wide significant variants ($p<5x10^{-8}$) for each trait and then map them to genes based on positional data.[68] The GENES2FUNC platform was subsequently used to assess druggability, which integrates information from DrugBank v5.1.4.[69]

Mendelian Randomization

To evaluate the potential causal relationships between left and right atrial traits and adverse clinical outcomes, we performed bidirectional two-sample Mendelian randomization (MR) analyses using

summary data from populations of European ancestry. First, we assessed the causal effects of $LAVI_{min,}$ $LAVI_{max}$, LAEF, $RAVI_{min}$, $RAVI_{max}$, and RAEF on the risk for AF, cardioembolic stroke, ischemic stroke, and heart failure (forward MR), using variant-imaging results from the GWAS we performed and variant-outcome results from the largest existing GWAS of each outcome (AF[25], ischemic stroke[60], cardioembolic stroke[60], heart failure[61], and Alzheimer's dementia[62]). In the forward MR analyses, genetic variants with $p<10^{-6}$ were selected as potential instruments; using the 1000 Genomes reference panel for linkage disequilibrium in those of European descent, a subset of independent instruments were selected using a clumping threshold of 0.001. To minimize horizontal pleiotropy, we excluded variants that were strongly associated with SBP, DBP, BMI, or type II diabetes; these cardiometabolic traits can impact both atrial size and cardiovascular outcomes. Specifically, variants were excluded if a Steiger directionality test indicated that they explained more variance in one of these traits than in the imaging trait of interest ($p < 0.05$). MR analyses using these instruments were conducted using a debiased inverse variance weighted method that assumes balanced pleiotropy.[70]

A similar approach was used to assess the causal effects of the clinical outcomes on the imaging measures (reverse MR). In the reverse MR analyses, instead of filtering by association with blood pressure, instruments were excluded if they were associated with AF ($p<5\times10^{-8}$) in analyses of other outcomes or if Steiger filtering favored association with imaging measures in analyses of AF. Since AF and individual variants can impact atrial measures, we excluded these variants to minimize the potential of reverse causation, rather than a true effect. Associations with a $p<0.010$ were considered statistically significant after Bonferroni correction for the number of outcomes (five).

Multivariable MR analyses were performed to examine the independent effects of left and right atrial measures on stroke outcomes while accounting for the effect of AF. For each atrial measure, variants with $p<10^{-6}$ for either the atrial measure or AF were selected for joint clumping at the 0.001 threshold. Multivariable MR of stroke outcomes using these instruments used a spectral regularized inverse variance weighted (SRIVW) estimator that assumes balanced pleiotropy.[71]

Supplemental Table 1: Cardiac Magnetic Resonance Imaging Atrial Measures

Exposures	Mean (SD)	Range (Min – Max)	*Men Ref LL-UL	*Women Ref LL-UL	Men Abnormal %	Women Abnormal %
$LAVI_{min}$ (mL/m^2)	16 (7)	3.3-19	3-24	4-23	11%	9.5%
$LAVI_{max}$ (mL/m^2)	38 (11)	10-45	17-59	17-61	6.2%	2.9%
LAEF (%)	61 (8)	10-86	46-77	48-78	5.8%	6.6%
$RAVI_{min}$ (mL/m^2)	24 (9)	3.2-29	5-32	6-24	25%	34%
$RAVI_{max}$ (mL/m^2)	46 (14)	10-53	15-61	16-54	18%	16%
RAEF (%)	47 (9)	11-83.5	32-68	38-74	6.6%	9.4%

*Reference LL to UL ranges were obtained from the Reference ranges (“normal values” for cardiovascular magnetic resonance (CMR) in adults and children: 2020 update through pooled weighted values.[72] The abnormal percentages were calculated as the percent of cohort values not within the reported reference LL-UL. Abbreviations: LL, lower limit; UL, upper limit; Max, Maximal; Min, Minimal; LAVI, Left Atrial Volume Indexed; LAEF, Left Atrial Ejection Fraction; RAVI, Right Atrial Volume Indexed; RAEF, Right Atrial Ejection Fraction; SD, standard deviation.

Supplemental Table 2: Associations of Left and Right Atrial Measures with Outcomes and Secondary Adjustment Variables.

	Atrial Fibrillation	Ischemic Stroke	Heart Failure	Dementia
Variable	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
$LAVI_{min}$ (mL/m^2)	**1.54(1.48-1.60)**	**1.26(1.16-1.38)**	**1.23(1.16-1.32)**	1.16(0.99-1.36)
$LAVI_{max}$ (mL/m^2)	**1.63(1.55-1.71)**	**1.19(1.05-1.34)**	**1.35(1.25-1.47)**	1.18(0.96-1.46)
LAEF (%)	**0.55(0.52-0.59)**	0.74(0.65-0.84)	**0.76(0.69-0.84)**	0.87(0.70-1.08)
$RAVI_{min}$ (mL/m^2)	**1.43(1.34-1.51)**	**1.17(1.02-1.36)**	**1.22(1.10-1.36)**	1.02(0.84-1.25)
$RAVI_{max}$ (mL/m^2)	**1.38(1.30-1.47)**	1.10(0.96-1.26)	**1.21(1.09-1.35)**	0.98(0.80-1.21)
RAEF (%)	**0.79(0.73-0.86)**	0.87(0.76-0.99)	0.92(0.82-1.02)	0.95(0.74-1.22)

Measures are reported per standard deviation increase in unit. Atrial fibrillation, ischemic stroke, and heart failure models were adjusted for primary model parameters plus Townsend index, CRP, and electrocardiographic measures of atrial cardiopathy (P-wave duration and PR interval). Dementia model was adjusted for primary model parameters plus history of ischemic stroke, history of heart failure, and history of myocardial infarction. Significant associations are bolded.

Supplemental Table 3: Associations of Left and Right Atrial Measures with Outcomes, adjusting for intercurrent Atrial Fibrillation events.

	Ischemic Stroke	Heart Failure	Dementia
Variable	HR (95% CI)	HR (95% CI)	HR (95% CI)
$LAVI_{min}$ (mL/m^2)	**1.27(1.18-1.37)**	**1.17(1.16-1.23)**	**1.21(1.03-1.42)**
$LAVI_{max}$ (mL/m^2)	**1.20(1.08-1.33)**	**1.29(1.21-1.38)**	1.22(1.00-1.49)
LAEF (%)	**0.71(0.64-0.79)**	**0.80(0.74-0.86)**	0.82(0.67-1.01)
$RAVI_{min}$ (mL/m^2)	**1.17(1.04-1.31)**	**1.17(1.08-1.26)**	1.04(0.82-1.31)
$RAVI_{max}$ (mL/m^2)	1.09(0.96-1.23)	**1.16(1.06-1.26)**	0.99(0.78-1.25)
RAEF (%)	**0.86(0.76-0.97)**	0.92(0.84-1.01)	0.91(0.73-1.15)

Measures are reported per standard deviation increase in unit. Models were adjusted for primary model parameters plus the presence of AF as a time-varying model during follow-up. Significant associations are bolded.

Supplemental Table 4: Effect Modification Testing for Incident Atrial Fibrillation.

	Men	Women	P-Value*	Age <65 years	Age ≥ 65 years	P-Value*
Variable	HR (95% CI)	HR (95% CI)		HR (95% CI)	HR (95% CI)	
$LAVI_{min}$ (mL/m^2)	1.49(1.42-1.56)	1.75(1.65-1.85)	<0.001	1.65(1.48-1.84)	1.54(1.48-1.60)	0.19
$LAVI_{max}$ (mL/m^2)	1.53(1.43-1.63)	1.77(1.64-1.92)	0.001	1.38(1.19-1.60)	1.64(1.56-1.74)	0.01
LAEF (%)	0.59(0.55-0.63)	0.47(0.42-0.53)	<0.001	0.56(0.48-0.64)	0.57(0.53-0.60)	0.48
$RAVI_{min}$ (mL/m^2)	1.38(1.29-1.48)	1.45(1.28-1.65)	0.11	1.33(1.14-1.54)	1.39(1.31-1.49)	0.67
$RAVI_{max}$ (mL/m^2)	1.32(1.12-1.42)	1.45(1.29-1.63)	0.03	1.23(1.07-1.42)	1.37(1.28-1.46)	0.17
RAEF (%)	0.76(0.69-0.85)	0.91(0.79-1.03)	0.09	0.81(0.67-0.95)	0.82(0.74-0.89)	0.58

Measures are reported per standard deviation increase in unit. Model was adjusted for age, sex, race, height, body mass index, systolic blood pressure, diastolic blood pressure, antihypertensive medication use, current smoking, prevalent diabetes, prevalent heart failure, and prevalent myocardial infarction. Interaction P-value* is reported for age and sex as binary variables.

Supplemental Table 5: Effect Modification Testing for Incident Ischemic Stroke.

	Men	Women	P-Value*	Age <65 years	Age ≥ 65 years	P-Value*
Variable	HR (95% CI)	HR (95% CI)		HR (95% CI)	HR (95% CI)	
$LAVI_{min}$ (mL/m^2)	1.27(1.14-1.41)	1.23(1.06-1.42)	0.96	1.16(0.91-1.48)	1.27(1.16-1.39)	0.55
$LAVI_{max}$ (mL/m^2)	1.16(0.98-1.38)	1.24(1.05-1.47)	0.47	1.17(0.91-1.51)	1.20(1.04-1.38)	0.96
LAEF (%)	0.73(0.61-0.86)	0.83(0.68-1.00)	0.55	0.94(0.75-1.17)	0.73(0.63-0.85)	0.07
$RAVI_{min}$ (mL/m^2)	1.20(1.00-1.42)	1.12(0.88-1.43)	0.82	1.22(0.93-1.61)	1.16(0.98-1.38)	0.94
$RAVI_{max}$ (mL/m^2)	1.09(0.92-1.30)	1.15(0.92-1.44)	0.66	1.18(0.89-1.56)	1.09(0.93-1.27)	0.54
RAEF (%)	0.82(0.69-0.97)	0.98(0.79-1.21)	0.18	0.89(0.72-1.11)	0.88(0.75-1.03)	0.87

Measures are reported per standard deviation increase in unit. Model was adjusted for age, sex, ethnicity, body mass index, systolic blood pressure, anti-hypertensive medication use, current smoking, prevalent diabetes, total cholesterol, and high-density lipoprotein levels. Interaction P-value* is reported for age and sex as binary variables.

Supplemental Table 6: Effect Modification Testing for Incident Heart Failure.

	Men	Women	P-Value*	Age <65 years	Age ≥ 65 years	P-Value*
Variable	HR (95% CI)	HR (95% CI)		HR (95% CI)	HR (95% CI)	
$LAVI_{min}$ (mL/m^2)	1.20(1.11-1.30)	1.41(1.28-1.56)	<0.001	1.33(1.07-1.65)	1.23(1.15-1.32)	0.22
$LAVI_{max}$ (mL/m^2)	1.31(1.19-1.44)	1.55(1.36-1.77)	<0.001	1.39(1.13-1.71)	1.36(1.25-1.48)	0.66
LAEF (%)	0.78(0.70-0.87)	0.71(0.59-0.85)	0.07	0.88(0.69-1.12)	0.76(0.68-0.84)	0.78
$RAVI_{min}$ (mL/m^2)	1.21(1.07-1.36)	1.24(1.00-1.54)	0.44	1.22(0.96-1.54)	1.21(1.08-1.36)	0.60
$RAVI_{max}$ (mL/m^2)	1.19(1.05-1.38)	1.29(1.05-1.60)	0.32	1.19(0.93-1.51)	1.22(1.08-1.37)	0.92
RAEF (%)	0.90(0.79-1.03)	0.99(0.82-1.21)	0.61	0.91(0.71-1.16)	0.94(0.83-1.06)	0.36

Measures are reported per standard deviation increase in unit. Model was adjusted for age, sex, race, systolic blood pressure, antihypertensive medication use, current smoking, prevalent diabetes, history of myocardial infarction, total cholesterol, high-density lipoprotein levels, and left ventricular ejection fraction. Interaction P-value* is reported for age and sex as binary variables.

Supplemental Table 7: Effect Modification Testing for Incident Dementia.

	Men	Women	P-Value*	Age <65 years	Age ≥ 65 years	P-Value*
Variable	HR (95% CI)	HR (95% CI)		HR (95% CI)	HR (95% CI)	
$LAVI_{min}$ (mL/m^2)	1.20(1.03-1.29)	1.18(0.88-1.60)	0.95	0.98(0.55-1.76)	1.20(1.03-1.39)	0.45
$LAVI_{max}$ (mL/m^2)	1.32(1.08-1.63)	1.06(0.72-1.56)	0.29	0.94(0.56-1.61)	1.23(0.99-1.52)	0.29
LAEF (%)	0.89(0.69-1.15)	0.79(0.55-1.14)	0.53	0.88(0.56-1.39)	0.85(0.68-1.07)	0.98
$RAVI_{min}$ (mL/m^2)	1.13(0.95-1.35)	0.84(0.51-1.38)	0.29	0.53(0.18-1.57)	1.08(0.89-1.31)	0.17
$RAVI_{max}$ (mL/m^2)	1.10(0.87-1.39)	0.79(0.55-1.16)	0.17	0.49(1.88-1.29)	1.04(0.85-1.27)	0.11
RAEF (%)	0.80(0.59-1.10)	1.08(0.73-1.58)	0.27	1.15(0.70-1.87)	0.91(0.69-1.19)	0.41

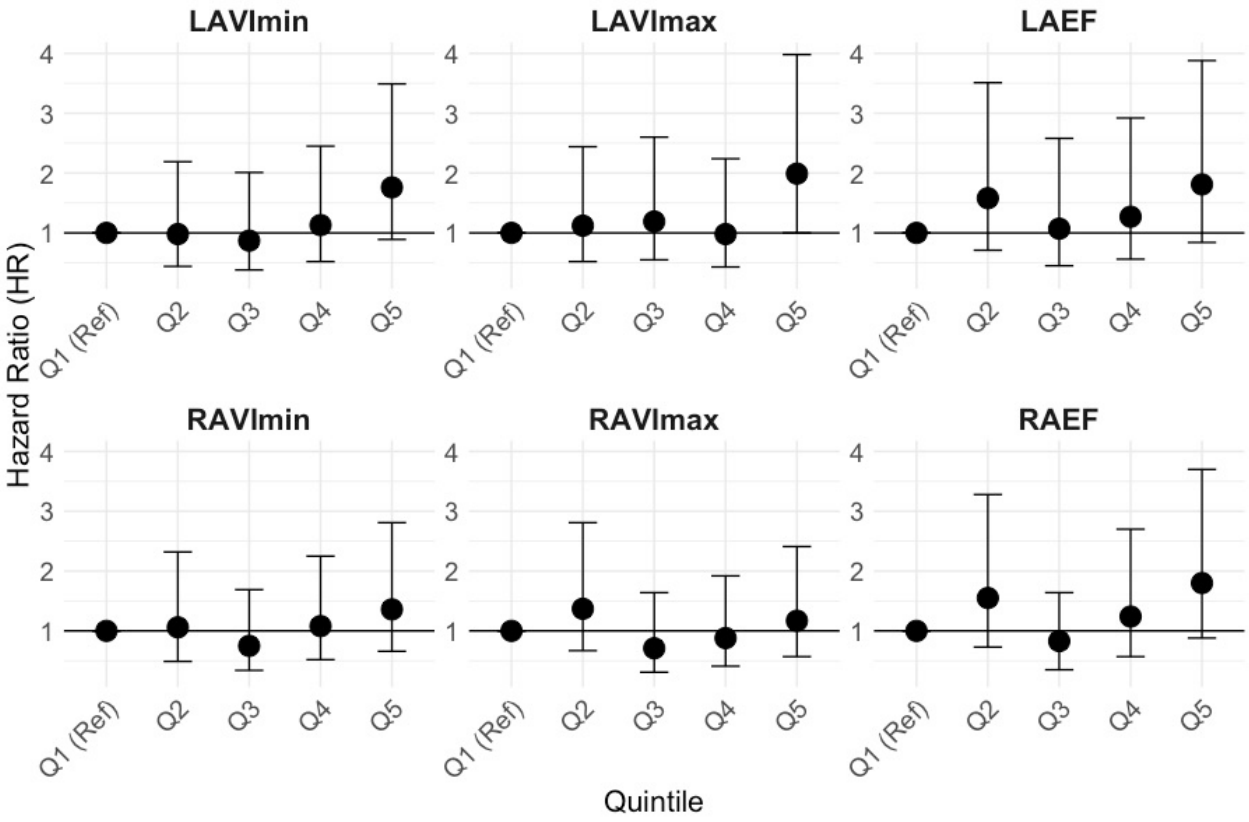
Measures are reported per standard deviation increase in unit. Model was adjusted for age, sex, race, body mass index, systolic blood pressure, antihypertensive medication use, current smoking, prevalent diabetes, Townsend index, and presence of APOE4 allele. Interaction P-value* is reported for age and sex as binary variables.

Supplemental Table 8: Heritability for Left and Right Atrial Measures

Trait	Lambda GC	h2 (SE)	Mean χ2	Ratio	Intercept
$LAVI_{min}$	1.11	0.12 (0.01)	1.13	0.08 (0.05)	1.01 (0.007)
$LAVI_{max}$	1.14	0.14 (0.02)	1.17	0.14 (0.05)	1.02 (0.009)
LAEF	1.09	0.09 (0.01)	1.1	0.03 (0.07)	1.00 (0.007)
$RAVI_{min}$	1.14	0.15 (0.01)	1.17	0.09 (0.04)	1.01 (0.007)
$RAVI_{max}$	1.16	0.16 (0.01)	1.18	0.08 (0.04)	1.01 (0.007)
RAEF	1.09	0.09 (0.01)	1.12	0.11 (0.06)	1.01 (0.007)

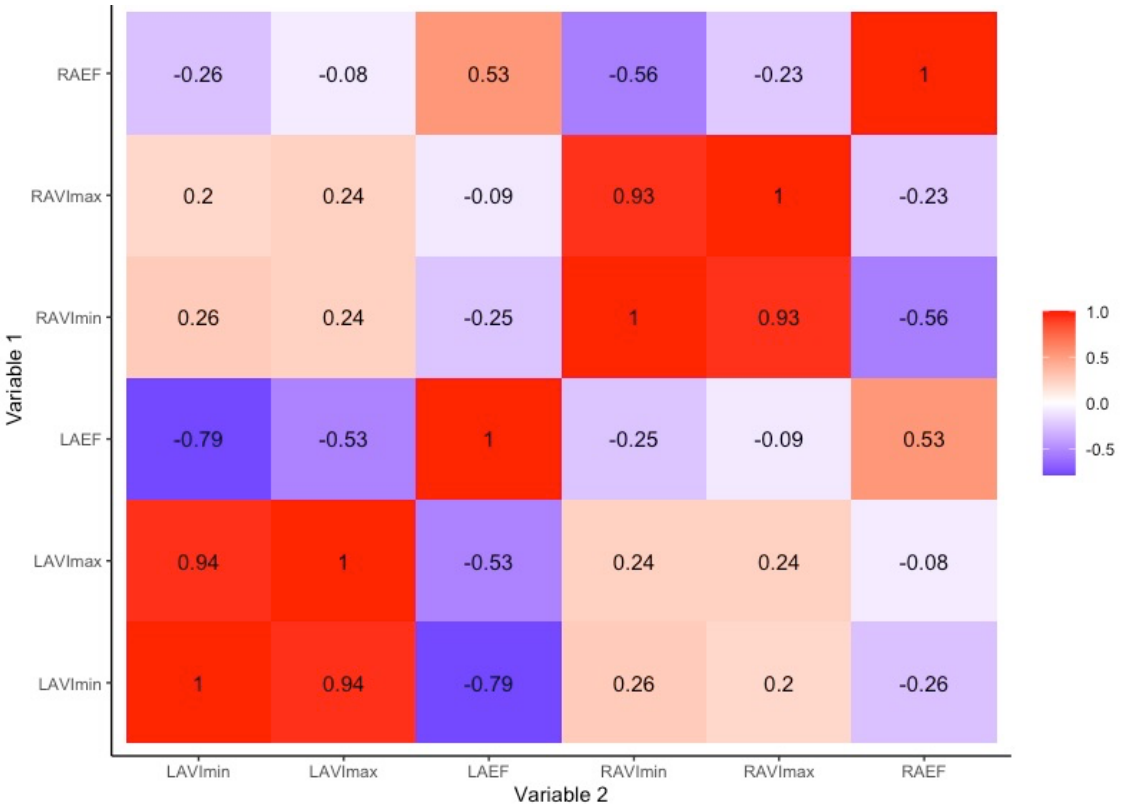
This table presents the genomic inflation factor and heritability estimates for each of the six atrial traits.

Supplemental Figure 1. Associations of Left and Right Atrial Measures as Quintiles with Incident Dementia.



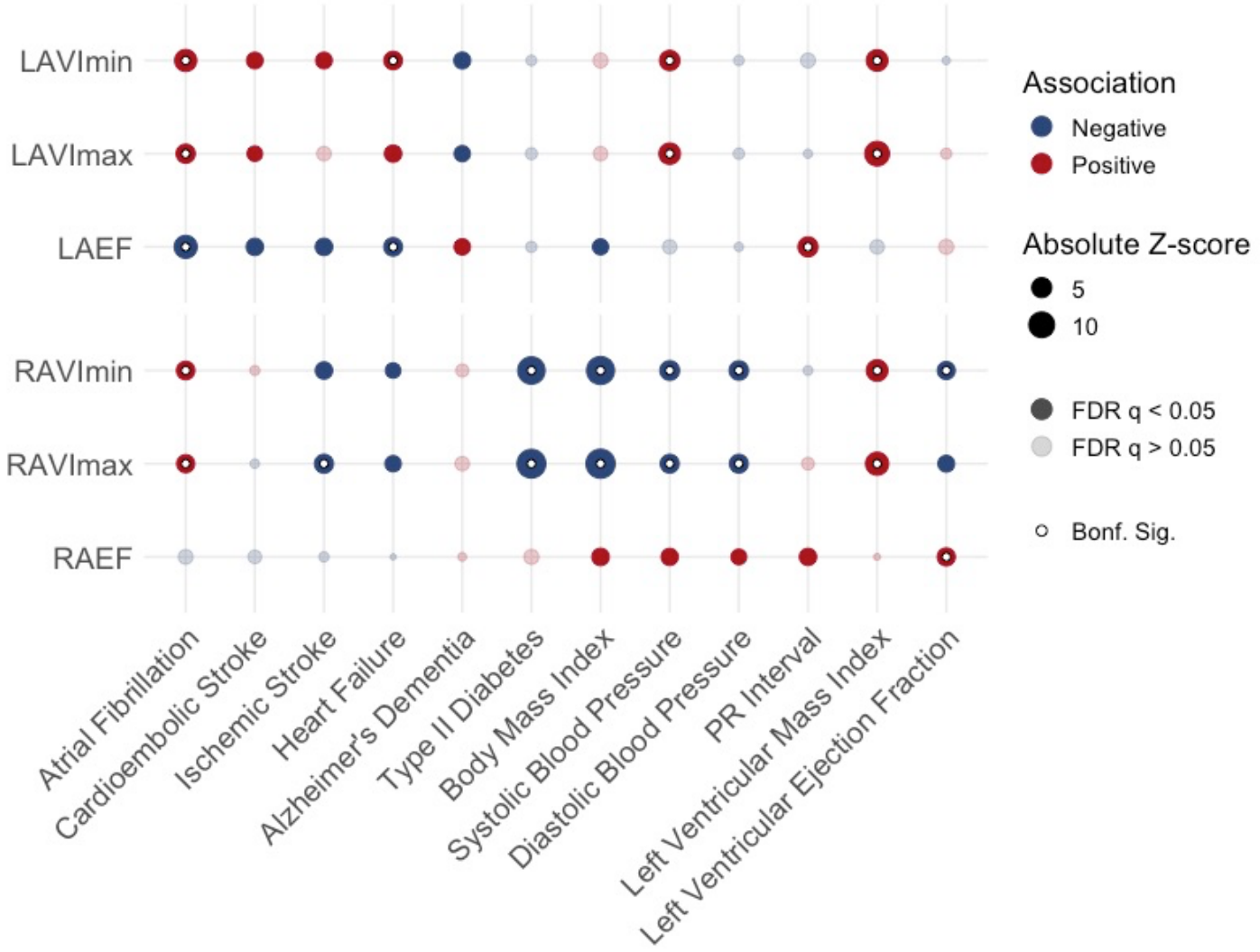
The highest quintile values of left atrial volume and right atrial volume measures were compared to a reference of the lowest quintile. The lowest quintile values of left atrial ejection fraction and right atrial ejection fraction were compared to a reference of the highest quintile. Model was adjusted for age, sex, race, body mass index, systolic blood pressure, antihypertensive medication use, current smoking, prevalent diabetes, Townsend index, and presence of APOE4 allele. Abbreviations: Q; quintile.

Supplemental Figure 2: Genetic Correlations of Atrial Measures



Heatmap of left and right atrial structure and function measure genetic correlations. Positive correlations are shown in red, with negative correlations in purple.

Supplemental Figure 3: Genetic Correlation of atrial measures with cardiovascular disease and risk factors



LD score regression was used to evaluate the genetic correlation between atrial traits, cardiovascular outcomes, and cardiovascular risk factors. The size of the bubble represents the absolute Z-score for each trait. Negative cross-trait associations are in blue, while positive cross-trait associations are in red. Outcomes and phenotypes with a significant correlation after Bonferroni correction contain a white core. Outcomes and phenotypes with a significant correlation after controlling for the false discovery rate (FDR) are saturated (dark), while insignificant correlations are in greyscale.

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