Atrial Fibrillation is Associated With Reduced Brain Volume and Cognitive Function Independent of Cerebral Infarcts

Hrafnhildur Stefansdottir, MD; David O. Arnar, MD, PhD; Thor Aspelund, PhD; Sigurdur Sigurdsson, MSc; Maria K. Jonsdottir, PhD; Haukur Hjaltason, MD, PhD; Lenore J. Launer, PhD; Vilmundur Gudnason, MD, PhD

**Background and Purpose**—Atrial fibrillation (AF) has been associated with cognitive decline independent of stroke, suggesting additional effects of AF on the brain. We aimed to assess the association between AF and brain function and structure in a general elderly population.

**Methods**—This is a cross-sectional analysis of 4251 nondemented participants (mean age, 76±5 years) in the population-based Age, Gene/Environment Susceptibility-Reykjavik Study. Medical record data were collected for the presence, subtype, and time from first diagnosis of AF; 330 participants had AF. Brain volume measurements, adjusted for intracranial volume, and presence of cerebral infarcts were determined with magnetic resonance imaging. Memory, speed of processing, and executive function composites were calculated from a cognitive test battery. In a multivariable linear regression model, adjustments were made for demographic factors, cardiovascular risk factors, and cerebral infarcts.

**Results**—Participants with AF had lower total brain volume compared with those without AF ($P<0.001$). The association was stronger with persistent/permanent than paroxysmal AF and with increased time from the first diagnosis of the disease. Of the brain tissue volumes, AF was associated with lower volume of gray and white matter hyperintensities ($P<0.001$ and $P=0.008$, respectively), but not of white matter hyperintensities ($P=0.49$). Participants with AF scored lower on tests of memory.

**Conclusions**—AF is associated with smaller brain volume, and the association is stronger with increasing burden of the arrhythmia. These findings suggest that AF has a cumulative negative effect on the brain independent of cerebral infarcts. (*Stroke,* 2013;44:1020-1025.)

**Key Words:** atrial fibrillation ■ brain imaging ■ cognition ■ cerebral infarct

The number of individuals with atrial fibrillation (AF) is projected to triple in the next 4 decades. Data have emerged showing that AF may be a risk factor for cognitive impairment and dementia independent of stroke, indicating that the arrhythmia has additional adverse effects on the brain. Brain atrophy, both of the gray and white matter, as well as increased white matter hyperintensities (WMHs) have been associated with detriment of brain function, but currently there are limited data regarding AF and brain volume.

Three previous studies did not find a significant association between AF and total brain atrophy. These studies did not report whether there was a difference between patients with paroxysmal and permanent AF, or whether the time from the first diagnosis of AF was of any significance. They also did not report differences in specific brain tissue volumes. Gaining a better understanding of the relationship between AF and brain structure might prove useful for developing interventions to potentially delay the progression to dementia in these patients.

The aim of this study was to examine the association between AF and brain measures on magnetic resonance imaging (MRI) as well as cognitive function using data from the large population-based Age, Gene/Environment Susceptibility-Reykjavik (AGES-Reykjavik) Study. Furthermore, the purpose was to assess the significance of the duration and type of AF (paroxysmal versus persistent/permanent) on these outcome measures.

**Materials and Methods**

The AGES-Reykjavik Study was designed to investigate the genetic and environmental factors contributing to clinical and subclinical diseases at older ages. The study is a continuation of the Reykjavik Study, which was a total population study of men and women born between 1907 and 1935 who were residents of the Greater Reykjavik area in 1967. The study was a longitudinal study performed from...
1967 to 1994 that collected midlife data on cardiovascular traits. The AGES-Reykjavik cohort is a random recruitment of survivors from the Reykjavik Study. It included 5764 subjects (2438 men and 3326 women) aged 67 to 93 years. From September 2002 to February 2006, new data were collected at the research center; a questionnaire was administered, a clinical examination was performed, and images were acquired of the brain, musculoskeletal system, body composition, vasculature, and heart. The study design and initial assessments of the cohort have been described previously in more detail.12

The AGES-Reykjavik Study has been approved by the Icelandic National Bioethics Committee, which acts as the Institutional Review Board for the Icelandic Heart Association, and by the Institutional Review Board for the Intramural Research Program of the National Institute on Aging, National Institutes of Health, Bethesda, MD. Informed consent was obtained from all participants.

Ascertainment of AF
AF was identified by reviewing hospital records and private physician’s records for all participants with the hospital discharge diagnosis codes for AF (International Classification of Diseases, revision 9, code 427.9 or International Classification of Diseases, revision 10, code I48) from any hospital in Reykjavik from January 1, 1987 until the day of the study examination, and by reviewing a 12-lead ECG performed during the AGES-Reykjavik Study comprehensive examination. Prolonged monitoring was not performed. Using information from the participants’ aforementioned records and from the study examination, AF was classified as either paroxysmal or persistent/permanent according to recently published guidelines.13 Those who only had AF that occurred <4 weeks from open heart surgery were excluded. Duration of AF was calculated from the date of first diagnosis of AF until the date of the study examination.

Potential Confounders
Age, sex, education level (primary/secondary/college or university), smoking status (never smoker/ever smoker), and alcohol consumption (none or low [0–7 drinks/week]/moderate or high [>7 drinks/week]) were assessed by a questionnaire. High depressive symptomatology was classified as a score of 26 on the 15-item Geriatric Depression Scale.14 Body mass index was calculated from measured height and weight. Hypercholesterolemia was defined as total cholesterol level >6.0 mmol/L or current use of lipid-lowering drugs. Hypertension was defined as self-reported doctor’s diagnosis, use of hypertensive medications, systolic blood pressure ≥140 mmHg, or diastolic blood pressure ≥90 mmHg. Myocardial infarction was defined as self-reported history of myocardial infarction or evidence on ECG of possible or probable myocardial infarction. Diabetes mellitus was defined as a self-reported doctor’s diagnosis, use of diabetes mellitus–related medications, or fasting blood glucose >7 mmol/L. The diagnosis of heart failure was based on hospital discharge diagnosis codes for heart failure.

MRI Image Acquisition and Image Processing
All participants without contraindications were eligible for a brain MRI performed on a study–dedicated 1.5-T Signa Twinspeed system (General Electric Medical Systems). The AGES-Reykjavik MRI image protocol previously has been described in detail.13 In brief, the protocol included a T1-weighted 3-dimensional spoiled gradient-echo sequence, a proton density/T2-weighted fast-spin echo sequence, a T2*-weighted gradient echo–type echo planar imaging sequence, and a T2-weighted fluid-attenuated inversion recovery sequence. All images were acquired to give full brain coverage in the oblique–axial plane. The T1-weighted and proton density/T2-weighted images were acquired to include the entire skull, inferiorly form the level of the foramen magnum. Brain tissue volumes, including cerebrospinal fluid on all pulse sequences and had associated hyperintensity on fluid-attenuated inversion recovery images with a minimal diameter of 4 mm, except for infarcts in the cerebel- lum and brain stem that had no size criteria and did not require associated hyperintensity. Infarcts with cortical involvement also had no size criteria. The average inter-rater reliability (weighted kappa) was 0.7 for cerebral infarcts, and the intrarater reliability score was 0.9 in 5% of all scans reread without knowledge of the previous reading.

Assessment of Cognitive Function
The battery of cognitive tests included multiple tests of 3 cognitive domains. Similar to other population-based studies, composite scores for memory (MEM), processing speed (SP), and executive function (EF) were constructed based on a theoretical grouping of tests. The MEM composite included the immediate and delayed recall of a modified version of the California Verbal Learning Test.19 The SP composite included the Digit Symbol Substitution Test, Figure Comparison Test, and the Stroop Test parts 1 and 2.20–22 The EF composite included the Digits Backward test, a shortened version of the Spatial Working Memory subtest of the Cambridge Neuropsychological Test Automated Battery, and the Stroop Test part 3.20–23 Sex-specific composite measures were computed by converting raw scores on each test to standardized Z scores separately by sex and averaging the Z scores across the tests in each composite.23 Inter-rater reliability for all tests was excellent (Spearman correlations range, 0.96−0.99). Ascertainment of dementia was performed in a 3-step process that has been described elsewhere.12 Briefly, a consensus diagnosis of dementia based on Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, guidelines was made by a panel that included a geriatrician, a neurologist, a neuropsychologist, and a neuroradiologist taking into account neuropsychological data, MRI of the brain, a neurological examination, and information from interviews of proxies about medical history and social, cognitive, and daily functioning relevant to the diagnosis.

Statistical Analyses
General characteristics and cardiovascular risk factors were compared among participants with and without AF with analysis of covariance (ANCOVA) for continuous outcomes and logistic regression for categorical outcomes. ANCOVA was used to assess the association between AF and each brain MRI measure and the 3 cognitive composite scores. Adjustment for covariates was performed in 2 steps: basic model (age, sex, and education) and multivariable model (basic model plus the previously described demographic and cardiovascular risk factors and presence of cerebral infarcts). To assess whether the association between AF and each cognitive composite score was mediated by brain volume, we adjusted the multivariable model for each brain MRI measure. The association of duration of AF (divided into tertiles) and type of AF (paroxysmal versus persistent/permanent) was then assessed. WMH volume was highly skewed, so that the measure was log-transformed. The means of WMH volumes are reported as antilogs.

In secondary analyses, we assessed for effect modification of cerebral infarcts by including interaction terms in the multivariable model. We also checked for effect modification of anticoagulation use by adding current user of anticoagulants as a covariate to the multivariable model and including interaction terms. Significance was set at P<0.05 for all models. All analyses were performed using SAS version 9.2 (SAS Institute).
Table 1. Characteristics of the Study Cohort by Presence of Atrial Fibrillation Data

<table>
<thead>
<tr>
<th></th>
<th>No AF (n=3921)</th>
<th>AF (n=330)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>75.9 (5.3)</td>
<td>78.0 (5.4)†</td>
</tr>
<tr>
<td>Sex, % men</td>
<td>39.8</td>
<td>62.4‡</td>
</tr>
<tr>
<td>Education, % primary</td>
<td>22.9</td>
<td>18.2</td>
</tr>
<tr>
<td>MMSE</td>
<td>27.1 (2.4)</td>
<td>26.6 (2.5)</td>
</tr>
<tr>
<td>Body mass index</td>
<td>27.0 (4.3)</td>
<td>27.1 (4.4)</td>
</tr>
<tr>
<td>Height, cm</td>
<td>166.8 (9.2)</td>
<td>170.9 (10.1)†</td>
</tr>
<tr>
<td>Ever smoker</td>
<td>56.7</td>
<td>63.9</td>
</tr>
<tr>
<td>Alcohol consumption, moderate/high</td>
<td>1.3</td>
<td>4.3†</td>
</tr>
<tr>
<td>Depressive symptoms</td>
<td>6.5</td>
<td>6.4</td>
</tr>
<tr>
<td>Hypertension</td>
<td>79.3</td>
<td>91.5‡</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>13.6</td>
<td>23.9†</td>
</tr>
<tr>
<td>Heart failure</td>
<td>1.6</td>
<td>14.9‡</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>10.6</td>
<td>15.2*</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>57.6</td>
<td>48.8</td>
</tr>
<tr>
<td>Warfarin use</td>
<td>1.9</td>
<td>46.4‡</td>
</tr>
<tr>
<td>Cerebral infarct on MRI</td>
<td>28.6</td>
<td>48.8‡</td>
</tr>
</tbody>
</table>

AF indicates atrial fibrillation; and MMSE, Mini-Mental State Examination. Data are shown as mean (standard deviation) for continuous variables and as % for categorical variables.

*P<0.05; †P<0.01; and ‡P<0.001 for age-adjusted and sex-adjusted comparison.

Analytical Sample
Of the 5764 participants of the AGES-Reykjavik Study, 5706 gave informed consent to match the study data to the hospital and the private physician’s records. Of these, 4569 had brain MRI scans from which brain volumes could be computed. Demented participants and those with missing information regarding cognitive status were then excluded, leaving 4251 subjects. A subgroup of 3960 had all 3 cognitive domain test composite scores.

Results
Characteristics of the Cohort
Of the 4251 participants, 330 had a diagnosis of AF. Compared with those without AF, participants with AF were older, more often men, consumed more alcohol, were more often using warfarin, and had a higher prevalence of hypertension, previous myocardial infarction, heart failure, diabetes mellitus, and cerebral infarcts on MRI (Table 1). AF was paroxysmal in 41.8% (n=138) of cases and persistent/permanent in 58.2% (n=192). The date of first diagnosis of AF could be confirmed for 315 of 330 cases. The mean duration of AF was 7.6±7.0 years (median value, 6.0 years; range, 0–41 years).

Brain Volumes and AF
In the basic model, AF was associated with lower volume of total brain, gray matter, and white matter, and higher volume of WMH (expressed as a percentage of total intracranial volume; Table 2). After adjusting for further potential confounders, these associations remained significant except for WMH volume (absolute brain volumes are presented in Table I in the online-only Data Supplement). There was a significant difference in total brain and gray matter volume depending on the type of AF, because those with persistent/permanent AF had lower volumes than those with paroxysmal AF (Figure 1 and Table 3). There was a linear trend between increased time since first diagnosis of AF and lower total brain and gray matter volume (Table 4).

![Figure 1. Mean brain volume expressed as percentage of total intracranial volume (with standard error [SE] bars) in individuals without atrial fibrillation (AF), with paroxysmal AF, and with persistent/permanent AF. Adjusted for age, sex, education level, hypertension, myocardial infarction, diabetes mellitus, heart failure, smoking, alcohol consumption, hypercholesterolemia, body mass index, height, and cerebral infarcts on magnetic resonance imaging.](http://stroke.ahajournals.org/)
Table 3. Association Between Types of Atrial Fibrillation and MRI-Measured Brain Volumes: The Age, Gene/Environment Susceptibility-Reykjavik Study

<table>
<thead>
<tr>
<th>Duration of AF</th>
<th>Total Brain Volume</th>
<th>Gray Matter Volume</th>
<th>White Matter Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>No AF (reference)</td>
<td>70.2</td>
<td>43.7</td>
<td>25.2</td>
</tr>
<tr>
<td>1</td>
<td>69.5*</td>
<td>43.1*</td>
<td>25.0</td>
</tr>
<tr>
<td>2</td>
<td>69.4†</td>
<td>42.9†</td>
<td>24.9*</td>
</tr>
<tr>
<td>3</td>
<td>69.3†</td>
<td>43.0†</td>
<td>25.0</td>
</tr>
<tr>
<td>P for linear trend</td>
<td>0.012</td>
<td>0.011</td>
<td>0.16</td>
</tr>
</tbody>
</table>

AF indicates atrial fibrillation.

Data are adjusted mean percentage of total intracranial volume, adjusted for age, sex, education level, hypertension, myocardial infarction, diabetes mellitus, heart failure, smoking, alcohol use, hypercholesterolemia, body mass index, height, and cerebral infaracts on magnetic resonance imaging. For tertiles of AF duration, the values are <3.7 years for tertile 1 (n=105), 3.7 to 8.6 years for tertile 2 (n=105), and >8.6 years for tertile 3 (n=105). Comparison with no AF: *P<0.05; †P<0.01.

In secondary analysis, neither cerebral infarcts nor current warfarin therapy modified the association between AF and the brain volumes (data not shown).

Tests of Cognitive Function and AF
Participants with AF scored lower on tests of all 3 cognitive domains: MEM, SP, and EF. After adjusting for cardiovascular risk factors and cerebral infarcts, AF was no longer significantly associated with SP or EF, but the association between AF and MEM remained largely unchanged (Table 5). Finally, the association between AF and MEM was no longer significant when we added total brain and, separately, gray matter volume corrected for total intracranial volume to the models (data not shown). There was no significant difference in any of the cognitive scores depending on the type of AF. Increased time since the first diagnosis of AF was associated with lower scores on test of MEM (P<0.045 for tertiles of AF duration). There was no significant interaction between cerebral infarcts and AF in their relation to MEM, SP, or EF. Similarly, current warfarin therapy was not a significant interaction factor (data not shown).

Discussion
In this large cross-sectional study of nondemented elderly individuals in the general population, we found a significant association between AF and lower total brain and gray and white matter volumes. For both total brain and gray matter volume, the association was stronger with persistent/permanent compared with paroxysmal AF, and with increased time from first diagnosis of AF, suggesting a cumulative effect. In tests of cognitive function, participants with AF scored significantly lower on tests of MEM. As with brain volume, longer duration of AF was associated with worse outcome. These findings remained significant even after adjusting for the higher prevalence of cardiovascular risk factors and cerebral infaracts in the AF population. The difference in total brain volume between individuals with and without AF equals a year and a half of normal loss of brain volume.17

AF and Brain Volume
Only a few previous studies have examined AF and brain volume. In a study published from the Cardiovascular Health Study of 303 adults 65 to 95 years of age, there was not a significant relation between AF and markers of total brain atrophy.7 However, as the authors point out, the relatively small study may have been underpowered to detect any association. A study from the Framingham Offspring Study of 1841 individuals did not find a significant association between AF and total brain volume.5 Similarly, in a recent case–control study, Knecht et al found no significant difference in total brain volume between those with and without AF. In both of these studies, the average age of the cohort was approximately 10 years younger than in the current study. As mentioned before, we found a linear trend between increased duration of AF and lower total brain volume (ie, the effect may be cumulative with increased AF burden). This may explain the lack of association between AF and total brain volume in younger cohorts.

AF and Cognitive Function
After controlling for vascular factors, AF was associated with MEM but not with EP or SP. The latter 2 cognitive domains are closely associated with subcortical vascular disease that manifests primarily as infarcts and WMH.24 Those having AF for the longest time scored the lowest on tests of MEM. There was a trend toward lower scores in those with persistent/permanent compared with paroxysmal AF, but it did not reach significance.

Table 4. Association Between Duration of Atrial Fibrillation by Tertile and MRI-Measured Brain Volumes: The Age, Gene/Environment Susceptibility-Reykjavik Study

<table>
<thead>
<tr>
<th>Duration of AF</th>
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Data are adjusted mean percentage of total intracranial volume, adjusted for age, sex, education level, hypertension, myocardial infarction, diabetes mellitus, heart failure, smoking, alcohol use, hypercholesterolemia, body mass index, height, and cerebral infarcts on magnetic resonance imaging. For tertiles of AF duration, the values are <3.7 years for tertile 1 (n=105), 3.7 to 8.6 years for tertile 2 (n=105), and >8.6 years for tertile 3 (n=105). Comparison with no AF: *P<0.05; †P<0.01.

Comparison with no AF: *P<0.05.
statistical significance. In the Framingham Offspring Study of men free of symptoms of stroke, AF was associated with lower scores on a number of cognitive tests, mainly on SP and EF rather than MEM.\(^5\) No adjustment was made for silent cerebral infarcts and, as previously mentioned, this pattern of cognitive performance is more consistent with subcortical vascular disease. In the previously mentioned study by Knecht et al\(^9\) that included 87 patients with AF, all participants were free of cerebral infarcts on MRI and, similar to the results of the current study, AF had the strongest association with MEM.

**Potential Mechanisms for the Associations Observed**

The association between AF and brain atrophy and lower performance on tests of MEM could be partially explained by increased comorbidity and cerebral infarcts in the AF population. One possible explanation is that AF causes multiple microembolisms to the brain, causing microinfarcts and subsequent atrophy. Additionally, altered cerebral blood perfusion, attributable to beat-to-beat variation in stroke volume, also may play a part. Cerebral hypoperfusion is associated with a reduction in both the gray and white matter volumes of the brain. However, it seems to have a greater negative effect on the gray matter, which could reflect the higher metabolic demand of the gray matter.\(^25,26\) We did find a stronger association between AF and lower gray matter than white matter, and this finding may support the cerebral hypoperfusion hypothesis. There are some limited data on AF and cerebral blood flow. A small study of patients with no clinical symptoms of heart failure showed that those with AF had reduced regional cerebral blood flow compared with controls.\(^27\) In addition, cerebral blood flow seems to increase after electric cardioversion of AF.\(^28\) These observations might suggest that patients with persistent/permanent AF have, on average, less cerebral perfusion than those with only paroxysmal bursts of AF. We found that those with persistent/permanent AF had lower total brain and gray matter volume compared with paroxysmal AF. It is, however, speculative that maintaining sinus rhythm could have an impact on the progress of brain atrophy and sequential cognitive decline in patients with AF. There are data, albeit limited, supporting this speculation. An observational study demonstrated that those who underwent radiofrequency ablation therapy for AF, which currently offers the most superior available rhythm control therapy for AF, had significantly lower risk for dementia than patients who did not have an ablation.\(^29\) The incidence of dementia in those undergoing ablation was similar to those without AF. Cognitive decline and brain atrophy need to be considered as end points in future prospective studies on treatment outcomes for AF.

**Strengths and Limitations of the Study**

The main strength of this study is the large number of well-described community-dwelling subjects. This study also has some limitations. Because this was a cross-sectional analysis, any inference on direct cause and effect cannot be made. We did not have sufficient information on ejection fraction or stroke volume to include it as a covariate because echocardiography was performed on a proportion of the AGES-Reykjavik Study cohort.\(^30\) Recently, subclinical reductions in cardiac output have been associated with less total brain volume.\(^31\) However, controlling for previous clinical diagnosis of heart failure did not affect the main conclusions of this study. Whether participants had paroxysmal or persistent/permanent AF was determined at the time of the study examination. However, we did not have sufficient information on frequency or length of previous episodes of AF. This is a limitation in our ability to fully assess the actual burden of AF. In general, individuals with AF are older, have increased comorbidities, and more often may have implanted cardiac electronic devices. This might have led to a selection bias in the study if a higher percentage of persons with AF declined to participate in the study or could not undergo the brain MRI. As such, the results may actually underestimate the association between AF and brain volumes and cognition.

**Conclusions**

In the general elderly population, AF is associated with lower total brain volume independent of cerebral infarcts. The association is stronger for persistent/permanent AF than paroxysmal and with increased duration of the disease, suggesting a cumulative effect. The difference is evident in the gray matter and in the white matter of the brain. Future prospective studies are needed to determine whether maintenance of sinus rhythm is of benefit to attenuate brain atrophy and impaired MEM performance.

**Acknowledgments**

The authors thank the participants of the Age, Gene/Environment Susceptibility-Reykjavik Study and the Icelandic Heart Association staff.

**Sources of Funding**

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**Disclosures**

None.

**References**

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Atrial fibrillation is associated with reduced brain volume and cognitive function independent of cerebral infarcts

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## Supplemental table 1 (S1): Association between atrial fibrillation (AF) and MRI measured brain volumes: the AGES-Reykjavik Study

<table>
<thead>
<tr>
<th></th>
<th>No AF</th>
<th>AF</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total brain volume</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>1082.8 (1079.6-1086.0)</td>
<td>1080.5 (1069.5-1091.5)</td>
</tr>
<tr>
<td>Model 1(^a)</td>
<td>1092.4 (1089.6-1095.2)</td>
<td>1076.0 (1066.9-1085.2)</td>
</tr>
<tr>
<td>Model 2(^b)</td>
<td>1059.0 (1045.8-1072.3)</td>
<td>1043.7 (1029.1-1058.3)</td>
</tr>
<tr>
<td><strong>Gray matter volume</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>677.3 (675.3-679.3)</td>
<td>669.3 (662.5-676.0) *</td>
</tr>
<tr>
<td>Model 1(^a)</td>
<td>682.2 (680.5-684.0)</td>
<td>669.0 (663.2-674.7) ‡</td>
</tr>
<tr>
<td>Model 2(^b)</td>
<td>657.6 (649.3-665.8)</td>
<td>645.2 (636.1-654.4) ‡</td>
</tr>
<tr>
<td><strong>White matter volume</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>386.0 (384.5-387.5)</td>
<td>386.2 (381.0-391.3)</td>
</tr>
<tr>
<td>Model 1(^a)</td>
<td>390.3 (388.9-391.6)</td>
<td>383.9 (379.6-388.3) †</td>
</tr>
<tr>
<td>Model 2(^b)</td>
<td>381.4 (375.0-387.7)</td>
<td>376.5 (369.5-383.5) *</td>
</tr>
<tr>
<td><strong>WMH volume</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>19.5 (18.8-20.1)</td>
<td>25.1 (22.9-27.3) ‡</td>
</tr>
<tr>
<td>Model 1(^a)</td>
<td>19.9 (19.2-20.5)</td>
<td>23.2 (21.0-25.3) †</td>
</tr>
<tr>
<td>Model 2(^b)</td>
<td>20.1 (17.0-23.2)</td>
<td>22.0 (18.6-25.4)</td>
</tr>
</tbody>
</table>

Data are mean volume in ml (95% confidence interval). Comparison to no AF: * \(P<0.05\), † \(P<0.01\), ‡ \(P<0.001\)

\(^a\) Model 1: adjusted for age, sex and education level

\(^b\) Model 2: adjusted for age, sex, education level, body mass index, height, smoking, alcohol consumtion, hypercholesterolemia, hypertension, diabetes, myocardial infarction and heart failure and cerebral infarcts on MRI

WMH = white matter hyperintesities
Abstract

Atrial Fibrillation is Associated With Reduced Brain Volume and Cognitive Function Independent of Cerebral Infarcts

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Background and Objectives: Atrial fibrillation (AF) is associated with cognitive dysfunction independently of cerebral infarcts. The present study aimed to evaluate the association of AF with brain function and structure in a general-aged population.

Methods: In this study, we performed a cross-sectional analysis of the Age, Gene/Environment Susceptibility-Reykjavik Study (Age, Gene/Environment Susceptibility-Reykjavik) involving 4,251 non-demented participants (mean age 76 ± 5 years). AF presence, subtypes, and time from the first diagnosis were determined from medical records, and 330 participants were identified as having AF. Brain volume was assessed using magnetic resonance imaging after adjustment for intracranial volume. Memory, information processing speed, and executive function were evaluated using composite scores derived from neuropsychological batteries. Multivariable linear regression models were applied with adjustment for patient background factors, cardiovascular risk factors, and stroke.

Results: Participants with AF had lower brain volume compared to those without AF (p < 0.001). The volume reduction was more pronounced in paroxysmal AF compared to persistent/long-term AF, and was also associated with the duration from first diagnosis. AF was associated with decreased gray matter (p < 0.001) and white matter volumes (p = 0.008), but not with high signal intensity lesions (p = 0.49). Participants with AF had lower memory test scores.

Conclusion: AF is associated with lower brain volume, and this association is increased with increasing AF load. These findings suggest that AF may have cumulative negative effects on brain structure, independent of cerebral infarcts.