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Atrial Fibrillation, Brain Structure and Cognitive Function: A Mediation Analysis

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AUTHOR'S SUMMARY

Our study investigated the association among atrial fibrillation (AF), magnetic resonance imaging measured brain parameters and cognitive function. In addition, mediating effect of brain structural change in the association between AF and cognitive function was measured. AF participants showed reduced brain volumes and poorer cognitive function than normal group. AF-cognition association was partially explained by brain volume. These findings suggest that AF is linked to both brain atrophy and cognitive decline, and that structural brain changes play a mediating role. Our results highlight the importance of integrating cardiovascular and cognitive assessments into AF management to better address long-term neurological outcomes.

ABSTRACT

Background and Objectives: Atrial fibrillation (AF) is associated with an increased risk of cerebrovascular disease and cognitive impairment. However, evidence on the mediating role of brain structural changes in this association remains limited, especially in Asian populations. This study investigated the associations among AF, magnetic resonance imaging (MRI)-measured brain structures, and cognitive function, and evaluated the mediation effect of brain structural changes in the AF–cognition link.
Methods: Two thousand, six hundred sixty-two participants from the KoGES-CAVAS-C cohort were analyzed, who without a history of stroke or missing data. AF was identified with electrocardiograms and confirmed by cardiologists. Cognitive function was assessed using the Seoul Neuropsychological Screening Battery-Core. Brain volumes and white matter integrity were measured using standardized MRI protocols. Multivariable linear regression and mediation analyses were performed.

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Conflict of Interest

The authors have no financial conflicts of interest.

Data Sharing Statement

The data generated in this study is available from the corresponding author upon reasonable request.

Author Contributions

Conceptualization: Shin MH; Formal analysis: Yang JH, Shin MH; Investigation: Yang JH, Kweon SS, Kim YM, Kim MK, Shin JH, Chung IS, Koh SB, Kim HC, Lee JM, Kang Y, Shin MH; Methodology: Shin MH; Supervision: Shin MH; Writing - original draft: Yang JH, Shin MH; Writing - review & editing: Kim YM, Kim MK, Chung IS, Koh SB, Kim HC, Lee JM.

Results: Among 2,662 participants, 50 (1.9%) had AF. Participants with AF showed lower total brain volume, regardless of tissue type, and reduced volumes in multiple brain regions. Overall cognitive function and specific domains (memory and executive function) were poorer in the AF group than in the normal group. AF remained significantly associated with lower total brain volume (p=0.005) and cognitive scores (p=0.037) after adjustment. Total brain volume partially mediated the AF–cognition association (p=0.007), accounting for 11% of the effect.

Conclusions: AF is associated with brain atrophy and cognitive impairment, and brain structure partially mediates the association between AF and cognitive function. Our study findings suggest integrated cardiovascular and cognitive assessments in AF management.

Keywords: Atrial fibrillation; Cognition; Brain; Mediation analysis; Cohort studies

INTRODUCTION

Atrial fibrillation (AF) is one of the most common cardiac arrhythmias and a major contributor to stroke, heart failure, and mortality.[1] With its prevalence increasing with age, the health burden of AF is growing along with the aging population.[2] Beyond its established cardiovascular risks, AF is increasingly recognized as a condition with potentially detrimental neurological effects.

Previous studies have consistently reported the association between AF and cognitive function decline or dementia. Several observational studies have shown that AF is associated with cognitive impairment.[3][4] A recent meta-analysis of 15 prospective studies found that AF was associated with the incidence of cognitive impairment in the general population.[5] However, findings have not been entirely consistent; some prospective studies found no significant association,[6] while others suggested the effect might depend on baseline cognitive status.[7]

Several mechanistic pathways have been proposed to explain how AF may lead to cognitive impairment, including cerebral thromboembolism, cerebral hypoperfusion, and systemic inflammation.[8][9] These pathways can result in brain morphometric changes such as clinical or subclinical cerebral infarcts, cerebral microhemorrhages, and brain atrophy. Consistent with these mechanisms, AF has been associated with structural brain changes detectable by magnetic resonance imaging (MRI). Several community-based studies have reported associations between AF and reduced brain volume. For instance, the Framingham Offspring cohort linked AF to lower total cerebral volume and reduced volumes in the frontal and temporal lobes.[10] Similarly, the ARIC study reported reduced volumes in the temporal, parietal, and occipital lobes, as well as in deep gray matter (GM) structures and the hippocampus, among participants with AF.[11] In addition to volumetric atrophy, AF has been associated with an increased burden of cerebrovascular damage, including white matter hyperintensity (WMH) as a marker of chronic small vessel ischemic injury and alterations in diffuse tensor imaging parameters, which reflect white matter (WM) integrity.[12][13] Nonetheless, the morphometric effects of AF have not been consistently observed. For instance, one population-based MRI study found no significant differences in WMH volume among individuals without a history of stroke.[12] Furthermore, a Mendelian randomization study evaluating the causal impact of AF on brain volume did not find a significant association between AF and WM volume.[14]

Most prior studies have examined the association between AF and cognitive function or its link to structural brain changes separately, without explicitly addressing the potential mediating relationship. A recent European study addressed this gap, reporting that structural brain differences partially mediated the association between AF and cognitive performance.[13)] However, evidence for this mediating pathway remains limited. In addition, the clinical course and characteristics of AF, as well as brain morphometry, may vary across ethnic groups.[15-17)] Despite the potential heterogeneity in the association between AF and cognition, few studies in Korea have investigated the interrelationships among AF, MRI parameters, and cognitive function.

Therefore, this study aimed to investigate the associations between AF, MRI-measured brain structural alterations, and cognitive function in a community-based Korean cohort without a history of stroke. In addition, we assessed whether structural brain changes mediate the relationship between AF and cognitive impairment.

METHODS

Ethical statement

The study protocol was approved by the Institutional Review Boards of Hanyang University (HYU-2019-11-002-1, HYUIRB-202011-012-1, HYUIRB-202011-012-2), Chonnam University (06-062), Keimyung University (DSMC-2020-01-058-015), Yonsei Wonju College of Medicine (CR320120), and Yonsei University (4-2019-1206, 4-2020-0817).

Participants

This study analyzed participants from the KoGES-CAVAS-C cohort, a subcohort of KoGES-CAVAS. KoGES-CAVAS-C enrolled individuals aged 55 years or older who were enrolled between 2019 and 2022. The parent cohort, KoGES-CAVAS, initially recruited community-dwelling adults from 2004 to 2012 to investigate epidemiological factors associated with chronic diseases in the Korean population.[18)] Of the 2,908 participants enrolled in KoGES-CAVAS-C, 246 were excluded for the following reasons: missing brain MRI data (n=51), missing cognitive assessment data (n=25), history of overt cerebrovascular accident (n=161), and missing values in key covariates (n=9). Therefore, 2,662 participants were included in the final analysis.

Variables

All participants underwent a 12-lead electrocardiogram, and potential AF cases including atrial flutter were confirmed by cardiologists. MRI data was obtained through standardized protocol including MRI data standardization. MRI scan protocol included T1, T2-weighted, diffusion tensor imaging (DTI), and fluid-attenuated inversion recovery. Volumetric analysis was performed using the CIVET pipeline to measure regional cortical volumes (frontal, temporal, parietal, and occipital lobes), globus pallidus, putamen, thalamus, caudate nucleus, hippocampus. Volumes of globus pallidus, putamen thalamus and caudate nucleus were defined as deep GM volume. Additionally, GM and WM volumes were quantified, and WMH burden was measured. WMH were log transformed due to its right skewed distribution. DTI was used to derive metrics of WM microstructure, including fractional anisotropy, mean diffusivity, radial diffusivity, and axial diffusivity.

The covariates included in the analysis were age, sex, educational attainment, living alone, lifestyle factors (current smoking, drinking status, and physical activity), comorbidities (hypertension, diabetes, dyslipidemia), body mass index (BMI), and study centers.

Educational attainment was categorized into 4 groups: less than middle school, middle school, high school, and college/university or above. Living alone was defined as not residing with a surviving spouse. Drinking status were divided into 3 categories: Current drinker, former drinker and never drinker. Physical activity was defined as engaging in walking for more than 30 minutes per day, at least 5 days per week. Comorbidities (hypertension, diabetes, dyslipidemia) were defined based on a physician's diagnosis.

Cognitive test

Cognitive functions were assessed using the Seoul Neuropsychological Screening Battery-Core (SNSB-C), a validated battery for evaluating overall cognition and specific cognitive domains in Korean populations.[19)] SNSB-C consists of 14 sub-tests: Digit Span Test, a shortened version of the Korean-Boston Naming Test, Rey Complex Figure Test, Seoul Verbal Learning Test-Elderly's version, a shortened version of the Korean-Color Word Stroop Test, Controlled Oral Word Association Test, Korean-Trail Making Test-Elderly's version, and Digit Symbol Coding. Domain-specific scores were derived from the following SNSB-C subtests, based on previous research[20)]: forward and backward digit span tests for the attention domain, the short form of the Korean-Boston Naming Test for the language domain, the Rey Complex Figure Test for the visuospatial function domain, the delayed recall score from the Seoul Verbal Learning Test for the memory domain, and the Korean version of the Trail Making Test for Elderly (part B) for the executive function domain. For illiterate participants, executive function domain scores were treated as missing. In the present study, cognitive functions were assessed using previously developed z-scores, which had been standardized within age–education subgroups in prior research.

Statistical analysis

Participants characteristics, MRI parameters and cognitive function were compared according to prevalent AF status using χ^2 test for categorical variables and independent t test for continuous variables. Potential nonlinearity in the association between age and brain volume were assessed by generalized additive models. As the association was linear, age was included as a linear covariate in all regression analysis (**Supplementary Figure 1**). Association between AF and MRI brain parameters were evaluated with multivariable linear regression. Age, sex adjusted model and full model included all specified covariates were fitted. Additionally, multivariable linear regression analyses were used to examine associations between AF and cognitive functions. Mediation analyses were conducted to assess the indirect effect of AF on cognitive function via brain structural pathways. First, total brain volume was tested as a mediator. Subsequently, mediation analyses were performed to assess whether specific MRI-derived brain structures that showed significant associations with AF in the primary linear regression models mediated the relationship between AF and cognitive outcomes. For these analyses, standardized volumes of the significantly associated brain structures were included as mediators to quantify their indirect effects on the relationship between AF and both overall cognitive function and individual cognitive domains. All statistical analyses were performed using R software (version 4.4.2, R Foundation for Statistical Computing, Vienna, Austria), with mediation analyses conducted specifically using the "mediation" package.

RESULTS

Table 1 shows the baseline characteristics of participants according to their AF status. Among 2,662 participants, 50 had AF and 2,612 did not. Compared to those without AF, participants

Table 1. Participants' characteristics according to atrial fibrillation

Characteristic	Normal group (n=2,612)	AF group (n=50)	p value
Age (years)	67.2±6.4	72.8±4.7	<0.001
Sex			<0.001
Male	919 (35.2)	30 (60.0)	
Female	1,693 (64.8)	20 (40.0)	
Education attainment			0.059
Less than middle school	947 (36.3)	27 (54.0)	
Middle school	506 (19.4)	9 (18.0)	
High school	750 (28.7)	10 (20.0)	
College/University or over	409 (15.7)	4 (8.0)	
Living alone	371 (14.2)	13 (26.0)	0.019
Current smoking	140 (5.4)	5 (10.0)	0.192
Drinking status			0.208
Never drinker	1,521 (58.2)	24 (48.0)	
Former drinker	221 (8.5)	7 (14.0)	
Current drinker	870 (33.3)	19 (38.0)	
Physical activity	1,530 (58.6)	27 (54.0)	0.515
Hypertension	1,229 (47.1)	32 (64.0)	0.017
Diabetes	511 (19.6)	11 (22.0)	0.667
Dyslipidemia	1,168 (44.7)	26 (52.0)	0.305
Body mass index (kg/m^2)	24.8±3.1	24.8±3.7	0.957
Study center			0.539
Center 1	490 (18.8)	10 (20.0)	
Center 2	434 (16.6)	9 (18.0)	
Center 3	422 (16.2)	4 (8.0)	
Center 4	418 (16.0)	7 (14.0)	
Center 5	848 (32.5)	20 (40.0)	
Total brain volume (cc)	971.0±89.9	937.5±74.0	0.003
Gray matter (cc)	506.1±47.3	486.8±44.2	0.004
White matter (cc)	464.9±53.9	450.6±42.3	0.023
Frontal lobe (cc)	423.4±44.3	412.8±35.0	0.038
Temporal lobe (cc)	277.6±27.9	273.6±26.2	0.291
Occipital lobe (cc)	121.9±14.4	121.4±12.9	0.771
Parietal lobe (cc)	234.3±26.5	230.7±20.7	0.221
Deep gray matter (cc)	31.2±2.7	30.0±2.5	0.002
Hippocampus (cc)	6.08±0.71	5.64±0.63	<0.001
White matter hyperintensity (cc)	4.63±5.95	5.54±4.98	0.207
Log transformed WMH	1.05±0.94	1.30±0.96	0.067
Diffuse tensor imaging			
Fractional anisotropy	0.414±0.024	0.406±0.020	0.006
Mean diffusivity (10–^{3}mm/s^2)	0.96±0.07	1.01±0.07	<0.001
Radial diffusivity (10–^{3}mm/s^2)	0.75±0.07	0.80±0.07	<0.001
Axial diffusivity (10–^{3}mm/s^2)	1.38±0.07	1.43±0.07	<0.001
SNSB-C total score (z)	0.03±1.06	−0.28±1.05	0.047
Attention (z)	0.03±1.06	−0.21±1.08	0.133
Language (z)	0.24±0.93	0.40±0.98	0.280
Visuospatial function (z)	−0.62±1.26	−0.89±1.32	0.161
Memory (z)	−0.07±1.06	−0.34±0.91	0.045
Executive function (z)	0.21±1.01	−0.35±1.80	0.038

Values are presented as mean ± standard deviation or number (%). χ^2 tests were conducted for categorical variables and independent t-tests were conducted for continuous variables.
AF = atrial fibrillation; SNSB-C = Seoul Neuropsychological Screening Battery-Core; WMH = white matter hyperintensity.

with AF were significantly older, more likely to be male, and had higher rates of living alone and hypertension. Other demographic and lifestyle characteristics, such as educational attainment, current smoking, drinking status, physical activity, diabetes, dyslipidemia, BMI, and study center distributions, showed no significant differences between the 2 groups. Regarding MRI brain parameters, participants with AF exhibited significantly lower volumes of total brain (937.5±74.0 cc vs. 971.0±89.9 cc, p=0.003), GM, WM, frontal lobe, deep GM, and hippocampus. DTI parameters indicated significant differences as well, with lower fractional anisotropy, higher mean diffusivity, radial diffusivity, and axial diffusivity in the AF group. In terms of cognitive performance assessed using SNSB-C, participants with AF demonstrated significantly lower total cognitive scores (z-score: −0.28±1.05 vs. 0.03±1.06, p=0.047), memory scores, and executive function scores. No significant differences were observed in attention, language, or visuospatial domains.

Table 2 presents the associations between AF, total brain volume and overall cognitive function, initially adjusted for age and sex, and then in a fully adjusted model. After adjusting for all covariates, AF was significantly associated with lower total brain volume (β=−29.71; 95% confidence interval [CI], −50.43 to −8.98; p=0.005) and lower SNSB-C total scores (β=−0.31; 95% CI, −0.60 to −0.02; p=0.037). Regression coefficients of the covariates in full models were presented in **Supplementary Table 1**. Notably, the effect size of AF on cognitive function (β=−0.31) was more than double that of diabetes (β=−0.15) and over 4 times that of hypertension (β=−0.07), indicating a comparatively greater impact than these established vascular risk factors. Furthermore, given that −1.0 and −2.0 z scores are conventionally used to define mild and major cognitive impairment, respectively,[21] the observed −0.31 decline also represents a clinically relevant absolute reduction in cognitive performance.

Supplementary Table 2 represents the association between AF and specific brain structures. In the fully adjusted model, AF was significantly associated with reduced volumes in GM (β=−17.89; 95% CI, −28.72 to −7.06; p=0.001), frontal lobe (β=−13.56; 95% CI, −24.45 to −2.67; p=0.015), temporal lobe (β=−7.16; 95% CI, −13.45 to −0.87; p=0.026), occipital lobe (β=−4.36; 95% CI, −7.88 to −0.83; p=0.016), deep GM (β=−1.41; 95% CI, −2.11 to −0.70; p<0.001), hippocampus (β=−0.17; 95% CI, −0.35 to −0.00; p=0.044). WM volume showed marginal significance after full adjustment (p=0.076), while no significant associations were found for parietal lobe, WMH volume, or DTI metrics in the fully adjusted model.

Supplementary Table 3 shows the association between AF and cognitive domains. In the fully adjusted model, AF was significantly associated with decreased performance in attention (β=−0.31; 95% CI, −0.60 to −0.02; p=0.037), visuospatial function (β=−0.39; 95% CI, −0.72 to −0.05; p=0.026), and executive function (β=−0.48; 95% CI, −0.78 to −0.19; p=0.001). Language and memory domains did not show statistically significant associations with AF.

Figure 1 illustrates the mediation analysis between AF and cognitive function through total brain volume. AF was significantly associated with lower total brain volume (β=−29.705, p=0.005), and total brain volume was positively associated with cognitive function (β=0.0012, p<0.001). The total effect of AF on cognitive function was statistically significant (β=−0.310, p=0.043), and the indirect effect mediated by brain volume was also significant (β=−0.035, p=0.007), suggesting partial mediation.

Table 2. Association between atrial fibrillation and total brain volume and overall cognitive function

Characteristic	Age, sex adjusted		Full model	
	Coefficients (95% CI)	p value	Coefficients (95% CI)	p value
Total brain volume	−30.89 (−51.84 to −9.93)	0.004	−29.71 (−50.43 to −8.98)	0.005
SNSB-C total score	−0.27 (−0.57 to 0.03)	0.074	−0.31 (−0.60 to −0.02)	0.037

Values are regression coefficients (β) with 95% CIs. Age- and sex-adjusted and fully adjusted linear regression models were used. The full model was adjusted for age, sex, education level, living alone status, smoking, alcohol consumption, physical activity, hypertension, diabetes, dyslipidemia, body mass index, and study center.
CI = confidence interval; SNSB-C = Seoul Neuropsychological Screening Battery-Core.

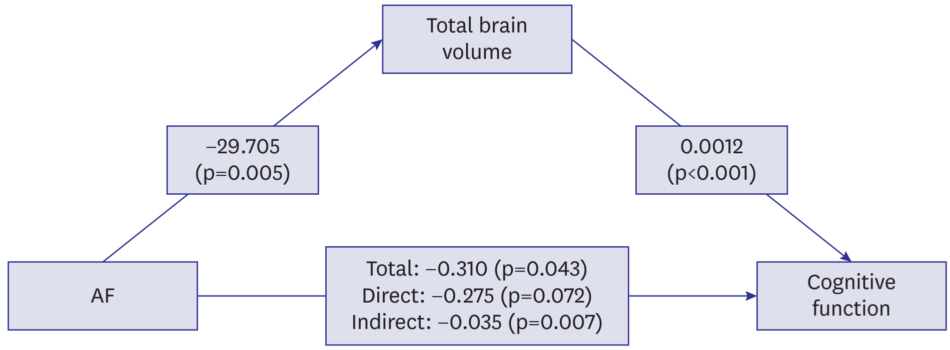

Figure 1. Mediation analysis of the association between AF and cognitive function via total brain volume. Figure shows the results of a mediation analysis assessing whether total brain volume mediates the association between AF and cognitive function. Models were adjusted for age, sex, education level, living alone status, current smoking, drinking status, physical activity, hypertension, diabetes, dyslipidemia, body mass index, and study center. AF = atrial fibrillation.

Supplementary Figure 2 displays the mediating proportion of several brain structures between AF and each cognitive domain. For overall cognitive function, significant mediation was observed through total brain volume (10.9%), GM (11.6%), and occipital lobes (6.7%). Although hippocampal volume had the highest mediating proportion (14.0%), the effect was not statistically significant. In addition, attention domain impairments were notably mediated by GM (10.6%) and total brain volume (9.4%). In contrast, visuospatial function impairments were significantly mediated by total brain volume (6.4%), GM (6.7%), frontal (5.8%), occipital lobes (6.5%), whereas deep GM did not show significant mediation. Regarding executive function, significant mediation was observed for total brain volume (7.4%), GM (9.7%), temporal lobe (4.5%), occipital lobe (4.4%), hippocampus (5.9%), while frontal lobe and deep GM did not demonstrate statistically significant mediation.

As a sensitivity analysis, the associations between AF, total brain volume and overall cognitive function including participants with cerebrovascular disease history were described in **Supplementary Table 4**. AF were significantly associated with total brain volume ($\beta=-33.51$, $p<0.001$). However, association between AF and overall cognitive function was attenuated compared to main analysis in population without cerebrovascular disease history ($\beta=-0.24$, $p=0.082$).

DISCUSSION

The present study found significant associations between AF and structural alterations in multiple brain regions, specifically total brain volume, GM, frontal, temporal, occipital lobes, deep GM, and hippocampus. Additionally, AF was significantly associated with impairments in overall cognitive function, particularly in the domains of attention, visuospatial function, and executive function. Mediation analyses further indicated that structural changes, especially reductions in total brain volume, GM, temporal lobe, occipital lobe, and hippocampus, significantly mediated the relationship between AF and cognitive impairments.

Our findings on brain volumetric changes align with previous neuroimaging research. The inverse association between AF and total brain volume observed in our study corresponds with findings from the Framingham Offspring study (n=2,144).[10] Similarly, our regional volume findings are consistent with the ARIC study, which demonstrated associations between AF and reduced volumes in the temporal lobe, parietal lobe, deep GM, and hippocampus.[11] Furthermore, our results are supported by a recent Mendelian randomization study that established a causal relationship between genetic predisposition to AF and lower GM volume.[22] Regarding cognitive outcomes, our findings complement the existing literature on AF-related cognitive decline. Previous studies consistently indicate that AF is independently associated with cognitive decline; a meta-analysis of prospective longitudinal studies demonstrated an approximately 40% increased risk of dementia or cognitive impairment among individuals with AF, independent of stroke history.[23]

Interestingly, our study did not find significant associations between AF and WM integrity measurements (WMH and DTI parameters). Despite biologically plausible mechanisms linking AF to WM integrity, previous research shows mixed results. While a retrospective study associated AF with anterior subcortical WMH[24] and the Rotterdam Scan Study found associations with periventricular WM lesions,[25] a cross-sectional analysis from ARIC-NCS reported no association between prevalent AF and WM measures.[26] These discrepancies likely arise from variations in study populations—such as the inclusion of embolic stroke patients,[24] where the AF-WMH association is stronger with a history of clinical cerebrovascular accidents[12]—and methodological differences, like limited statistical power in studies with few persistent AF patients.[25]

Several mechanisms have been proposed to explain the observed relationships between AF and cognitive decline.[9] Chronic cerebral hypoperfusion, resulting from irregular cardiac output associated with AF, may lead to reduced blood flow and insufficient oxygen delivery to the brain, ultimately contributing to neuronal damage and brain volume loss. Repetitive microembolic events, originating from thrombi formed in the fibrillating atrium, may cause silent cerebral infarctions and subsequent cumulative microstructural damage to the brain, further exacerbating brain volume reduction and cognitive dysfunction. Systemic inflammation and oxidative stress, commonly elevated in AF patients, can induce endothelial dysfunction, damage the blood-brain barrier, and facilitate neuronal injury and degeneration. Lastly, cerebral small vessel disease, characterized by WM lesions and microbleeds, has also been proposed as a critical pathway linking AF to cognitive impairment.

Despite significant mediation effects, the proportion of the AF-cognition association mediated by total brain volume was approximately 10%. This is similar to a previous mediation analysis involving UK Biobank participants, which reported that GM volume mediated approximately 12% of the association between AF and cognitive domains (attention/executive function and reasoning).[13] This implies that the majority of the association may be attributable to other factors. In particular, additional mechanisms such as silent infarctions and systemic inflammation are proposed to contribute to cognitive decline in AF patients.[8,9] Furthermore, the exclusion of participants with a history of overt cerebrovascular accidents in both the previous mediation study and ours may have led to an underestimation of the contribution of brain atrophy to the AF–cognitive function association.

Several limitations should be acknowledged in interpreting the findings of this study. First, causal inference between AF, brain structural changes, and cognitive impairments cannot be definitively established due to the cross-sectional observational design. Our study design inherently carries the possibility of residual confounding from unevaluated factors

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including alcohol consumption and other lifestyle behaviors. In addition, the design raises the possibility of reverse causation between AF and brain changes AF can be induced after neurological changes through autonomic dysfunction or immune-inflammatory responses.[27) Second, the relatively small number of AF cases may have limited statistical power to detect subtle differences. Future larger research should include prospective longitudinal studies with larger AF cohorts to clearly elucidate temporal relationships between AF onset, structural brain alterations, and cognitive decline. Third, the study participants were exclusively recruited from the Korean general population, potentially limiting the generalizability of these findings to other ethnicities or populations with different clinical profiles. Fourth, clinical factors which are associated with both AF and cognitive function were not assessed in our study, including the AF type and treatment status. Persistent AF may have consistent associations with cognitive decline than paroxysmal AF.[28) Similarly, anticoagulation and rhythm control have been proposed to mitigate adverse cognitive effect of AF. However, existing evidence remains inconsistent and future investigations are warranted to determine their potential contribution to cognitive outcomes.[8)9) In addition, atrial structural and pathophysiological factors such as atrial cardiomyopathy and cardiac amyloid deposition, which have been implicated in the mechanism from AF to cognitive decline,[29)30) were not evaluated.

In conclusion, this study results suggests evidence linking AF and brain structures and cognitive function, especially in Korean general population without of overt cerebrovascular accidents. In addition, brain structure accounted for modest proportion of AF-cognition relationship. These findings highlight the importance of comprehensive neurological assessment and targeted intervention strategies in the managing AF to mitigate cognitive risks. Further longitudinal studies with larger samples are required to clarify causal association.

SUPPLEMENTARY MATERIALS

Supplementary Table 1

Multivariable regression results of covariates in the full model about the association between AF and total brain volume and overall cognitive function

Supplementary Table 2

Association between atrial fibrillation and magnetic resonance imaging brain parameters

Supplementary Table 3

Association between atrial fibrillation and domains of cognitive function

Supplementary Table 4

Association between atrial fibrillation and total brain volume and overall cognitive function in population including cerebrovascular disease history

Supplementary Figure 1

Association between age and total brain volume according to AF status.

Supplementary Figure 2

Mediating proportion of brain structures in the association between AF and cognitive function.

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