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The association of
Atrial Fibrillation and Renal Biomarkers with Brain MRI Abnormalities: An investigation using Systolic Blood Pressure Intervention Trial (SPRINT) research materials

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Abstract

Objective & Background

The increased risk of dementia and cognitive impairment associated with atrial fibrillation (AF), independent of stroke, suggests additional effects of AF on the brain. Due to the paucity of research investigating AF and brain morphology, this study seeks to examine (1) the impact of AF and renal dysfunction on brain structure and morphology and (2) evaluate the synergistic effect between AF and biomarkers of renal dysfunction on brain volumetric measures.

Methods

Data were obtained from the SPRINT (Systolic Blood Pressure Intervention Trial), a single-blind randomized clinical trial designed to test a lower systolic blood pressure (SBP) target to prevent cardiovascular disease in persons with elevated cardiovascular risk but without diabetes or stroke. In 2010–2012 participants completed questionnaires, a clinical exam and provided blood and urine samples. This cross-sectional analysis evaluated a subset of participants who underwent brain magnetic resonance imaging at baseline. Variables of interest included lobar brain volumes, cerebral blood flow and markers of white matter disease. AF diagnoses were based on self-report and scheduled ECG. Serum creatinine was used to obtain estimated glomerular filtration rate (eGFR) and albumin creatine ratio was measure in urine samples.

Results

We studied 625 (mean age=67±8.1 years; 60% men) individuals; 41 (6.5 %) participants had prevalent AF at the time of MRI. Mild eGFR and high albuminuria categories were associated with prevalent AF (OR= 3.45; 95% CI: 1.06, 11.21). In multivariate analysis, AF was associated with reduced entorhinal cortex volume (-0.12 mm^3; 95% CI -0.22, -0.02) and posterior cingulate gyrus volume (-5.63 mm^3; 95% CI -10.9, -0.35) and lower frontal cerebral blood flow (-3.4 mL/min, 95% CI -6.69, -0.07). No significant effect modification by CKD was observed in the associations between AF and brain imaging characteristics.

Conclusion

AF is associated with smaller brain volumes in selected areas. The association was not modified by lower renal function. These findings suggest that AF has a cumulative negative effect on the brain independent of stroke.

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A Dissertation
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Introduction

Atrial fibrillation (AF) is the most prevalent clinically relevant heart arrhythmia. The Global Burden of Disease project estimated a worldwide prevalence of 37.8 million individuals with AF in 2017, and estimated numbers will continue to rise as the population ages globally (1,2). Associated with a high degree of mortality and morbidity, AF increases the risk of heart failure, stroke, thromboembolism, and renal function decline (3, 4).

Renal dysfunction is defined as estimated glomerular filtration rate (eGFR) below 60 mL/min per 1.73 m^2 and/or the presence of increased urinary albumin extraction (≥30 mg/g). Persistent damage is known as chronic kidney disease (CKD). Similar to AF, CKD is also a major comorbidity with increasing prevalence and substantial socioeconomic impact (4,5). Atrial fibrillation and CKD are bidirectional and often co-exist (6). Prevalent AF in renal failure populations range from 19 to 24%, and rise to 27% in patients with end-stage renal disease (7,8), with their synergistic relationship exacerbating cardiovascular, kidney, and cognitive health outcomes (9,10,11,12,13, figure 1).

Cognitive impairment (CI) and dementia are cognitive health outcomes that describe the progressive state of deteriorating cerebral functions and capabilities necessary for independent living. Atrial fibrillation has been well documented as a risk factor for cognitive decline and dementia, independent of stroke (15-18). A meta-analysis identified 11 prospective cohorts to assess and synthesize the association between AF and dementia incidence, reporting AF as an independent risk factor for dementia in patients with normal baseline cognitive function, independent of stroke (HR = 1.34, 95% CI: 1.24–1.44) (14). In CKD, prospective studies have shown an increased risk for cognitive impairment and dementia in patients with low eGFR and increased albuminuria (19,20,21). For example, the Intervention Project Cerebrovascular

Diseases and Dementia (INVADE, n = 3679) reported that a low eGFR (<45 mL/min/1.73m^2) at baseline was independently associated with developing cognitive impairment after a 2-year follow-up (OR = 2.14, 95%CI: 1.18 –3.87) (22). However, few studies concerning renal function have comprehensively examined the cumulative effect of eGFR and albuminuria thresholds on AF and dementia. In this context, evaluating renal biomarkers in patients with AF may provide insight into specific pathways by which AF affects brain function.

Studies investigating the impact of AF on brain structure and morphology mechanisms are also scarce. Recent brain MRI and structural imaging studies have clinically identified multiple markers of cognitive dysfunction such as cerebral microbleeds (23,24), brain hypoperfusion (25), brain atrophy/volume loss (26,27), white matter pathology (28), and silent cerebral infarcts (SCI) (28,29) but it is not known whether AF operates through these mechanisms.

A 2019 cross-sectional study analysis of the Atherosclerosis Risk in Communities Neurocognitive Study (ARIC-NCS) assessed brain magnetic resonance imaging (MRI) scans for volume and anatomical measurements in 1,930 participants, of which 130 were diagnosed with AF. The study reported individuals with prevalent AF to have smaller regional brain volumes (including temporal, occipital, and parietal lobes; deep gray matter; and hippocampus) (30). A second cross-sectional study evaluated 122 subjects with a history of AF but no history of stroke participating in the German Competence Network of AF and compared them to 563 individuals with no prior history of AF or stroke from the same community (31). The study also found hippocampal volume to be significantly lower in the subjects with AF compared to participants without AF. However, the study also reported no significant relationship in total brain volumes and white matter hyperintensities volumes (31). These results may partly help explain the

adverse neurocognitive effects of AF; however, data reporting is inconsistent. For example, an analysis conducted within the Framingham Heart Study reported that AF has no relation to regional and total brain volumes. Furthermore, few studies to date have utilized the gamut of brain imaging parameters associated with dementia, such as fractional anisotropy, a valuable measure of connectivity in the brain (32).

Given the conflicting evidence, it is essential to provide a more comprehensive understanding of the association of AF and the pathophysiological mechanisms involved. Therefore, the aim of the present study is to better understand the pathways linking AF with cognitive impairment and dementia by examining (1) the impact of AF and renal dysfunction on brain volumes and (2) the synergistic effect between AF and renal dysfunction on brain volumetrics including cerebral blood flow, fractional anisotropy, total, lobar, and regional brain volumes.

Methods

Study Population

The SPRINT (Systolic Blood Pressure Intervention Trial) was a single-blind randomized clinical trial designed to investigate how treating to a lower systolic blood pressure (SBP) target can contribute to the reduction of cardiovascular disease and disability. Initiated in 2010, patients 50 years or older with SBP $\geq$ 130 mmHg and at least one additional CVD risk factor were eligible for participation, whilst excluding patients with diabetes, patients with polycystic kidney disease (PKD) or an eGFR < 20 mL/min per 1.73 m^2, and patients who had a history of stroke (33). In coordination with five clinical center networks (CCNs) over a 2-year period, the SPRINT intervention recruited 9,250 participants (33, 34). After a baseline exam (visit 0), participants underwent post-randomization exams from 2012 to 2015.

As part of a large secondary study, SPRINT Memory and Cognition in Decreased Hypertension (SPRINT-MIND) took a representative sample of 2,800 participants hypothesizing that SBP treatment would reduce all-cause dementia. Cognitive assessments were conducted alongside the main trial, at baseline (visit 0) and bi-annually until study completion. Volumetric brain MRI scans were also obtained in a further subset of the SPRINT-MIND participants (n=640) to evaluate brain structure at baseline and a 4-year follow-up MRI. We excluded patients with incomplete data. After exclusions, 625 participants remained for our cross-sectional analysis, of whom 41 (6.5%) had AF.

The SPRINT intervention and SPRINT-MIND study protocol were approved by the institutional review board at each participating study site. Informed consent was obtained from all participants, and the study was conducted in accordance with the Declaration of Helsinki and to Title 45, Protection of Human Subjects Act.

Ascertainment of AF

Prevalent AF was identified at scheduled electrocardiographs (ECG) and self-reported AF. Digital ECG data were recorded with the GE MAC 1200 electrocardiograph (GE, Milwaukee, Wisconsin) at baseline, the two- and four-year follow-up visits, and close-out visits. Interpretation for the presence of AF (Minnesota code 8.3) was adjudicated centrally by the Epidemiological Cardiology Research Center (EPICARE), Wake Forest School of Medicine (Winston-Salem, NC) (35). All ECG tracings were examined for technical errors and quality assurance by the ECG EPICARE and the Measurement Procedures and Quality Control Subcommittee.

Assessment of Kidney Function

Study laboratory measurements were drawn at baseline SPRINT visit. Serum creatinine was determined by enzymatic procedure on a Roche Cobas 8000 and is IDMS-traceable for calibration. Urine albumin was measured by an immunoturbidometric method on a Roche analyzer. Renal function was assessed using both glomerular filtration rate (GFR) estimated by the Modification of Diet in Renal Disease (MDRD) equation and urine albumin-to-creatinine ratio (UACR) via urine spot specimens.

MRI acquisition and image processing

The imaging parameters, measurement protocols, and reproducibility of these measures have been described in prior publications (35,36). Structural MR images were scanned on several different models, 3T Phillips Achieva 3.2 (University of Alabama at Birmingham, Boston University, and Vanderbilt University), 3T Siemens Skyra VD11B (Wake Forest University), 3T Siemens Tim Trio VB17 (University of Miami and University of Pennsylvania), and 3T Siemens Verio VB17 (Case Western Reserve University), using protocol including 1-mm isotropic T1, T2, and fluid-attenuated inversion recovery (FLAIR) imaging. All images were processed by the Center for Biomedical Image Computing and Analytics in the Department of Radiology at the University of Pennsylvania, with each analyst blinded to treatment group. An automated pipeline was applied for preprocessing, including correction of inhomogeneity (37) and multi-atlas skull stripping (38) in order to segment T1 scans into 145 anatomic regions of interest (ROI) encompassing the entire brain.

MRI volumetric ROI included total brain volume (TBV), frontal, temporal, hippocampal, entorhinal cortex volume, posterior cingulate cortex volume, and white and gray matter hyperintensity brain volumes. For each ROI, cerebral blood flow (CBF), fractional anisotropy (FA), and Virchow-Robin volumes (VR) were extracted. Total cerebral blood flow (mL/min)

was measured using phase-contrast MRI at the level of the skull base for flow measurement in all the cervical arteries. FA is affected by axon tract structural integrity, with decreases in value associated with pathology. FA scalar maps were calculated from diffusion tensor imaging (35), and VR dilation was computed from axial T2 sequences scans. All volumetric measures were adjusted for total intracranial volume (ICV) to correct for differences in head size.

Covariates

As part of the SPRINT baseline visit, study participants completed questionnaires, a clinical exam and provided blood and urine samples. Information on age, race, sex, education (less than high school/high school/college or university), current smoking status (lifetime cigarettes < 100 / lifetime cigarettes ≥ 100), previous blood pressure medication use (yes/no), and cardiovascular history was reported. Cardiovascular history was inclusive of previous myocardial infarction (MI), percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG), carotid endarterectomy (CE), carotid stenting, peripheral artery disease (PAD), acute coronary syndrome, and abdominal aortic aneurysm (AAA). Body mass index (BMI) was defined as weight in pounds times 703 divided by squared height in inches. Seated blood pressure was calculated using automated devices; both systolic and diastolic blood pressure (mmHg) was measured three times and averaged after a brief rest period. Circulating cholesterol and high-density lipoprotein (HDL) were measured in blood samples at baseline.

Statistical analyses

We reported means with SD and counts with percentages for categorical variables unless indicated otherwise. General characteristics, cardiovascular risk factors, and renal biomarkers were compared between groups with and without AF. Ordinal logistic regression models evaluated the association of AF with measures of kidney function using eGRF stages (normal,

≥90 ml/min per 1.73 m^2; mild, eGFR < 90 and ≥60 ml/min per 1.73 m^2; moderate-to-severe < 60 ml/min per 1.73 m^2) and UACR levels (UACR ≥ or <30 mg/g). In secondary polytomous analyses, eGFR stages and UACR categories were combined into five groups to evaluate all clinical manifestations of kidney damage: Normal eGFR/Low and High albuminuria, Mild eGFR/ Low albuminuria, Mild eGFR/ High albuminuria, Mod-Severe eGFR/Low albuminuria, Mod-Severe eGFR/ High albuminuria. Models were adjusted for age, sex, and race (model 2).

Generalized linear models (GLM) were used to examine the association between AF with brain volumetric measures and the interaction with CKD. Normal distribution of volumetric measures was verified by examining q^2-plots of residuals. For the cross-sectional analysis, regression models were constructed based on prevalent AF status at baseline. Linear regression models for volumetric measures were adjusted for ICV (model 1). Additional multivariate regression models were adjusted for demographic data: age, race, and sex (model 2); sociodemographic and health data: smoking status, education, CVD history, systolic blood pressure, diastolic blood pressure, cholesterol, HDL, and previous medication use (Model 3). To assess for effect modification by CKD, interaction terms were included in the multivariable model. CKD was constructed as a binary variable, inclusive of participants with an eGFR < 60 ml/min per 1.73 m^2 and/or ACR ≥30 mg/g. In sensitivity analyses, we estimated the association between AF status and volumetric brain measurements for subgroups of interest, including age and sex; no significant interaction was present. Analyses were performed using Statistical Analysis Systems software, version 9.2 (SAS Institute Inc).

Results

Baseline characteristics of the SPRINT cohort are presented in Table 1. Of the 625 participants included in the cross-sectional analysis, 41 (6.5%) had prevalent AF; mean age was

67±8.1 years, 60% were men, and 31% were non-Hispanic black. Mean baseline creatinine levels were (1.05 ± 0.31 mg/g) and mean eGFR level was (72.2 ± 20.1 ml/min/1.73 m^2**)**; 18.2% of participants had a normal kidney function (eGFR ≥90 mL/min/1.73m^2), 54.2% had a mildly decreased kidney function (eGFR < 90 and ≥ 60 ml/min per 1.73 m^2), and 27.5% had moderate-to-severely decreased kidney function (eGFR < 60 ml/min per 1.73 m^2). Median UACR levels were (9.61 ± 15.1), with 80.8% of SPRINT participants having low or no albuminuria. Overall, patients with AF at baseline were older, more likely to be male, with lower kidney function and greater kidney damage, systolic blood pressure, and creatinine levels. Individuals with AF also had smaller relative brain volumes (81.8%) compared to those without prevalent AF.

Kidney Markers and AF

Table 2 describes the associations of prevalent AF with kidney damage and kidney function. AF was not independently associated with any clinical markers of kidney health; however, combined eGFR and UACR groups presented significant outcomes. In the basic model, AF was associated with mild kidney function (eGFR) and high albuminuria (OR = 3.45 [95% CI: 1.06, 11.21]). After adjusting for demographic confounders (model 2), the association no longer remained significant. No significant relationship was observed between AF and independent makers of kidney health.

AF and Brain Volumes

Table 3 displays the association between prevalent AF and MRI volumes after adjusting for intracranial volume (model 1), demographics (age, race, sex) (Model 2), and socioeconomic and cardiovascular risk factors (Model 3). In the basic model none of the lobar brain volumes, nor white and gray matter volumes were independently associated with AF after adjustment for all potential covariate models. However, an inverse association between AF and frontal cerebral

blood flow was observed; regions of significance also include the entorhinal cortex and posterior cingulate gyrus. After additional adjustment for the models above, right entorhinal cortex volume: beta = -0.12 mm^3 [95%CI -0.22, -0.02] and right posterior cingulate gyrus volume: beta = -5.63 mm^3 [95%CI -10.9, -0.35] remained significant. No associations were detected with FA, VR, and white matter disease. Analysis of interaction, adjusted for Model 3 covariates, produced no evidence of significant heterogeneity for sex-, race-, and CKD- categories.

Discussion

In a large RCT of non-diabetic, stroke, and kidney disease-free participants, we observed significant associations between AF and MRI brain abnormalities, including smaller volumes and reduced cerebral blood flow in selected regions. Notably, no significant sex-, race-, nor CKD- based interactions with AF were present. In addition, no associations were found in crude models between AF and individual markers of kidney disease, UARC, and eGFR. These findings remained after adjusting for demographic information and cardiovascular risk factors. Our significant results with combined kidney categories, suggest that complementing eGFR by the quantification of UACR may provide more insight into detection and staging of kidney function in patients with AF.

AF and CKD

Evidence of the relationship between AF and CKD are largely supported by prior studies that suggest the presence of several shared pathological pathways associated including generalized endothelial dysfunction and systemic vascular remodeling (39, 40, 41). Subsequent characterization of AF across the spectrum of glomerular filtration rate and albuminuria suggests that AF may be a risk factor for low GFR and albuminuria levels. In two extensive community-based studies conducted in the Netherlands and Japan, independent associations between reduced

eGFR and albuminuria were observed in populations with AF (42,43). In both studies, participant data underwent examinations in outpatient clinics and health screening programs. In the Netherlands study, albuminuria was associated with prevalent AF [OR = 1.93 (95%CI: 1.10, 3.37)] in individuals with an eGFR ≥ 60 ml/min per 1.73 m^2. In the second study, prevalent AF was evaluated across eGFR tertiles, finding that participants among the lowest GRF tertile (<62.6 ml/min per 1.73 m^2) were 1.91 (95% CI, 1.54 to 2.38) times more likely to have AF than those included in the high eGFR category (>75.5 ml/min per 1.73 m^2). In our sample, there were no associations between AF and eGFR quartiles or UARC levels. This may be in part to the limited statistical power when conducting analyses including a small number of participants with AF (N=41). However, after the consolidation of eGFR and UARC thresholds, AF was associated with both albuminuria and reduced eGFR. Despite our wide confidence interval, due to the low sample size of concurrent CKD and AF in our cohort (N=20, 3.20%), the current findings are consistent with previous reports of individuals with both reduced eGFR and albuminuria (44). The lack of interaction in our MRI metric outcomes may also be attributable to the low statistical power. These results suggest the utilization of both kidney function and albuminuria biomarkers can also provide a more granular renal assessment in populations with AF.

Our significant results with combined kidney categories, suggest that complementing eGFR by the quantification of UACR may provide more insight into detection and staging of kidney function in patients with AF.

AF and Brain Abnormalities

The associations between AF and brain abnormalities in our results have several potential explanations. Overall, AF patients are clinically identified with a higher burden of cerebrovascular markers of disease. AF is a common cause of cardioembolic and ischemic stroke

or transient ischemic attack. Subsequent outcomes of irregular sinus rhythm have been attributable to brain hypoperfusion (25) and brain atrophy/volume loss (26,27), but no evidence of causality has been convincingly demonstrated.

Cerebral blood flow is regulated by the interplay of powerful mechanisms to safeguard the balance between cerebral metabolic demand and supply. The brain demands twelve percent of cardiac output, making CBF fundamentally dependent on cardiac output (47). Decreased cardiac output, due to the beat-by-beat variations in AF, has been associated both with decreased CBF and cerebral perfusion. A cross-sectional analysis of a large community-based cohort study of 2291 participants who underwent contrast MRI imaging, reported that those with persistent AF had significantly lower total cerebral blood flow (472.1 mL/min) and estimated whole brain perfusion (46.4 mL/100 g/min) compared to those without AF (541.0 mL/min, 52.8 mL/100 g/min, respectively) (48). A second study evaluating regional CBF observed a 17.5% reduction in regional CBF in 27 patients with AF between the ages of 35-50 years; despite the observed reduction in CBF, it is important to note that none of the patients reached a threshold for cerebral manifestation (49). In our sample we observed similar patterns in CBF for the frontal lobe. Although our data is supported by prior MRI-based publications, existing literature is retrospective and cross-sectional by design; therefore, cerebrovascular markers of disease in patients with AF might be associated with other conditions, such as anticoagulant use (17), diabetes (49), or hypertension (50).

Previous studies investing the role of AF on brain structure and morphology have linked reduced total, lobar, and regional brain volumes, although supporting associations come from cross-sectional studies comparing individuals with and without AF. No other studies to date have analyzed the entorhinal cortex nor the posterior cingulate gyrus, regions highly associated with

cerebrovascular disease and damage, in cohorts evaluating AF (50, 51). A study conducted within the community-based Atherosclerosis Risk in Communities Neurocognitive Study (ARIC-NCS) reported that those with AF (mean age,76.3 ± 5.2) who underwent 3T brain MRI had significant lower temporal (beta = -0.18; 95% CI, -0.31, -0.04) and hippocampal volumes (beta = -0.18; 95% CI, -0.30, -0.03) (30). A second study in a large German community-based cohort evaluating 122 subjects with a history of AF but with no history of stroke also reported significantly lower hippocampal volumes (52); however, our results contradict prior associations in hippocampal volumes. These observations may be a result of SPRINT (mean age, 67 ± 8.1) being a younger cohort, precluding the study of aging-related outcomes. Given the uncertainty in published literature reporting associations between AF and additional significant MRI dimensions, this topic warrants further investigations.

The fractional anisotropy (FA) metric provides a simple and robust means to assess the degree of anisotropic diffusion occurring within a region and is a metric that has not been extensively investigated in AF populations. Because FA reflects the degree of anisotropic diffusion, reductions in FA are associated with microstructural integrity (53). In a sub-regional analysis, both decreased frontal FA and preservation of posterior high-anisotropy WM in elderly subjects compared with a younger cohort were reported (53). Other findings show the topographical concordance between cerebral diffusivity changes in cerebrovascular disease (54). Despite the vast heterogeneity in FA in our results, and the relatively small cohorts in previous literature, each study demonstrates the usefulness of ultrastructural brain investigations and the potential for a diagnostic role in brain morphology.

Strength and Limitations

The main strengths of our study include the exclusion of stroke, diabetes, and polycystic kidney diseased participants, the interrogation of multiple biomarkers, the diversity of the study population, and the availability of an extensive array of brain imaging measures. However, there are several limitations. Due to the cross-sectional design of our study, any inference on direct causality or temporality cannot be made. Next, the number of AF cases in our sample was relatively low (n = 41), which may have attenuated power to detect associations and obtain precise estimates of association. Atrial fibrillation status was ascertained by electrocardiographs and self-reports, meaning misclassification of AF status could be an issue in persons with clinically unrecognized paroxysmal AF. Additionally, we were unable to characterize AF status-based subtypes, as studies show that persistent rather than paroxysmal AF was more strongly associated with global brain atrophy (55).

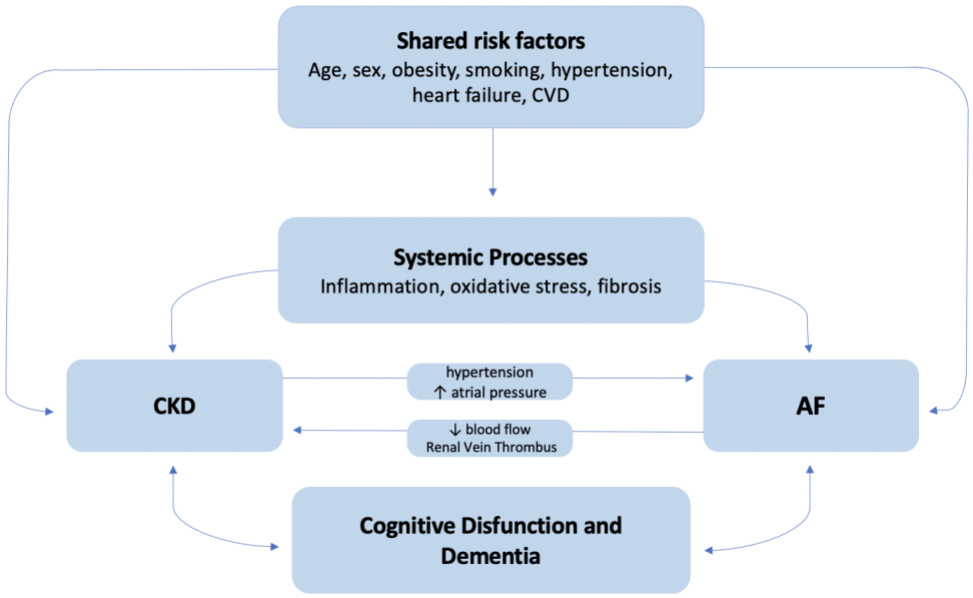
Conclusion

Collectively, our findings suggest that AF is associated with smaller brain volumes in selected areas, and the association is unmodified by the burden of renal dysfunction. Notably, these associations were observed in non-diabetic, stroke, and kidney disease-free participants independent of demographic and cardiovascular risk factors. Due to the cross-sectional design of this study, prospective research is warranted to investigate longitudinal changes in brain architecture in patients with AF to characterize conclusions about potential pathomechanisms of dementia.

Acknowledgments

This Manuscript was prepared using SPRINT Research Materials obtained from the NHLBI Biologic Specimen and Data Repository Information Coordinating Center and does not necessarily reflect the opinions or views of the SPRINT or the NHLBI.

Figure 1



Relationship between atrial fibrillation and chronic kidney disease: shared risk factors and outcomes. Chronic kidney disease and atrial fibrillation share several risk factors and conditions that promote their incidence, possibly via systemic processes such as inflammation, oxidative stress, or fibrosis. It is established that chronic kidney disease increases the incidence of atrial fibrillation, and evidence that atrial fibrillation also increases chronic kidney disease progression. When examining the strength of these associations, we must acknowledge the potential synergistic impact these conditions may have on the brain. AF, atrial fibrillation; CKD, chronic kidney disease; CVD, cardiovascular disease.

Table 1. Characteristics of **SPRINT participants**, stratified by presence of **Atrial Fibrillation** at baseline			
Sample Characteristic	**MRI/MIND Subset** N=625	**AF**	**No AF**
		41 (6.6)	584 (93.4)
Age, mean (SD)	67.2 (8.1)	69.8 (6.9)	67.1 (8.1)
Age 75 years or older, %	136 (21.7)	11 (26.8)	125 (21.4)
BMI, mean (SD)	30.2 (5.4)	29.8 (4.9)	30.3 (5.4)
BMI, % obese	227 (36.3)	14 (34.2)	213 (36.5)
Sex, %male	377 (60.3)	27 (65.9)	350 (59.9)
Education			
Less than High School	40 (6.4)	2 (4.8)	38 (6.5)
High School/ Vocational School	154 (24.6)	11 (26.8)	143 (24.5)
College/ University	431 (68.9)	28 (68.3)	403 (69)
Race			
Non-Hispanic White	387 (61.9)	33 (80.5)	354 (60.6)
Non -Hispanic Black	199 (31.8)	8 (19.5)	191 (32.7)
Hispanic	32 (5.1)	0	32 (5.5)
Non-Hispanic Other (Native American, Hawaiian, Asian, Other)	7 (1.1)	0	7 (1.2)
Current Smoker	91 (14.6)	2 (4.9)	89 (15.3)
SBP, mean (SD), mmHg	137 (16.6)	141 (14.3)	137 (16.8)
DBP, mean (SD), mmHg	77.9 (11.4)	78.9 (10.6)	77.9 (11.5)
Prevalent CVD History, %	76 (12.2)	12 (29.3)	64 (11)
Study Arm, %control	335 (53.6)	18 (43.9)	272 (46.6)
Anticoagulants use, %	12 (1.9)	9 (21.9)	3 (1.0)
Total cholesterol, mean (SD), mg/dL	193 (40.6)	188 (38.2)	194 (40.7)
HDL cholesterol, mean (SD), mg/dL	53.4 (14.7)	52.5 (15.7)	53.6 (14.6)
eGFR mean (SD), mL/min/1.73m^2	72.2 (20.1)	69.8 (20.2)	77.0 (21.4)
eGFR Classification (%)			
Normal	111 (18.2)	5 (12.5)	106 (18.6)
Mild Kidney Failure	330 (54.2)	24 (60)	306 (53.8)
Moderate-to-Severe Kidney Failure	168 (27.6)	11 (27.5)	157 (27.6)
Urine Albumin to Creatinine ratio, mean (SD), mg/g	45.3 (219)	37.6 (64.4)	45.8 (225)
Urine Albumin to Creatinine ratio, median (IQR), mg/g	9.68 (15.1)	10.6 (27.4)	8.68 (14.5)
Urine Albumin Classification, %			
Low Risk (<30 mg/g)	502 (80.3)	30 (73.6)	472 (80.8)
Moderate/High Risk (≥30 mg/g)	123 (19.9)	11 (26.8)	112 (19.2)
TBV volume, mean (SD), cm^3	1135 (114)	1150 (110)	1134 (114)
ICV volume, mean (SD), cm^3	1383 (147)	1407 (151)	1382 (SD??)
Relative TBV (TBV/ICV*100), mean, (SD), cm^3	82.2 (3.65)	81.8 (3.8)	82.2 (3.6)

Note: Values are mean (SD) for continuous covariates, N (%) for categorical covariates, or median (IQR) where noted. AF indicates atrial fibrillation; SPRINT, Systolic Blood Pressure Intervention Trial; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high-density lipoprotein; eGFR, estimated glomerular filtration rate; eGFR classification; TBV, total brain volume; ICV, intracranial volume.

Table 2: Association Between Prevalent AF with Kidney Dysfunction by Glomerular Filtration Rate and urine albumin-to-creatinine ratio Categories, 2012 to 2015		
Biomarker	Crude Model OR (95%)	Model 2 OR (95%)
eGFR	1.17 (0.63, 2.16)	0.91 (0.48, 1.70)
UACR (≥30 vs <30 mg/g)	1.54 (0.75, 3.18)	1.65 (0.80, 3.44)
Joint Classification	Crude Model OR (95%)	Model 2 OR (95%)
Normal eGFR/Low or High UACR	REF.	REF
Mild eGFR/ Low UACR	1.27 (0.45, 3.56)	0.91 (0.31, 2.60)
Mild eGFR/ High UACR	4.35 (1.34, 14.01)	3.41 (1.02, 11.4)
Mod-Severe eGFR/Low UACR	1.57 (0.49, 4.96)	1.04 (0.31, 3.41)
Mod-Severe eGFR/ High UACR	1.30 (0.29, 5.65)	0.92 (0.20, 4.19)

Note: Logistic regression was used for categorical outcomes to calculate association. Biomarker ORs are calculated using ordinal regression, and Joint classification ORs calculated using polytomous regression. Model 1 represents the unadjusted univariate model, and Model 2 adjusted for age, race, and sex. eGFR indicates estimated glomerular filtration rate; UACR: Urinary albumin to creatinine ratio.

Table 3. Cross-Sectional Association of Prevalent AF With Brain MRI Abnormalities in the SPRINT MRI Substudy, 2012 to 2015

Brain MRI Variable	AF (n=41)	No AF (n=584)	Model 1	Model 2	Model 3
	Mean (SD)	Mean (SD)	Difference (95% CI)	Difference (95% CI)	Difference (95% CI)
TBV	1150 (110)	1134 (114.5)	-2.7 (-17.9, 2.4)	6.8 (-5.3, 18.9)	6.3 (-4.2, 20.6)
R. Hippocampus	3.89 (0.39)	3.91 (0.43)	-0.05 (-0.17, 0.06)	-0.02 (-0.14, 0.08)	-0.02 (-0.13, 0.09)
R Hippo CBF	37.4 (12.9)	41.2 (12.8)	-3.31 (-7.3, 0.69)	-3.13 (-7.17, 0.92)	-3.26 (-7.39, 0.87)
R. Hippo FA	0.12 (0.02)	0.12 (0.02)	-0.003 (-0.01, .004)	-0.0005 (-0.007, 0.006)	-0.0003 (-0.008, 0.007)
R. Hippo VR	0.98 (0.46)	1.01 (0.47)	-0.03 (-0.19, 0.12)	-0.04 (-0.19, 0.12)	-0.03 (-0.18, 0.13)
R. Entorhinal	2.53 (0.34)	2.62 (0.40)	**-0.13 (-0.22, -0.03)**	**-0.12 (-0.21, -0.03)**	**-0.12 (-0.22, -0.02)**
L. Hippo	3.62 (-0.39)	3.65 (0.41)	-0.06 (-0.17, 0.04)	-0.03 (-0.13, 0.07)	-0.04 (-0.14, 0.07)
L. Hippo CBF	37.9 (10.9)	41.3 (12.7)	-2.93 (-6.88, 1.01)	-2.84 (-6.82, 1.14)	-2.75 (-6.80, 1.30)
L. Hippo FA	0.124 (0.02)	0.13 (0.02)	-0.003 (-0.01, 0.004)	-0.0004 (-0.008, 0.007)	0.0003 (-0.007, 0.008)
L. Hippo VR	0.90 (0.46)	0.99 (0.48)	-0.09 (-0.24, 0.06)	-0.01 (-0.25, 0.06)	-0.01 (-0.26, 0.06)
L. Entorhinal	2.54 (0.40)	2.53 (0.40)	-0.03 (-0.13, 0.07)	-0.02 (-0.11, 0.07)	-0.02 (-0.11, 0.08)
Frontal Vol.	370 (37.5)	367 (41)	-2.7 (-9.7, 4.32)	1.94 (-3.98, 7.86)	2.42 (-3.66, 8.51)
Frontal GM	173 (17.4)	172 (20.9)	-1.63 (-6.31, 3.05)	1.45 (-2.35, 5.27)	1.82 (-2.06, 5.70)
Frontal WM	196 (22.4)	194 (22.7)	-1.09 (-4.67, 2.50)	0.48 (-2.93, 3.89)	0.60 (-2.90, 4.10)
Frontal CBF*	32.7 (10.5)	36.6 (10.8)	**-3.4 (-6.69, -0.07)**	-3.29 (-6.61, 0.02)	-3.38 (-6.78, 0.02)
Frontal FA*	0.19 (0.01)	0.19 (0.02)	-0.003 (-0.009, 0.003)	-0.002 (-0.008, 0.005)	-0.001 (-0.008, 0.005)
Frontal VR*	1.03 (0.37)	1.10 (0.54)	-0.07 (-0.24, 0.10)	-0.05 (-0.22, 0.12)	-0.05 (-0.23, 0.13)
WMV	525.5 (58.7)	516.1 (56.2)	0.22 (-6.51, 6.97)	2.54 (-3.99, 9.07)	2.84 (-3.85, 9.54)
Deep WM	11.07 (1.23)	11.07 (1.25)	-0.14 (-0.43, 0.14)	-0.0004 (-0.26, 0.26)	-0.02 (-0.29, 0.25)
Deep GM	14.5 (1.38)	14.5 (1.40)	-0.14 (-0.48, 0.20)	-0.04 (-0.26, 0.34)	0.06 (-0.25, 0.37)
Temporal vol	216 (10.9)	212 (23.8)	0.07 (-3.08, 3.24)	1.44 (-1.40, 4.28)	1.39 (-1.51, 4.30)

Temporal FA*	0.22 (0.01)	0.22 (0.01)	-0.003 (-0.009, 0.003)	-0.002 (-0.008, 0.004)	-0.002 (-0.008, 0.004)
Temporal GM	101 (11.1)	99.6 (12.1)	0.11 (-2.25, 2.48)	1.23 (-0.79, 3.26)	1.33 (-0.73, 3.39)
Temporal VR*	1.24 (0.37)	1.26 (0.52)	-0.03 (-0.19, 0.14)	-0.04 (-0.20, 0.13)	-0.02 (-0.20, 0.14)
Temporal WM	114 (13.3)	112 (13.3)	-0.03 (-1.73, 1.66))	0.21 (-1.50, 1.91)	0.06 (-1.68, 1.80)
Ventricle Vol	36.1 (21.6)	32.2 (18.1)	2.64 (-2.69, 7.98)	0.40 (-4.52, 5.33)	0.81 (-4.28, 5.90)
Ventricle FA	0.13 (0.02)	0.13 (0.03)	0.001 (-0.007, 0.01)	0.005 (-0.004, 0.01)	0.004 (-0.004, 0.01)
Ventricle VR	0.83 (0.40)	0.85 (0.50)	-0.01 (-0.17, 0.14)	0.006 (-0.15, 0.16)	0.036 (-0.12, 0.20)
R. posterior cingulate gyrus*	52.9 (15.5)	59.3 (26.7)	**-5.67 (-10.8, -0.54)**	**-5.52 (-10.68, -0.37)**	**-5.63 (-10.9, -0.35)**
L. posterior cingulate gyrus*	52.5 (15.5)	58.5 (17)	**-5.21 (-10.41, -0.01)**	-4.87 (-10.1, 0.34)	-5.06 (-10.38, 0.27)

Note: Values may not sum to the total due to missing data. Linear regression was used for continuous outcomes to calculate differences Model 1: adjusted for ICV. Model 2: adjusted for intracranial volume, age, race, and sex. Model 3: adjusted for ICV, age, race, sex, smoking status, education, marital status, body mass index, systolic blood pressure, diastolic BP, cholesterol, high-density lipoprotein, CVD history, and BP medication. Model 4: adjusted for ICV, age, race, sex, smoking status, education, marital status, body mass index, systolic blood pressure, diastolic BP, cholesterol, high-density lipoprotein, CVD history, and BP medication, dementia prognosis, treatment-arm assignment, and a study outcome event. AF indicates atrial fibrillation; SPRINT, Systolic Blood Pressure Intervention Trial; MRI, magnetic resonance imaging; TBV, total brain volume; CBF, cerebral blood flow; WMV, white matter volume, and GM, gray matter; FA, fractional anisotropy; VR.

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