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ORIGINAL RESEARCH

Left Atrial Function and Arrhythmias in Relation to Small Vessel Disease on Brain MRI: The Multi-Ethnic Study of Atherosclerosis

Thomas R. Austin, PhD; Paul N. Jensen, PhD; Ilya M. Nasrallah, MD, PhD; Mohamad Habes, PhD; Tanweer Rashid, PhD; Jeffrey B. Ware, MD; Lin Yee Chen, MD, MS; Philip Greenland, MD; Timothy M. Hughes, PhD; Wendy S. Post, MD, MS; Steven J. Shea, MD, MS; Karol E. Watson, MD, PhD; Colleen M. Sitlani, PhD; James S. Floyd, MD, MS; Richard A. Kronmal, PhD; W. T. Longstreth Jr, MD, MPH; Alain G. Bertoni, MD, MPH; Sanjiv J. Shah, MD; R. Nick Bryan, MD, PhD; Susan R. Heckbert, MD, PhD

BACKGROUND: Atrial fibrillation (AF) is associated with increased stroke risk and accelerated cognitive decline, but the association of early manifestations of left atrial (LA) impairment with subclinical changes in brain structure is unclear. We investigated whether abnormal LA structure and function, greater supraventricular ectopy, and intermittent AF are associated with small vessel disease on magnetic resonance imaging of the brain.

METHODS AND RESULTS: In the Multi-Ethnic Study of Atherosclerosis, 967 participants completed 14-day ambulatory electrocardiographic monitoring, speckle tracking echocardiography and, a median 17 months later, magnetic resonance imaging of the brain. We assessed associations of LA volume index and reservoir strain, supraventricular ectopy, and prevalent AF with brain magnetic resonance imaging measures of small vessel disease and atrophy. The mean age of participants was 72 years; 53% were women. In multivariable models, LA enlargement was associated with lower white matter fractional anisotropy and greater prevalence of microbleeds; reduced LA strain, indicating worse LA function, was associated with more microbleeds. More premature atrial contractions were associated with lower total gray matter volume. Compared with no AF, intermittent AF (prevalent AF with <100% AF during electrocardiographic monitoring) was associated with lower white matter fractional anisotropy (−0.25 SDs [95% CI, −0.44 to −0.07]) and greater prevalence of microbleeds (prevalence ratio: 1.42 [95% CI, 1.12–1.79]).

CONCLUSIONS: In individuals without a history of stroke or transient ischemic attack, alterations of LA structure and function, including enlargement, reduced strain, frequent premature atrial contractions, and intermittent AF, were associated with increased markers of small vessel disease. Detailed assessment of LA structure and function and extended ECG monitoring may enable early identification of individuals at greater risk of small vessel disease.

Key Words: atrial fibrillation ■ brain magnetic resonance imaging ■ left atrium ■ white matter injury

Atrial fibrillation (AF) is an important risk factor for stroke[1,2] and is associated with accelerated cognitive decline.[3,4] However, emerging consensus suggests that atrial cardiomyopathy[5] itself, even in the absence of AF, may be causally related to stroke, cognitive decline, and dementia.[6] Yet relatively little is known about the association of measures of left atrial (LA) impairment with subclinical abnormalities on brain

Correspondence to: Thomas R. Austin, PhD, Department of Epidemiology, University of Washington, 1730 Minor Ave, Suite 1360, Seattle, WA 98101. Email: austintr@uw.edu

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CLINICAL PERSPECTIVE

What Is New?

- The association of early manifestations of left atrial (LA) impairment with subclinical changes in brain structure is unclear.
- Our study investigated whether abnormal LA structure and function, greater supraventricular ectopy, and intermittent atrial fibrillation are associated with small vessel disease on magnetic resonance imaging of the brain.
- Our analysis found that early manifestations of LA abnormalities, including enlargement and abnormal function, were associated with small vessel disease markers of reduced white matter microstructural integrity and the presence of microbleeds.
- Participants with intermittent atrial fibrillation had more evidence of small vessel disease than those without atrial fibrillation.

What Are the Clinical Implications?

- Alterations of LA structure and function were associated with increased markers of small vessel disease.
- Early assessment of LA structure and function, including electrocardiographic monitoring, may identify individuals at risk of small vessel disease and facilitate intervention.

Nonstandard Abbreviations and Acronyms

CABL	Cardiovascular Abnormalities and Brain Lesions
FA	fractional anisotropy
GM	gray matter
MESA	Multi-Ethnic Study of Atherosclerosis
QSM/SWI	quantitative susceptibility mapping/susceptibility weighted imaging
SVE	supraventricular ectopy
SVT	supraventricular tachycardia
WM	white matter
WMH	white matter hyperintensity

magnetic resonance imaging (MRI). Studies of AF in relation to brain MRI findings have not examined separately AF that occurs infrequently or is subclinical. We hypothesized that markers of LA abnormality (namely, abnormal LA function, greater supraventricular ectopy [SVE], and low-burden AF) are associated with markers of small vessel disease on brain MRI that are closely associated with cognitive impairment, dementia, and stroke.[7,8] Additionally, because gray matter (GM) loss is a late manifestation of small vessel disease,[9] we hypothesized that these manifestations of LA abnormality are also associated with reduced GM volume.

In MESA (Multi-Ethnic Study of Atherosclerosis) Atrial Fibrillation ancillary study, participants with 14 to 18 years of close follow-up for clinical cardiovascular disease completed extended ambulatory electrocardiographic monitoring and speckle-tracking echocardiography. After a median interval of 17 months, they completed MRI of the brain. We analyzed associations of echocardiography-derived measures of LA structure and function, SVE quantified by ambulatory monitoring, and AF detected either clinically or by monitoring, with brain volumes and MRI measures of small vessel disease.

METHODS

The data used in this analysis are available through the MESA Coordinating Center with an approved paper proposal.

Study Population

MESA is an observational cohort study of subclinical cardiovascular disease that includes 6814 men and women 45 to 84 years of age and initially free of clinically recognized cardiovascular disease when enrolled at 6 field centers (Baltimore, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles County, California; New York, New York; and St. Paul, Minnesota). Study details have been reported previously.[10] The baseline examination for MESA occurred between 2000 and 2002, and 5 follow-up examinations have been performed, including Exam 6 in 2016 to 2018. During Exam 6, almost all participants had echocardiography, and a subset of 1942 participants was invited to participate in the Atrial Fibrillation ancillary study, involving extended ambulatory ECG rhythm monitoring[11] in 2016 to 2018, followed by MRI of the brain in 2018 to 2019. Each field center obtained Institutional Review Board approval, and all participants provided written informed consent.

Echocardiography Measures

Resting 2-dimensional and speckle-tracking echocardiography was performed at Exam 6 (2016–2018) at each field center by trained sonographers.[12] LA volume was measured using the biplane method of disks from apical 4- and 2-chamber views. LA volume index was defined as maximum biplane LA volume divided by body surface area.[13] Enlarged LA volume index reflects impaired LV diastolic function.[14] Speckle-tracking echocardiography of the LA was performed by an experienced sonographer blinded to other clinical data using GE EchoPAC software; strain curves were verified by 2

cardiologists. The endocardial border of each cardiac chamber was traced, and regions of interest spanning epicardium to endocardium were defined. LA reservoir strain, defined as the sum of booster and conduit strain, was used in this analysis; lower strain values correspond to worse LA function.

Ambulatory ECG Measures

Ambulatory ECG monitoring was performed with the Zio Patch XT (iRhythm Technologies, Inc, San Francisco, CA), a single-channel patch monitor capable of recording up to 14 days of continuous cardiac rhythm. Study staff applied the monitor and asked the participant to wear it for 14 days and to return it by mail to the manufacturer for interpretation. A subset of participants had 2 monitoring periods of up to 14 days each, with a median interval of 23 days between monitoring periods.[11] All arrhythmias reported by the manufacturer were verified by the Epidemiological Cardiology Reading Center at Wake Forest University School of Medicine, Winston-Salem, NC.

The rate of premature atrial contractions (PACs) was expressed as the average rate of PACs per hour. A run of supraventricular tachycardia (SVT) was defined as ≥4 consecutive PACs and expressed as the average rate of runs of SVT per 24 hours.[15] AF on the monitor was identified as an irregularly irregular rhythm lasting at least 30 seconds, as previously described.[11] The AF burden was defined as the percent of monitoring time during which a participant was in AF, including both AF and atrial flutter.

Clinical AF was identified from study of 12-lead ECGs at the 2000 to 2002 and 2010 to 2012 MESA examinations; from *International Classification of Diseases, Ninth or Tenth Revision* (*ICD9*; *ICD-10*) hospital discharge diagnosis codes identified through MESA hospitalization follow-up; for participants enrolled in fee-for-service Medicare, from inpatient, outpatient, or carrier claims[16]; and by self-report at Exam 6 of a physician diagnosis of AF.

For analyses, prevalent AF was defined as a history of clinical AF or monitor-detected AF at Exam 6 and was further categorized as continuous or intermittent AF. Participants with 100% AF burden during ambulatory monitoring were classified as having continuous AF. Participants with a history of clinical AF who did *not* have 100% AF burden during ambulatory ECG monitoring, including those with no AF during monitoring, were classified as having intermittent AF. We did not use the terms paroxysmal, persistent, and permanent AF because the medical record information available on MESA participants did not permit this clinical classification.

Brain MRI Measures

Brain MRI scans were acquired on 3-Tesla Siemens scanners. Imaging included 1-mm isotropic sagittal 3D T1-weighted, T2-weighted, fluid attenuated inversion recovery (FLAIR), axial 2D echo-planar diffusion-tensor imaging, and axial 3D multi-echo quantitative susceptibility mapping/susceptibility weighted imaging, as previously described.[17] Brain MRI variables of primary interest for the present analysis were 3 measures of small vessel disease: white matter (WM) fractional anisotropy (FA), WM hyperintensity (WMH) volume, and microbleeds; and 1 measure of atrophy, total GM volume. Secondary variables were total brain volume and total WM volume. FA reflects the degree to which water diffusion is limited to a single dimension and is a scalar, ranging from 0, indicating equivalent motion in all directions, to 1, indicating motion restricted to a single direction. Decreased WM FA is interpreted as indicating reduced WM microstructural integrity, which is a feature of small vessel disease. Microbleeds were initially identified by a deep learning-based segmentation method that used T2-weighted images and quantitative susceptibility mapping/susceptibility weighted imaging to segment the lesions and to differentiate microbleeds from iron deposits.[18] Identified lesions were then reviewed by a radiologist (J.B.W.) who made the final classification. The 99th percentile of the total microbleed count distribution was 12 microbleeds. In the primary analysis, the 8 participants with 12 to 112 microbleeds (74% lobar) were considered to have outlying values and were excluded.

Participant Characteristics

Data on age, sex, self-reported race and ethnicity, and educational attainment were collected at baseline (2000–2002). Other risk factor data were collected at Exam 6 (2016–2018), including family income, height, weight, blood pressure, smoking status, glucose, hemoglobin A1c, and creatinine levels, medication use, and diabetes status (Data S1). Mean neighborhood socioeconomic status between baseline exam and Exam 5 (2010–2012) was calculated from American Community Survey 2005 to 2009 and 2007 to 2011 estimates[19] reflecting education, employment, housing, household income, and wealth, as described elsewhere.[20] Participants reported new hospitalizations and diagnoses at telephone contacts every 9 to 12 months during follow-up. Medical records were obtained and myocardial infarction, heart failure, stroke, and transient ischemic attack were adjudicated through 2017 as previously described.[10,21,22] Participants were excluded from this analysis if they had a clinical history of stroke or transient ischemic attack before Exam 6.

Statistical Analysis

We performed relative risk regression using a Poisson model[23] to examine associations with presence of any microbleeds. We used linear regression to examine

associations with total WMH volume, mean WM FA, microbleed count among those with ≥1 microbleed, and total GM volume. Because of their skewed distributions, rates of PACs and SVT were $\log_2$ transformed, and regression estimates represent differences in outcomes per doubling of PACs and SVT. All multivariable models were adjusted for age, sex, MESA field center, race and ethnicity, body mass index, smoking status, cigarette pack-years, systolic and diastolic blood pressure, treated hypertension, high-density lipoprotein and low-density lipoprotein cholesterol, use of cholesterol medications, diabetes status, estimated glomerular filtration rate, educational attainment, income, and neighborhood socioeconomic status. Covariates were chosen a priori based on their associations with atrial arrhythmias and measures of brain structure and small vessel disease.[17] Analyses of AF as an exposure were adjusted for health insurance status because clinical AF detection may depend upon health care access. Analyses of brain volumes were adjusted for total intracranial volume. We used variance inflation factors to investigate the potential for bias caused by multicollinearity in these models.

Total WMH volume and microbleed count had right-skewed distributions and were log-transformed to minimize the influence of large values. Regression results for WMH volume and microbleed count are expressed as the percent difference in the brain MRI measure per increment of the exposure. FA was expressed as a *z*-score (in units of SD) to aid in interpretation of results.

In secondary analyses, we used linear regression to assess the associations of echocardiographic LA measures, SVE, and AF with total brain volume and total WM volume. In sensitivity analyses, we excluded participants with prior myocardial infarction or heart failure, or those taking oral anticoagulants at Exam 6. We adjusted for alcohol consumption in addition to our main models. We ran analyses including 8 participants with 12 or more microbleeds who were excluded from the main analysis. We further examined models for evidence of nonlinearity using splines and assessed whether associations differed in subgroups defined by sex or race and ethnicity. Missing values in any covariate (<2% missing for all covariates except 4.1% missing for family income) were imputed using multiple imputation with chained equations. Stata 14 software (StataCorp, College Station, TX) was used for the analysis, and a 2-sided *P* value≤0.05 was considered statistically significant.

RESULTS

Participant Characteristics

A total of 1535 MESA participants completed ≥24 hours of ambulatory ECG monitoring with a median (interquartile range) monitoring duration of 14.0 (13.5, 26.1) days. Among these participants, 1010 completed the MRI of the brain a median (interquartile range) of 17 (15–19) months later, and 967 were free of a prior history of stroke or transient ischemic attack and had MRI images of the brain that met quality control criteria (Figure 1). Characteristics at Exam 6 of these 967 participants are described in Table 1. Participants had a mean age of 72 years (SD, 8), and 53% were women. Self-identified race and ethnicity was 26% Black, 12% Chinese-American, 22% Hispanic, and 40% White. Characteristics of MESA participants who attended Exam 6 but were not included in the analysis sample are also presented in Table 1. Nonparticipants were slightly older, and a larger proportion had prevalent cardiovascular disease. Of the 967 participants with ECG monitoring and brain MRI data, 915 with complete echocardiography data and not in AF at the time of echocardiography were included in the analyses of LA volume and strain (Figure 1).

The LA and arrhythmia measures are presented in Table 2. We identified 116 participants (12%) with prevalent AF at Exam 6. Twenty had 100% AF burden during ambulatory monitoring and were categorized as having continuous AF. Among the remaining 96, categorized as having intermittent AF, 65 had a history of AF but no AF on the monitor. Among the remaining 31 with AF on the monitor, the median (interquartile range) AF burden was 0.95 (0.1, 4.9) %. Prevalent AF was identified by *ICD* codes in 59 participants, by self-report in 57 participants, and by ambulatory monitoring in 51. Thirteen participants had AF identified through all 3 methods, 27 only through *ICD* codes, 23 only through self-report, and 29 only through ambulatory monitoring. Twenty participants, 14 of whom had prevalent AF, were on oral anticoagulants at Exam 6. Only 12% of participants with prevalent AF were on oral anticoagulants, 40% of those with continuous AF and 6% of those with intermittent AF.

Summary measures for brain MRI outcomes are presented in Table S1. Briefly, mean total intracranial volume was 1359 mL (SD, 146), and total GM volume was 597 mL (SD, 66). Mean WMH volume was 6.6 mL (SD, 10.1), and mean WM FA was 0.39 (SD, 0.03). A total of 313 (32%) participants had microbleeds detected, and among those participants, the mean number of microbleeds was 2.1 (SD, 1.8). Deep microbleeds (located in the basal ganglia, thalamus, internal capsule, corpus callosum, brainstem, cerebellum, and near the ventricle) accounted for 19.4% of total microbleeds in this data set.

Primary Outcomes

In adjusted analysis of LA structure and function, among participants not in continuous AF at time of

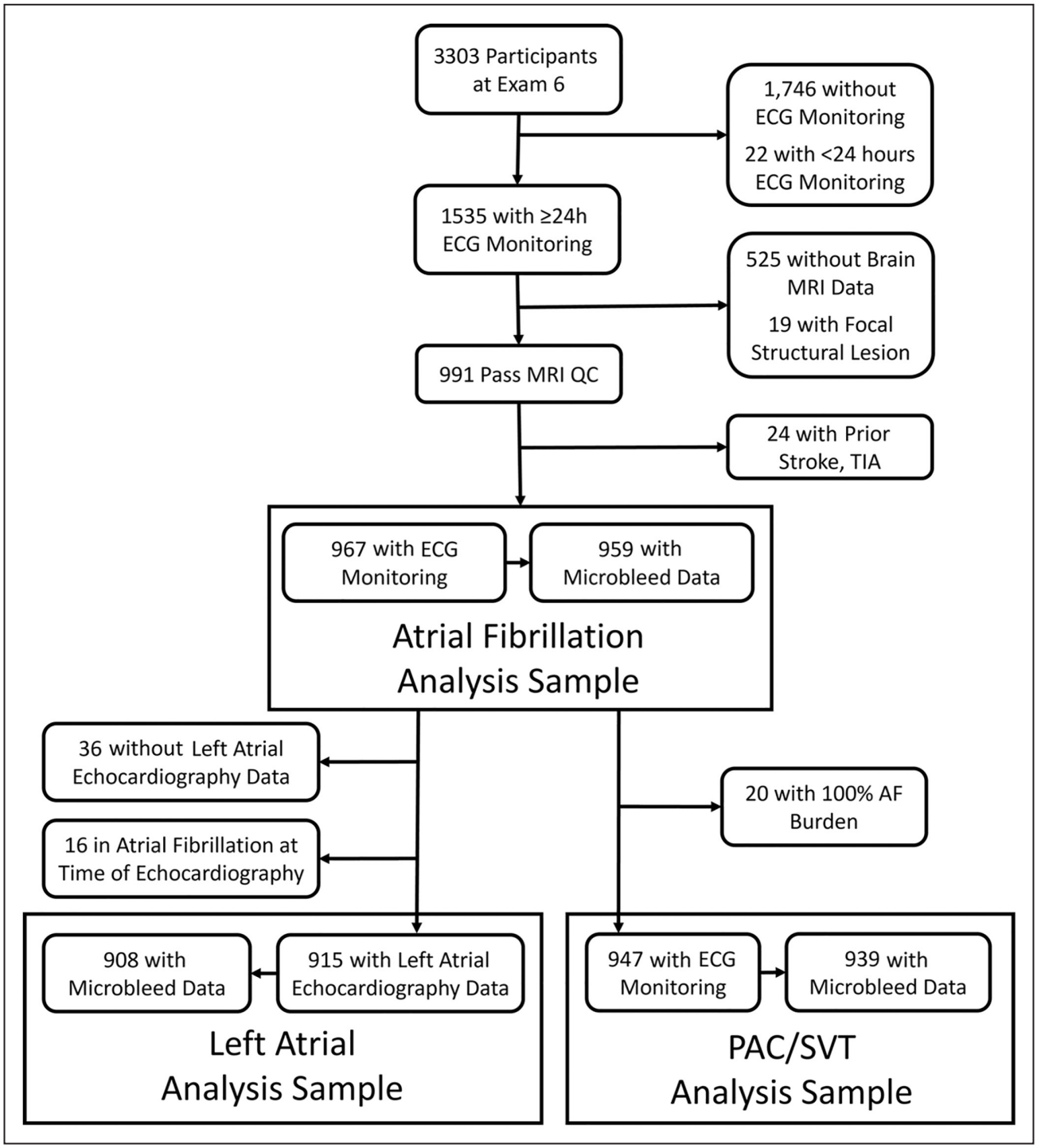

Figure 1. Study inclusion diagram.
AF indicates atrial fibrillation; ECG, electrocardiographic; MRI, magnetic resonance imaging; PAC, premature atrial contractions; QC, quality control; SVT, supraventricular tachycardia; and TIA, transient ischemic attack.

echocardiography, larger LA volume was associated with lower FA (–0.07 SD per 1 SD higher LA volume index: 95% CI, –0.13 to –0.01) and a higher probability of microbleeds (prevalence ratio per 1 SD: 1.17, 95% CI, 1.08–1.27; Figure 2). Among participants with microbleeds, lower reservoir strain (worse function) was associated with more microbleeds (7.6% more microbleeds per 1 SD lower LA strain, 95% CI, 1.46–13.45).

More frequent PACs were associated with lower GM volume (–0.76 mL, 95% CI, –1.52 to –0.01 per rate doubling, Figure 2). More frequent SVT was not associated with any of the brain MRI findings.

Table 1. Characteristics at Exam 6 (2016–2018) of MESA Participants Included and Not Included in the Analysis

Characteristic	Analysis sample	Not included in analysis sample
N	967	2336
Female, n (%)	514 (53)	1246 (53)
Race and ethnicity, n (%)		
Black	231 (26)	620 (27)
Chinese-American	147 (12)	273 (12)
Hispanic	189 (22)	521 (22)
White	400 (40)	922 (39)
Age, y, mean (SD)	72 (8)	75 (9)
Cigarette use, n (%)		
Never	460 (48)	1061 (46)
Former	452 (47)	1136 (49)
Current	54 (6)	130 (6)
Systolic BP, mm Hg, mean (SD)	127 (21)	129 (21)
Diastolic BP, mm Hg, mean (SD)	69 (10)	68 (10)
Body mass index, mean (SD)	28 (5)	29 (6)
HDL cholesterol, mg/dL, mean (SD)	60 (18)	59 (19)
LDL cholesterol, mg/dL, mean (SD)	107 (35)	105 (35)
eGFR, mL/min per 1.73 m^2, mean (SD)	77 (19)	74 (21)
Hypertension medication, n (%)	561 (58)	1471 (63)
Diabetes, n (%)	200 (21)	581 (26)
Prevalent cardiovascular disease*, n (%)	78 (8)	459 (14)
Family income per year, n (%)		
<$25 000	209 (23)	621 (28)
$25 000–$49 999	231 (25)	551 (25)
$50 000–$99 999	287 (30)	584 (26)
>$100 000	200 (21)	464 (21)
Education, n (%)		
<High school	108 (11)	316 (14)
High school	152 (15)	387 (17)
Some college	230 (24)	558 (24)
College degree	255 (26)	539 (23)
Graduate degree	220 (23)	531 (23)

BP indicates blood pressure; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; and MESA, Multi-Ethnic Study of Atherosclerosis.

*Prevalent cardiovascular disease = clinical diagnosis of myocardial infarction, stroke, atrial fibrillation, or heart failure before Exam 6 (2016–2018).

Table 2. Summary of Echocardiographic Left Atrial Structure and Function Measures and Supraventricular Arrhythmias at MESA Exam 6 (2016–2018)

Left atrial measures and arrhythmias	Mean (SD), median (IQR), or No. (%)	N with data
LA volume index, mL/m^2, mean (SD)	27.7 (8.4)	915
LA reservoir strain (%), mean (SD)	24.0 (5.7)	915
Premature atrial contractions per hour, median (IQR)	3.6 (1.3–16.7)	947
Supraventricular tachycardia, runs per day, median (IQR)	0.4 (0.2–1.2)	947
Prevalent atrial fibrillation, n (%)	116 (12)	967
Intermittent atrial fibrillation, n (%)	96 (9)	967
Continuous atrial fibrillation, n (%)	20 (2)	967

IQR indicates interquartile range; LA, left atrial; and MESA, Multi-Ethnic Study of Atherosclerosis.

Compared with no AF, prevalent AF was associated with lower mean WM FA (–0.22 SD, 95% CI, –0.39 to –0.04) and higher probability of microbleeds (prevalence ratio: 1.44, 95% CI, 1.16–1.78; Figure 3). In the analyses of AF subtypes, compared with no AF, participants with intermittent AF had lower WM FA (–0.25 SD, 95% CI, –0.44 to –0.07) and higher probability of microbleeds (prevalence ratio: 1.42, 95% CI, 1.12–1.79). Among participants with microbleeds, continuous AF was associated with a greater number of microbleeds (65.9% more, 95% CI, 7.4–156.0), but intermittent AF was not. Compared with participants with no AF, those with continuous AF had smaller total GM volume (–18.6 mL, 95% CI, –32.4 to –4.9, Figure 3).

In sensitivity analyses using splines, we did not find evidence of nonlinearity of associations described above. ANOVA inflation factors suggested no meaningful collinearity in the regression analyses. Additional adjustment for alcohol consumption did not materially change our findings. Associations did not differ in subgroups defined by race and ethnicity or sex, when excluding participants with prevalent myocardial infarction or heart failure, when including participants with 12 or more microbleeds, or when excluding those taking oral anticoagulants at Exam 6.

Secondary Outcomes

Lower LA reservoir strain was associated with lower total brain volume (–3.12 mL per 1 SD lower strain, 95% CI, –5.73 to –0.51), but not with total WM volume (Figure S1). Rates of SVT and prevalent AF were not associated with total brain volume and total WM volume (Figure S2).

DISCUSSION

In a community-based multi-ethnic study of older adults, after adjustment for cardiovascular risk factors, early manifestations of atrial impairment including LA enlargement and abnormal LA function were associated with markers of small vessel disease of the brain, including lower mean WM FA, reflecting

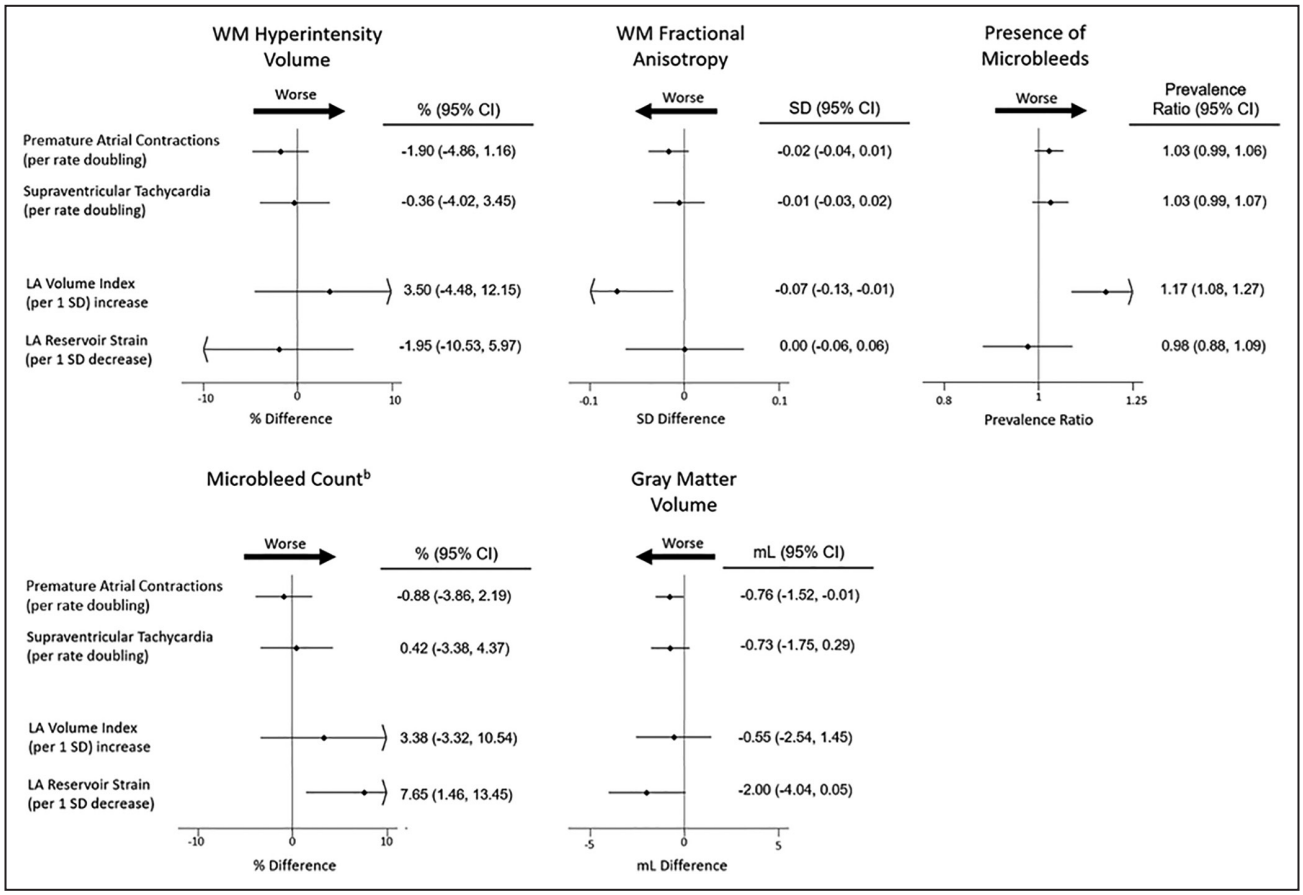

Figure 2. Adjusted[a] associations of premature atrial contractions, supraventricular tachycardia, and echocardiography measures of left atrial structure and function with brain MRI measures.

[a]Adjusted for age, sex, field center, race and ethnicity, total intracranial volume (for volume measures only), smoking history (never, current, former), body mass index, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, estimated glomerular filtration rate, systolic blood pressure, diastolic blood pressure, diabetes, hypertension medication, neighborhood socioeconomic status, education, and income. [b]Analysis restricted to those with ≥1 microbleed (n=313). LA indicates left atrium; MRI, magnetic resonance imaging; and WM, white matter.

abnormal microstructural integrity, and the presence of microbleeds. In addition, despite the low AF burden in this subsample, participants with intermittent AF had more evidence of small vessel disease than those without AF. Continuous AF was associated with lower total GM volume, a late manifestation of small vessel disease.

In the CABL (Cardiovascular Abnormalities and Brain Lesions) study, LA enlargement and lower emptying fraction by echocardiography were associated with silent brain infarcts and greater WMH volume on brain MRI in participants without a history of stroke.[24] Although the LA measures and brain MRI findings studied here were not identical to those in CABL, the results are concordant: LA enlargement and abnormal function were associated with MRI markers of small vessel disease of the brain. In another study that used a qualitative visual scale to rate severity of WMH changes rather than automated quantification of WMH volume, excessive SVE was associated with higher WMH burden.[25] In the present study, greater SVE was not associated with WMH volume or FA, but more frequent PACs were associated with lower GM volume.

A previous report that examined clinically detected AF in relation to total WM FA reported no association.[26] Several studies have reported no association of AF with WMH volume[26–29] or with cortical and lobar microhemorrhages.[29] In the present study, greater spatial resolution and automated digital image analysis methodology may have offered greater precision in MRI measures and supplementing clinical AF with extended ambulatory monitoring more accurately classified AF. Regarding brain volumes, lower total brain, total GM and total WM volumes,[30] lower regional brain volumes,[29] and lower frontal lobe volume[27] have been reported in individuals with AF than in those without AF. Consistent with our findings of lower total GM volume in participants with continuous AF, Stefansdottir

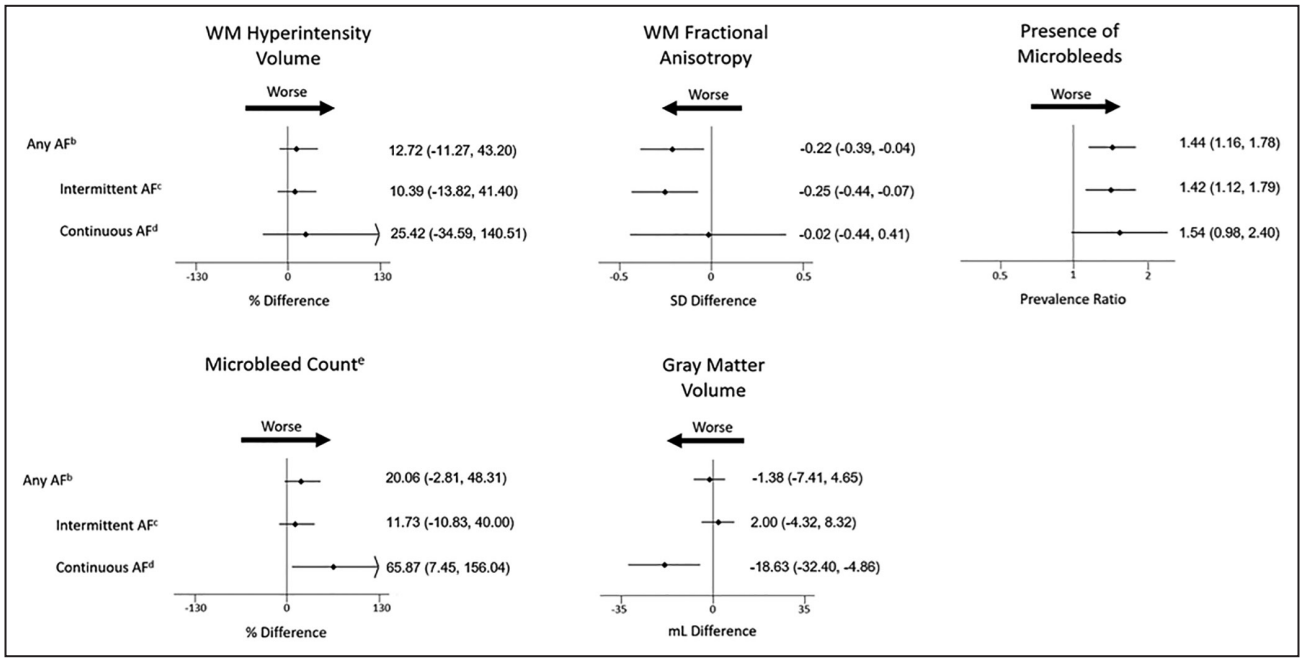

Figure 3. Adjusted[a] associations between atrial fibrillation (any, intermittent, and continuous) and brain magnetic resonance imaging measures.

[a]Adjusted for age, sex, field center, race and ethnicity, total intracranial volume (for volume measures only), smoking history (never, current, former), body mass index, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, estimated glomerular filtration rate, systolic blood pressure, diastolic blood pressure, diabetes, hypertension medication, neighborhood socioeconomic status, education, and income. [b]N with AF=116. Comparison group is those without any AF (n=851). [c]N with intermittent AF=96. Comparison group is those without any AF (n=851). [d]N with continuous AF=20. Comparison group is those without any AF (n=851). [e]Analysis restricted to those with ≥1 microbleed (n=313). AF indicates atrial fibrillation; and WM, white matter.

et al reported lower total GM volume with permanent/persistent AF than with paroxysmal AF.[30]

Reduction in WM FA may be a more sensitive or earlier marker of small vessel disease than increased WMH volume.[31,32] In the present analysis, the findings that early manifestations of LA impairment and intermittent AF were associated with reduced WM FA but not with WMH volume are consistent with this hypothesis.

A small proportion of the participants with AF were treated with anticoagulation, especially among those with intermittent AF. Anticoagulation has been associated with bleeding in patients with microbleeds,[33] and its role in the treatment of patients with abnormal LA function or supraventricular arrhythmia remains to be clarified.

Limitations

The number of participants with AF (n=116) in the present analysis was relatively small, limiting study power to identify associations with brain MRI measures. Selection bias is a possibility, because participants willing to undergo the ECG monitoring, echocardiography, and MRI of the brain were somewhat younger and healthier than nonparticipants. The present analysis grouped together cortical and subcortical microbleeds, but their pathophysiology may differ. In particular cortical microbleeds may be small hemorrhagic emboli, while subcortical microbleeds may be more related to small vessel disease. Additionally, brain MRI readings of subclinical infarcts were not available in this MESA data set. Finally, our analysis included several tests for significance, and type 1 error is possible as a result. However, correction for multiple testing would be overly conservative because the various LA measures are highly correlated with one another and the outcomes are correlated with one another as well. We have presented point estimates and 95% CIs without focusing exclusively on statistical significance. While the present analysis demonstrates associations of measures of LA structure and function with measures of small vessel disease, the cross-sectional nature of this study does not allow us to infer causal or mechanistic links between these measures. Additionally, it is possible that residual confounding is present in our analysis from measurement error of covariates or unmeasured confounders. Strengths of this analysis include the racially and ethnically diverse cohort and the precise and extensive data collection procedures in MESA.

Because AF is a growing public health concern, a better understanding of its antecedents and their association with measures of brain structure

will inform efforts at prevention and may elucidate mechanisms contributing to cognitive decline and dementia. The findings from the present analysis suggest that echocardiography with detailed measurement of LA structure and function and extended ECG monitoring to detect subclinical AF may be important ways to stratify risk and may facilitate early intervention on modifiable risk factors to improve brain health.

ARTICLE INFORMATION

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Affiliations

Department of Epidemiology (T.R.A., J.S.F., W.T.L., S.R.H.); and Department of Medicine (P.N.J., C.M.S., J.S.F.), University of Washington, Seattle, WA; Center for Biomedical Image Computing and Analytics, Department of Radiology, University of Pennsylvania, Philadelphia, PA (I.M.N.); Neuroimage Analytics Laboratory and the Biggs Institute Neuroimaging Core, Glenn Biggs Institute for Alzheimer's & Neurodegenerative Diseases, University of Texas Health Science Center, San Antonio, TX (M.H., T.R.); Department of Radiology, University of Pennsylvania, Philadelphia, PA (J.B.W., R.N.B.); Cardiovascular Division, Department of Medicine, University of Minnesota Medical School, Minneapolis, MN (L.Y.C.); Department of Preventive Medicine (P.G.); and Division of Cardiology, Department of Medicine (P.G., S.J.S.), Northwestern University Feinberg School of Medicine, Chicago, IL; Department of Internal Medicine, Wake Forest School of Medicine, Winston-Salem, NC (T.M.H.); Division of Cardiology, Department of Medicine, Johns Hopkins University, Baltimore, MD (W.S.P.); Departments of Medicine and Epidemiology, Columbia University, New York, NY (S.J.S.); Department of Medicine, David Geffen School of Medicine, University of California, Los Angeles, CA (K.E.W.); Department of Biostatistics (R.A.K.); and Department of Neurology (W.T.L.), University of Washington, Seattle, WA; and Department of Epidemiology and Prevention, Wake Forest School of Medicine, Winston-Salem, NC (A.G.B.).

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Disclosures

Dr Nasrallah was an educational speaker for Biogen. Dr Floyd has consulted for Shionogi Inc. Dr Shea has received research grants from Actelion, AstraZeneca, Corvia, Novartis, and Pfzer; and has served consulting fees from Abbott, Actelion, AstraZeneca, Amgen, Axon Therapeutics, Bayer, Boehringer-Ingelheim, Bristol-Myers Squibb, Cardiora, CVRx, Cytokinetics, Edwards, Eisai, Ionis, Ironwood, Merck, MyoKardia, Novartis, Prothena, Pfzer, Regeneron, Sanof, Shifamed, Tenax, and United Therapeutics. Dr Bryan reports nonfinancial support from Galileo CDS outside the submitted work; and has a patent licensed to Galileo CDS. The remaining authors have no disclosures to report.

Supplemental Material

Data S1
Reference [34–37]
Table S1
Figure S1–S2

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SUPPLEMENTAL MATERIAL

Data S1. Supplemental Methods

Participant Characteristics

From data collected at MESA Exam 6 (2016-2018), blood pressure was calculated as the average of the last two of three seated measurements in the right arm. Total and high-density lipoprotein (HDL) cholesterol, glucose, HbA1c, and serum creatinine were measured from fasting blood samples; low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald equation. Estimated glomerular filtration rate (eGFR) was calculated based on serum creatinine using the CKD EPI equation[34]. Diabetes was defined as use of diabetes medication, fasting glucose $\geq$ 126 mg/dL, or HbA1c $\geq$ 6.5%.

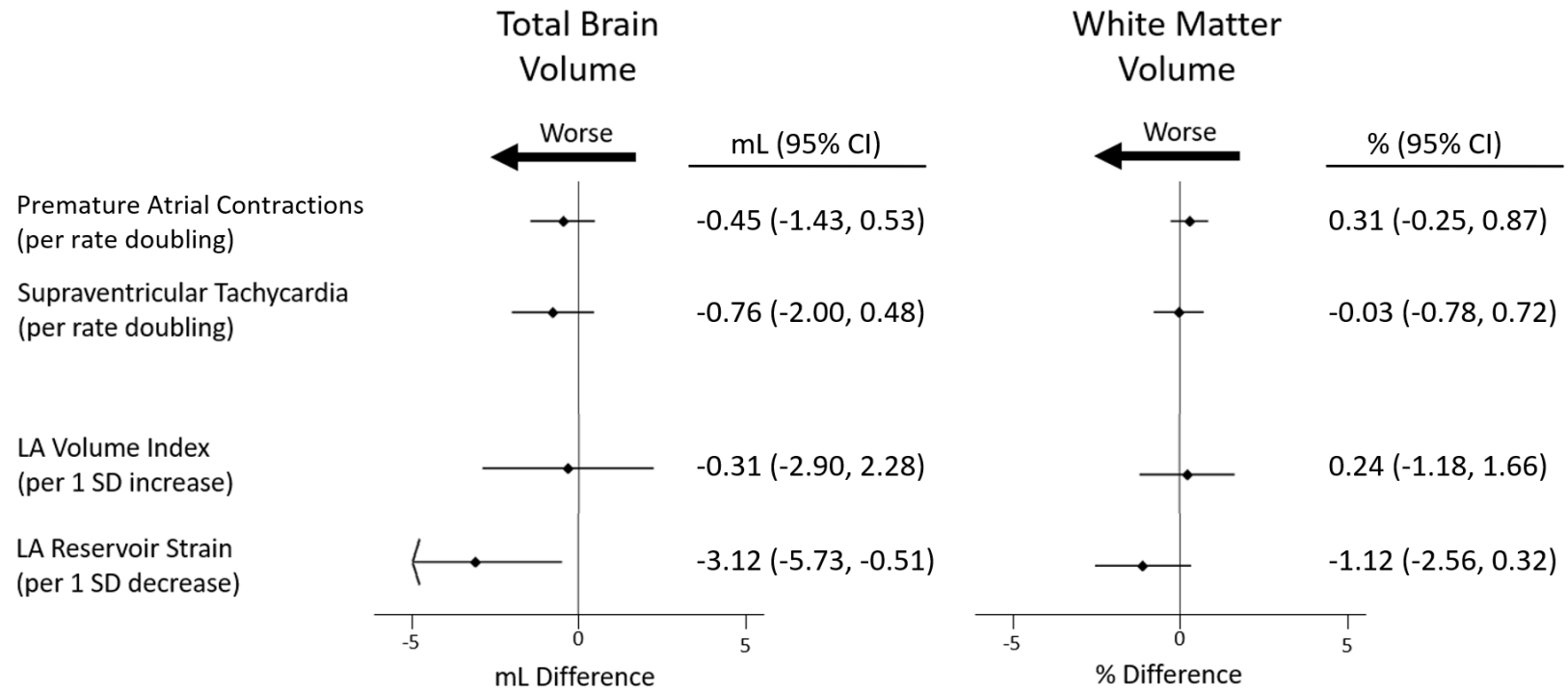
Brain MRI Measures

An automated pipeline was applied for pre-processing structural MRIs, segmenting GM and WM, and defining anatomical regions of interest[35]. The sum of GM and WM defined TBV. Total intracranial volume (ICV) was defined as the sum of all GM, WM, and cerebrospinal fluid. The volume of WMHs, or leukoaraiosis, was measured from FLAIR and T1-weighted images using a deep learning-based segmentation method[36]. Mean WM FA was calculated from diffusion tensor imaging (DTI) using automated pipelines[37].

Table S1. Summary of brain MRI measures at MESA Exam 6 (2018 – 2019)

Brain MRI Measure	
Total Intracranial Volume, mL, mean(SD)	1359 (146)
Total Brain Volume, mL, mean(SD)	1092 (115)
Gray Matter Volume, mL, mean(SD)	597 (66)
White Matter Volume, mL, mean(SD)	496 (56)
White Matter Hyperintensity Volume, mL, mean(SD)	6.6 (10.1)
White Matter Fractional Anisotropy, mean(SD)	0.39 (0.03)
Participants with any microbleeds, No. (%)	313 (32%)
Total microbleeds, mean(SD)	2.1 (1.8)

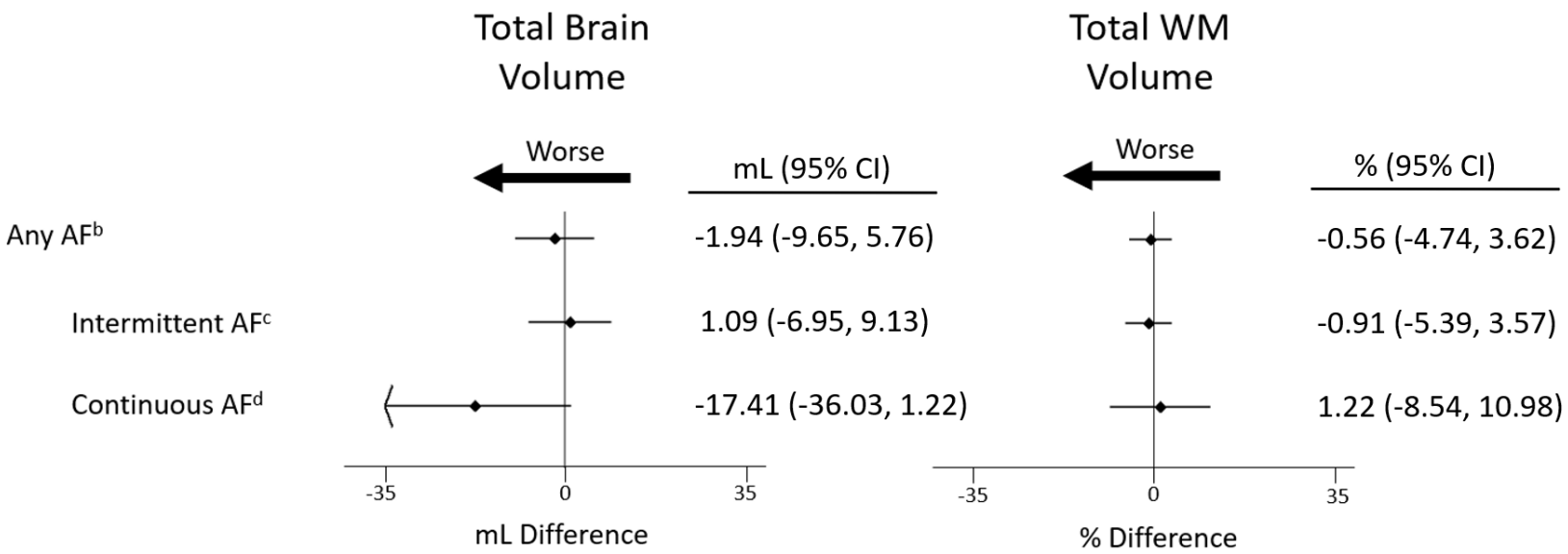
Figure S1. Adjusted[a] associations of premature atrial contractions, supraventricular ectopy, and echocardiography measures of left atrial structure and function with secondary brain MRI measures



[a] Adjusted for age, sex, field center, race/ethnicity, total intracranial volume (for volume measures only), smoking history (never, current, former), body mass index, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, estimated glomerular filtration rate, systolic blood pressure, diastolic blood pressure, diabetes, hypertension medication, neighborhood socioeconomic status, education, and income

MRI: Magnetic Resonance Imaging; LA = Left Atrium; WM = white matter

Figure S2. Adjusted[a] associations between atrial fibrillation (any, intermittent, and continuous) and secondary brain MRI measures



[a] Adjusted for age, sex, field center, race/ethnicity, total intracranial volume (for volume measures only), smoking history (never, current, former), body mass index, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, estimated glomerular filtration rate, systolic blood pressure, diastolic blood pressure, diabetes, hypertension medication, neighborhood socioeconomic status, education, and income

[b] N with AF = 116. Comparison group is those without any AF (n = 851)

[c] N with intermittent AF = 96. Comparison group is those without any AF (n = 851)

[d] N with continuous AF = 20. Comparison group is those without any AF (n = 851)

[e] Analysis restricted to those with ≥1 microbleed (n=313)

MRI: Magnetic Resonance Imaging; AF = atrial fibrillation; WM = white matter