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Philipp Krisai, Stefanie Aeschbacher, Michael Coslovsky, Nikki Rommers, Tobias Reichlin, Andreas S. Müller, Jürg H. Beer, Peter Ammann, Angelo Auricchio, Giorgio Moschovitis, Richard Kobza, Dipen Shah, Marcello Di Valentino, Giulio Conte, Georg Ehret, Elisa Hennings, Andreas Monsch, Rebecca E. Paladini, Nicolas Rodondi, Laurent Roten, Matthias Schwenkglenks, Christian Sticherling, Patrick Badertscher, Christine S. Zuern, Tim Sinnecker, Marco Duering, Felix Mahfoud, Leo H. Bonati, David Conen, Stefan Osswald, Michael Kühne & eMBA, for the Swiss-AF Investigators

Ischemic brain infarcts, white matter hyperintensities, and cognitive impairment are increased in patients with Atrial Fibrillation

Brief title: Atrial fibrillation and Cognition

Philipp Krisai[1,2] MD, Stefanie Aeschbacher[1,2] PhD, Michael Coslovsky[2,3] PhD, Nikki Rommers[3] PhD, Tobias Reichlin[4] MD, Andreas S. Müller[5] MD, Jürg H. Beer[6] MD, Peter Ammann[7] MD, Angelo Auricchio[8] MD, PhD, Giorgio Moschovitis[8] MD, Richard Kobza[9] MD, Dipen Shah[10] MD, Marcello Di Valentino[11] MD, Giulio Conte[8] MD PhD, Georg Ehret[10] MD, Elisa Hennings[1,2] MD, PhD, Andreas Monsch[12] PhD, Rebecca E. Paladini[1,2] PhD, Nicolas Rodondi[13,14] MD, MAS, Laurent Roten[4] MD, Matthias Schwenkglenks[15,16] PhD MPH, Christian Sticherling[1,2] MD, MHBA, Patrick Badertscher[1,2] MD, Christine S. Zuern[1,2] MD, Tim Sinnecker[17,18] MD, Marco Duering[18] MD, Felix Mahfoud[1,2] MD, MA, Leo H. Bonati[17,19] MD, David Conen[20] MD MPH, Stefan Osswald[1,2#] MD, Michael Kühne[1,2#] MD eMBA, for the Swiss-AF Investigators

#Stefan Osswald and Michael Kühne contributed equally and should be considered shared last authors.

*A list of authors and their affiliations appears at the end of the paper

1) Cardiology Division, Department of Medicine, University Hospital Basel, University Basel, Basel, Switzerland
2) Cardiovascular Research Institute Basel, University Hospital Basel, University Basel, Basel, Switzerland
3) Department of Clinical Research, University Basel, University Hospital Basel, Basel, Switzerland
4) Department of Cardiology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland.
5) Department of Cardiology, Triemli Hospital Zürich, Zürich, Switzerland
6) Department of Medicine, Cantonal Hospital of Baden and Molecular Cardiology, University Hospital of Zürich, Zürich, Switzerland
7) Department of Cardiology, Kantonsspital St. Gallen, St. Gallen Switzerland
8) Division of Cardiology, Ente Ospedaliero Cantonale (EOC), Cardiocentro Ticino Institute, Regional Hospital of Lugano, Lugano, Switzerland.
9) Department of Cardiology, Luzerner Kantonsspital, Lucerne, Switzerland
10) Division of Cardiology, Department of Medical Specialities, University Hospital Geneva, Geneva, Switzerland
11) Division of Cardiology, Ospedale San Giovanni, Ente Ospedaliero Cantonale, Bellinzona, Switzerland
12) Memory Clinic, Universitäre Altersmedizin, Felix Platter Spital Basel, University of Basel, Basel, Switzerland
13) Institute of Primary Health Care (BIHAM), University of Bern, Bern, Switzerland
14) Department of General Internal Medicine, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland
15) Epidemiology, Biostatistics, and Prevention Institute, University of Zürich, Zürich, Switzerland
16) Health Economics Facility, Department of Public Health, University of Basel, Basel, Switzerland

17) Department of Neurology and Stroke Center, University Hospital Basel, University of Basel, Basel, Switzerland
18) Medical Image Analysis Center (MIAC) and Department of Biomedical Engineering, University of Basel, Basel, Switzerland
19) Rheinfelden Rehabilitation Clinic, Rheinfelden, Switzerland.
20) Population Health Research Institute, McMaster University, Hamilton, Canada

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Address for correspondence:
Philipp Krisai, MD
Department of Cardiology
University Hospital Basel
Petersgraben 4, 4031 Basel, CH
E-Mail: philipp.krisai@usb.ch
Phone: +41 61 265 25 25

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Abstract

Background

The interrelationships between atrial fibrillation (AF), brain lesions and cognitive function are poorly understood. We aimed to investigate the relationship of AF with brain lesions and cognition.

Methods

We enrolled 1,480 patients with and 959 without AF in a multicenter prospective study (Swiss-AF; NCT02105844). We assessed brain structure, and cognition using the Montreal Cognitive Assessment (MoCA). Brain magnetic resonance imaging (MRI) was performed to assess large non-cortical and cortical infarcts (LNCCI), small non-cortical infarcts (SNCI), white matter hyperintensities (WMH), and microbleeds. Using causal mediation analyses, we investigated the direct (lesion-independent) and indirect (lesion-mediated) effects of AF on cognition.

Results

Mean age in AF patients is 75.0 vs. 74.2 years in no-AF patients, 28.6% vs. 36.9% are female, and comorbidities are comparable. The prevalence of MRI-detected brain infarcts (LNCCI and/or SNCI) is 40.1% in AF patients vs. 24.0% in no-AF patients, adjusted OR (95% CI): 1.78 (1.30; 2.44), p = 0.0003. WMH (Fazekas ≥2) are more prevalent in AF patients (59.2% vs 44.4%), adjusted OR (95% CI): 2.03 (1.50; 2.77), p = 4.6e-06. The mean MoCA score is 25.3 in AF patients and 26.4 in no-AF patients. In mediation analysis, the total effect of AF on cognition is -1.05 MoCA points, decomposed into a direct effect of -0.99 and an indirect, lesion-mediated, effect of -0.06 points.

Conclusions

The prevalence of ischemic brain infarcts and WMH is higher in patients with AF than without AF despite comparable comorbidities. AF is associated with lower cognitive function, primarily through a direct effect rather than mediated by brain lesions.

Key words: Atrial fibrillation; brain infarcts; cognitive function.

Plain Language Summary

Atrial fibrillation is a common heart rhythm disorder in which there is an irregular heartbeat. It has been associated with damage to the brain and reduced cognitive function, which is the mental processes involved in thinking, learning, and processing information. However, the relationship is poorly understood. We assessed brain structure and cognitive function in people with similar characteristics that either had or did not have atrial fibrillation. We found that people with atrial fibrillation had more brain damage visible by brain imaging and lower cognitive function, compared to people without atrial fibrillation. The brain damage seen did not seem to be the main cause of the lower cognitive function. The main driver of lower cognitive function was most probably the arrhythmia itself.

Abbreviations and Acronyms

AF	atrial fibrillation
MRI	magnetic resonance imaging
LNCCI	large non-cortical infarcts and cortical infarcts
MoCA	Montreal Cognitive Assessment
SNCI	small non-cortical infarcts
TIA	transient ischemic attack
WMH	white matter hyperintensities

Introduction

Atrial fibrillation (AF) and cognitive function are both highly prevalent, with their incidence continuing to rise in aging populations.[1–3] Patients with AF have an increased risk of reduced cognitive function, but the mechanisms driving this association remain incompletely understood and cannot be fully explained by clinically overt brain infarcts alone.[4] It has been shown that patients with AF have, in addition to overt brain infarcts, a high burden of covert brain infarcts on brain magnetic resonance imaging (MRI), even when treated with oral anticoagulation. Moreover, both overt and covert brain infarcts have been similarly associated with reduced cognitivefunction.[5,6] In addition to AF, patients with reduced cognitive function or dementia often share similar cardiovascular risk factors, such as hypertension, diabetes, and vascular disease.[7–12] This overlap of risk factors makes it challenging to isolate the independent effect of AF on brain lesions and cognitive function from that of these comorbidities.

The hypothesis underlying this population-based study was that vascular brain lesions are more frequent and the main drivers of reduced cognitive function in patients with AF. To examine this hypothesis, we compared the prevalence of brain lesions and cognitive function in patients with and without AF but similar baseline characteristics and comorbidities. Additionally, we employed causal mediation analysis to decompose the total effect into a natural direct (brain lesion-independent) and a natural indirect (brain lesion-mediated) effect of AF on cognitive function.

We show that AF was associated with an increased burden of brain infarcts, moderate to severe white matter hyperintensities, and lower cognitive function. The effect of AF on cognitive function was mostly not mediated by brain lesions and independent of comorbidities, suggesting that AF may impair cognition through a direct, arrhythmia-related mechanism.

Methods

Patient population

The present study is based on the Swiss Atrial Fibrillation (Swiss-AF) cohort (NCT02105844). The study complies with the Declaration of Helsinki, the study protocol was approved by the local ethics committees (lead ethics committee: Nordwest- und Zentralschweiz (EKNZ); participating ethics committees: Kantonale Ethikkommission Bern, Commission Cantonale d'éthique de la recherche Genève (CCER), Ethikkommission Ostschweiz (EKOS), Comitato etico cantonale Ticino, Commission cantonale d'Éthique de la Recherche sur l'être humain Vaud (CER-VD), Kantonale Ethikkommission Zürich; ID: 2014-067; PB_2016-00793; 2021-00701) and informed written consent was obtained from each patient.

The Swiss-AF study is an ongoing, prospective cohort study at 14 centres in Switzerland investigating the association of AF with brain lesions and cognitive function.[5,6,13] The main inclusion criteria were previously documented AF and age ≥65 years. A small number of patients aged 45-64 years were enrolled to assess effects of AF on individuals in the active workforce. Exclusion criteria were the inability to give informed consent or secondary AF due to reversible causes. After enrolment of 2,415 patients with AF from 2014 to 2017, we extended the study and enrolled 1,003 patients without AF from 2018 to 2023 (no-AF group). Inclusion criteria for the no-AF group were age ≥65 years, sinus rhythm on the ECG at enrolment and to have no history of AF. About 10% of patients in the no-AF group underwent a Holter-ECG in addition to the mandatory 12-lead ECG at enrolment. Exclusion criteria were the inability to give informed consent, history of AF, atrial flutter or other relevant supraventricular arrhythmias, contraindications for MRI, and diagnosed or suspected dementia. The enrolment of patients with an acute illness was delayed for 4 weeks.

Of the 3,418 enrolled patients, we excluded those <65 years of age (AF group n=315, no-AF group n=5), those who had no available MRI data (AF group n=604, no-AF group n=24), or cognitive assessment at baseline (AF group n=11, no-AF group=12) and those with incomplete MRI measurements (AF group n=5, no-AF group n=3), leaving 2,439 (71.4%) patients for the current analysis (**Supplementary Figure 1**). Main reasons for missing MRI data were cardiac devices and claustrophobia.

Baseline characteristics of excluded patients compared to included patients are shown in **Supplementary Table 9**.

Clinical variables

At a baseline, in-person study visit, trained study personnel acquired information about patient demographics, prior medical history, interventional and medical treatment and risk factors, using standardized case report forms. After 5 minutes of rest in a sitting, upright position with legs uncrossed and back supported, blood pressure was measured automated with an appropriately sized cuff and validated device. The mean of three consecutive blood pressure measurements was used in all analyses. AF was categorized into paroxysmal or non-paroxysmal AF according to guideline recommendations at the time of study inception.[14] Prior stroke was defined as a focal neurological dysfunction with clinical, imaging or pathological evidence of focal infarction due to ischemic, hemorrhagic or undetermined origin. Transient ischemic attack (TIA) was defined as a transient focal neurological dysfunction without evidence of focal infarction.

Brain magnetic resonance imaging

Brain MRI images were acquired by 1.5 or 3 Tesla scanners with a standardized protocol installed on all MR-scanners at local study centres as described previously.[5]

After local evaluation, all brain MRI data were centrally analyzed by a neuroimaging core lab (Medical Image Analyses Centre, Basel, Switzerland). Blinded expert readers marked and segmented lesions in standardized analyses. Board-certified neuroradiologists confirmed the assessments. Small non-cortical infarcts (SNCI) were defined as lesions ≤20 mm in diameter on FLAIR on axial sections. These lesions could not involve the cortex and had to be consistent with ischemic infarction in the territory of a perforating arteriole located in the white matter, internal or external capsule, deep brain nuclei, thalamus, or brainstem.[15] There was no differentiation between SNCIs and lacunes. Large non-cortical infarcts were defined with a diameter of >20mm. Cortical infarcts were defined as lesions of any size on FLAIR involving the cortex. Large non-cortical infarcts and any cortical infarct (LNCCIs) were combined into one category. White matter hyperintensities (WMH) of presumed vascular origin were identified according to STRIVE-2 criteria.[16] WMH were rated visually using the Fazekas scale, and Fazekas ≥2 was considered to indicate moderate WMH. Cerebral microbleeds (Mb) were defined according to STRIVE-2 criteria and counted on T2*-weighted or susceptibility-weighted imaging. Detailed information on MRI is provided in the supplement.

Cognitive testing

Centrally trained study personnel assessed cognition using the Montreal Cognitive Assessment (MoCA).[17] The MoCA evaluates visuospatial abilities, short-term memory, abstraction, language and executive functions divided into 13 individual test sections. Obtainable scores range from 0-30 points with higher scores indicating better cognitive function across all domains. One point is added to the total test score if the patient had 12 years or less of formal education.

Statistics and Reproducibility

The full analysis set included all patients with MRI and MoCA scores, as described above. Analyses were based on full outcome measurements of the respective outcome with no outcome imputation performed. Missing covariate measurements were very rare, with up to four missing BMI observations and three patients with unknown smoking status. These were imputed using mean values of continuous variables and the most frequent value for categorical variables. We report continuous baseline characteristics as mean (standard deviation) or median (interquartile range) if strongly skewed, and categorical variables as frequencies (percentages).

In line with our underlying hypothesis, we performed the following analyses: We first investigated the association of AF, AF type and oral anticoagulation with the presence of brain lesions using logistic regression models. At a second step, we used linear regression models to investigate the association of AF with the MoCA score. As MoCA predictors, we included AF and each of the brain lesion types (separate models), or AF and the presence of any of the lesion types. We report effect estimates and 95% confidence intervals, as well p-values for the interaction terms between AF and lesion presence.

Next, we considered that according to our underlying hypothesis brain lesions lie on the causal pathway between AF and cognition, potentially having a mediating effect (**Supplementary Figure 2**). Accordingly, as a third step we performed a causal mediation analysis to decompose the potential causal effect of AF to natural direct (brain lesion-independent) and natural indirect (brain lesion-mediated) effects on cognitive function. Again we investigated each brain lesion type separately, as well as the presence of any brain lesion, implementing a weighting-based approach.[18] Confidence intervals (CI) for the estimated natural effects were calculated via bootstrapping. We used simulations to perform a sensitivity analysis assessing the robustness of our findings to the effect of a potential unmeasured confounder.

Finally, we repeated the analyses of the association between AF and cognitive function in patients without any brain lesions to assess these independently of brain lesions.

All regression analyses were performed unadjusted and adjusted for the following predefined variables: age, sex, BMI, smoking status (active vs. non-smoker), history of hypertension, history of diabetes, education level (basic: ≤6 years, middle: 6 to ≤12 years, advanced: >12 years) and use of oral anticoagulation.

In this exploratory, hypothesis-generating analysis we provided p-values without correction for multiple testing. These should be seen as complementary to the effect sizes, indicating the probability of these effects, or more extreme, under the relevant null-hypothesis, and not as confirmatory with respect to a specific threshold. All statistical analyses were performed using R 4.3.3.

Results

Baseline characteristics for 1,480 patients with AF and 959 patients without AF are shown in **Table 1**. Mean age was 75.0 vs. 74.2 years in patients with and without AF, 28.6% vs. 36.9% were female, and mean CHA_2DS_2-VASc score was 3.7 vs. 3.5 points, respectively. Patients with AF more frequently had a history of stroke or TIA (22.1% vs. 13.1%) and a lower rate of coronary heart disease (29.2% vs. 35.0%). Patients with AF had a higher rate of oral anticoagulation (91.6% vs. 8.9 %), but a lower rate of anti-platelet therapy (18.9% vs. 59.1%), than patients without AF. Forty five percent of patients with AF had paroxysmal AF.

AF and brain lesions

The prevalence of brain lesions in both groups is shown in **Figure 1**. LNCCI and/or SNCI were found in 594 (40.1%) patients with AF and in 229 (24.0%) patients without AF. In both groups ≥99% had any WMH, but moderate WMH (Fazekas ≥2) were more prevalent in patients with AF (59.2% vs 44.4%). Mb were found in 351 (24.5%) patients with AF and in 256 (27.0%) patients without AF. Frequency of brain lesions stratified by oral anticoagulation status, is provided in **Supplementary Table 1.**

The odds of infarcts and Fazekas ≥2 were higher in patients with AF, with adjusted odds ratios (aOR) (95% CI) estimated at 1.79 (1.30; 2.45; p = 0.0003) for LNCCI and/or SNCI and 2.03 (1.50; 2.77; p = 4.6e-06) for WMH (Fazekas ≥2). For Mb the aOR was 0.72 (0.51; 1.01; p=0.06) (**Figure 2**). ORs were consistent for paroxysmal and non-paroxysmal AF (**Supplementary Table 2)**. There were no significant interactions of AF and oral anticoagulation for any brain lesion (**Supplementary Table 3**).

AF and cognitive function

The mean MoCA was 1.1 point lower in patients with AF compared to patients without AF (25.3 vs. 26.4 points) (**Figure 3A**). In adjusted linear regression analyses, AF was associated with lower

MoCA scores (β [95% CI] -0.93 [-1.33; -0.54; p = 3.44e-06]) **(Supplementary Table 4)**. This difference in cognitive function was consistent across different age groups, and is comparable to the observed difference in MoCA of patients without AF and with a 9.2-year age difference **(Supplementary Figure 3)**. Importantly, this effect did not vary with age (AF-age interaction p=0.32). When including only patients with no brain lesions of any type, differences in MoCA between patients with and without AF were consistent, though effect estimates were smaller (**Figure 3B** and **Supplementary Table 5**).

In linear regression models, there was a consistent, negative, association of both AF and lesion presence with MoCA score, except for Mb (**Table 2**). The interactions of AF and lesion were not significant, except for LNCCI (**Supplementary Table 6**).

Mediation analysis of AF and cognition

The results of the causal mediation analysis for the natural direct and natural indirect effect of AF on cognitive function are shown in **Figure 4**. The total effects of AF on cognition ranged from -1.02 to -1.05 points of the MoCA score across different lesion types. The natural direct effects of AF were estimated between -0.98 to -1.01 points, while the natural indirect effects, via brain lesions, ranged from 0 to -0.06 points of the MoCA score. For example, when considering the presence of SNCI and/or LNCCI, the total causal effect of AF on MoCA was estimated at -1.02 (-1.39; -0.68), with the natural direct effect of AF estimated at -0.98 (-1.36; -0.63) and the natural indirect effect, via SNCI and/or LNCCI, estimated at -0.04 (-0.09; -0.01). Sensitivity analyses, evaluating the potential impact of unmeasured confounders, showed consistent results. These analyses suggest that even in the presence of a hypothetical strong unmeasured confounder, the natural causal direct effect of AF would still remain substantially larger than the natural indirect effects (**Supplementary Table 7**).

Discussion

In this elderly population with a high prevalence of vascular brain lesions on MRI, ischemic brain infarcts were approximately 1.7 times, and moderate to severe white matter hyperintensities about 1.3 times more prevalent in patients with AF compared to patients without AF. These higher rates of brain lesions were found despite comparable comorbidities and the widespread use of oral anticoagulation in AF patients. Patients with AF exhibited lower cognitive function, and AF was independently associated with ischemic brain infarcts, moderate to severe white matter hyperintensities, and lower cognitive function. Mediation analysis suggested that the impact of AF on cognitive function was predominantly independent of brain lesions. These findings suggest that AF may contribute to reduced cognitive function through mechanisms beyond brain lesions.

Ischemic brain infarcts were more frequent in patients with AF compared to patients without AF, despite comparable baseline characteristics and comorbidities. In the ASSERT trial, the lack of a temporal relationship of device-recorded AF episodes and strokes questioned the role of AF as an independent risk factor for stroke, and instead suggested that AF might serve as an indicator of stroke risk through associated comorbidities.[19] This interpretation could be supported by the high prevalence of brain lesions even in our non-AF cohort and a higher stroke risk in individuals with a high CHA_2DS_2-VASc score, even in the absence of AF. [20–22] Alternatively, a driver of brain lesions in our non-AF cohort might have been non-detected subclinical AF, that was previously shown to be present in about 30% of patients without a prior AF diagnosis,[23,24] though this would be expected to attenuate the currently found association of AF and brain lesions. Recent evidence from a large study involving nearly half a million patients with continuous device monitoring found an increased stroke risk within 5 days of AF episodes lasting >5.5 hours, reinforcing the direct role of AF as a risk factor for stroke.[25] In our analysis, AF was strongly associated with ischemic brain infarcts and microvascular disease, independent of comorbidities, consistent across

different AF types, and unconditional of anticoagulation. Therefore, our results favor the hypothesis that AF itself may be a major risk factor for ischemic brain infarcts and microvascular disease.

In our study, AF was an independent predictor of lower cognitive function, with patients with AF scoring about 1-point lower on MoCA than patients without AF. Although this difference may appear modest, it is comparable to the difference in cognitive function observed in patients with an age difference of about 10 years. This is concerning given the rising prevalence of AF in the aging population. Based on our previous work showing that in patients with AF covert brain lesions lead to a similar decline in cognitive function as overt infarcts,[5,6] we hypothesized that the effect of AF on cognitive function was driven mainly by MRI-detected brain lesions. While we found that micro- and macrovascular brain lesions do associate with cognition similar to prior studies,[26] our current findings challenge the hypothesis: Using causal mediation analysis methods, we found that almost all of the association of AF with reduced cognitive function could be explained via the direct path rather than being mediated via any of the investigated brain lesions. The direct path may comprise multiple undifferentiated paths, including unknown mechanisms with potential other, unknown or unmeasured mediators. An effect of AF on cognition, independent of brain lesions, is also supported by our sensitivity analyses, in which we analysed only patients without any brain lesion, and in which results were consistent. The underlying AF related mechanisms remain speculative but may involve blood pressure fluctuations due to irregular AF and varying ventricular cycle lengths, potentially impairing cerebral perfusion.[27] Among other non-ischemic mechanisms of inflammation and neurodegeneration,[28] impaired brain glymphatic function has recently been implicated in cognitive decline in patients with AF.[29] Moreover, AF may be associated with mental health conditions, including depression and/or

anxiety, that may accentuate the relation of AF and cognitive function.[30,31] These potential confounders may be a limitation to the mediation analysis reported here. However, the sensitivity analysis to the presence of unmeasured confounders suggests that this confounding would have to be unreasonably large to change our conclusions.

The higher prevalence of ischemic brain infarcts and lower cognitive function compared to patients without AF, were found in a well anticoagulated AF population. While the cross-sectional design does not allow to draw conclusions on the effect or directionality of anticoagulation on incident brain lesions or cognitive decline over time, we have previously shown that a relevant number of micro- and macrovascular brain lesions and cognitive decline occurred in patients with AF despite a high rate of anticoagulation.[6] These findings suggest that oral anticoagulation alone does not prevent brain infarcts and loss in cognition in all AF patients. Whether early rhythm control in addition to anticoagulation, as investigated in the EAST-AFNET 4 trial,[32] attenuates the risk of MRI-detected brain lesions and cognitive decline requires further investigation.

The strengths of our study include the unselected, multicenter cohort with standardized MRI and cognitive assessment, allowing for robust comparisons between patients with and without AF. Limitations of the study population include potential confounding factors, cohort differences and unmeasured variables. The causal mediation analysis itself is prone to limitations in an observational, cross-sectional design, in which the sequential order of AF-diagnosis, development of brain lesions and cognition is not unequivocal – the order we examine is an assumption. This limitation is somewhat contracted in a supplemented analysis performed in the subgroup of patients that exhibited no lesions in MRI, which presented similar results with respect to cognitive differences (**Supplementary Table 8**). But, residual confounding remains in that analysis, despite our adjustment for known confounders. As randomization to AF or no-AF is not feasible, our

approach of comparing patients with and without AF and similar demographics and comorbidities represents a suitable method for addressing these questions. While we screened patients to exclude AF before enrolment, including Holter-ECG in about 10% of the patients in addition to a 12-lead ECG, some patients in the no-AF group might still have had subclinical, non-detected AF. This could have led to an underestimation of the true impact of AF on brain lesions and cognition. We did not have data on the location of brain lesions, brain atrophy and cerebral metabolism, which might have impacted cognitive function. In addition, a possible selection bias lies in the fact that a larger fraction of AF patients did not undergo MRI compared to the non-AF patients; however, the majority of these patients did not undergo MRI due to the presence of a device, and not due to other conditions, suggesting that the bias is likely unsubstantial.

In this population-based study of elderly patients with a high prevalence of vascular brain lesions, AF was associated with an increased burden of brain infarcts, moderate to severe white matter hyperintensities, and lower cognitive function, despite high rates of oral anticoagulation. Importantly, the effect of AF on cognitive function was mostly not mediated by brain lesions and independent of comorbidities, suggesting that AF may impair cognition through a direct, arrhythmia-related mechanism.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request. To protect participant privacy, this information is not publicly available. Supplementary Data 1 contains the source data for Figure 3.

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Author Contributions:

Author (Initials)	Roles
PK	Conceptualization, Methodology, Formal analysis, Data curation, Writing – original draft
SA	Methodology, Formal analysis, Writing – original draft
MC	Conceptualization, Methodology, Formal analysis, Data curation, Writing – original draft
NR	Methodology, Formal analysis, Data acquisition, Writing – original draft
TR	Investigation, Data acquisition, Writing – review & editing
ASM	Investigation, Data acquisition, Writing – review & editing
JHB	Investigation, Data acquisition, Writing – review & editing
PA	Investigation, Data acquisition, Writing – review & editing
AA	Investigation, Data acquisition, Writing – review & editing
GM	Investigation, Data acquisition, Writing – review & editing
RK	Investigation, Data acquisition, Writing – review & editing
DS	Investigation, Data acquisition, Writing – review & editing
MDV	Investigation, Data acquisition, Writing – review & editing
GC	Investigation, Data acquisition, Writing – review & editing
GE	Investigation, Data acquisition, Writing – review & editing
EH	Investigation, Data acquisition, Writing – review & editing
AM	Investigation, Data acquisition, Writing – review & editing
REP	Methodology, Data curation, Formal analysis, Writing – original draft
NR	Investigation, Data acquisition, Writing – review & editing

LR	Investigation, Data acquisition, Writing – review & editing
MS	Methodology, Data curation, Formal analysis, Writing – review & editing
CS	Investigation, Writing – review & editing
PB	Investigation, Writing – review & editing
CSZ	Investigation, Data curation, Writing – review & editing
TS	Investigation, Data curation, Writing – review & editing
MD	Investigation, Writing – review & editing
FM	Investigation, Writing – review & editing
LHB	Investigation, Data curation, Writing – review & editing
DC	Investigation, Funding acquisition, Formal analysis, Writing – review & editing
SO	Conceptualization, Methodology, Supervision, Project administration, Funding acquisition, Writing – original draft
MK	Conceptualization, Methodology, Supervision, Project administration, Funding acquisition, Writing – original draft

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Figure legends

Figure 1 Prevalence of brain lesions on MRI in patients with and without atrial fibrillation. The large bars represent the proportion of any brain lesions in the two groups. In addition, the relevant number of patients (N) and the prevalence of each specific lesion type is shown with individual bars within the groups. AF = atrial fibrillation; LNCCI = large non-cortical and cortical infarcts; Mb = microbleeds; SNCI = small non-cortical infarcts; WMH = white matter hyperintensities.

Figure 2 Summaries of logistic regression models for atrial fibrillation (predictor) and brain lesions (outcomes). The centre of the error bars indicates the odds ratio. Two-sided p-values of Wald-tests of the odds ratio are given without correction for multiple testing. N = number of patients included in the model. LNCCI = large non-cortical and cortical infarcts; Mb = microbleeds; SNCI = small non-cortical infarcts; WMH = white matter hyperintensities. Adjusting variables included age, sex, BMI, smoking status (active vs. non-smoker), history of hypertension, history of diabetes, education level (basic: ≤6 years, middle: 6 to ≤12 years, advanced: >12 years) and use of oral anticoagulation.

Figure 3 Cognitive function in patients with AF and patients without AF. (A) Summary MoCA scores in patients with AF and patients without AF and (B) summary conditional on the presence of any lesion identified in MRI. Boxes contain the 25 through 75% quantiles, the thick horizontal lines are the median. Whiskers indicate the most extreme values lying within the box-edge and 1.5 * the interquartile range. Mean values are represented with the crosses and listed below

the graph with standard deviation. The number of patients (N) of each group is shown within the plots. Source data is provided in Supplementary Data 2.

Figure 4 Summary of causal mediation analyses for effect decomposition of atrial fibrillation and different types of brain lesions as mediators for MoCA. The centre of the error bars indicates the estimate. LNCCI = large non-cortical and cortical infarcts; Mb = microbleeds; SNCI = small non-cortical infarcts; WMH = white matter hyperintensities.

Swiss-AF investigators

University Hospital Basel and Basel University: Stefanie Aeschbacher[1,2], Steffen Blum[1,2], Leo H. Bonati[17,19], Désirée Carmine[1,2], David Conen[20], Ludvig Dahlheim[1,2], Corinne Girroy[1,2], Andreas Gasser[1,2], Elisa Hennings[1,2], Ruben Kerler[1,2], Philipp Krisai[1,2], Michael Kühne[1,2], Vincent Meier[1,2], Christine Meyer-Zürn[1,2], Pascal B. Meyre[1,2], Andreas U. Monsch[12], Christian Müller[1,2], Stefan Osswald[1,2], Rebecca E. Paladini[1,2], Raffaele Peter[1,2], Adrian Schweigler[1,2], Christian Sticherling[1,2], Gian Völlmin[1,2], Priska Zuber[19].
Principal Investigator: Stefan Osswald[1,2]; Local Principal Investigator: Michael Kühne[1,2]

University Hospital Bern: Faculty: Drahomir Aujesky[14], Urs Fischer[14], Juerg Fuhrer[4], Laurent Roten[4], Simon Jung[14], Heinrich Mattle[14]; Research fellows: Seraina Netzer[14], Luise Adam[14], Carole Elodie Aubert[14], Martin Feller[14], Axel Loewe[14], Elisavet Moutzouri[14], Claudio Schneider[14]; Study nurses: Tanja Flückiger[14], Cindy Groen[14], Lukas Ehrsam[14], Sven Hellrigl[14], Alexandra Nuoffer[14], Damiana Rakovic[14], Nathalie Schwab[14], Rylana Wenger[14], Tu Hanh Zarrabi Saffari[14]. Local Principal Investigators: Nicolas Rodondi[14], Tobias Reichlin[4]

Stadtspital Triemli Zurich: Alain Bernheim[5], Roger Dillier[5], Michèle Deubelbeiss[5], Franz Eberli[5], Christine Franzini[5], Daniel Hofer[5], Raban Jeger[5], Isabel Juchli[5], Claudia Liedtke[5], Samira Murugiah[5], Jacqueline Nadler[5], Thayze Obst[5], Jasmin Roth[5], Fiona Schlomowitsch[5], Xiaoye Schneider[5], Peter Sporns[5], Katrin Studerus[5], Noreen Tynan[5], Dominik Weishaupt[5], Caroline Wiederkehr[5]. Local Principal Investigator: Andreas Müller[5]

Kantonspital Baden: Corinne Friedli[6], Silke Kuest[6], Karin Scheuch[6], Denise Hischier[6], Nicole Bonetti[6], Alexandra Grau[6], Jonas Villinger[6], Eva Laube[6], Marcel Frick[6], Stefanie Leuenberger[6], Franziska Rutz[6]. Local Principal Investigator: Jürg-Hans Beer[6]

Cardiocentro Lugano: Angelo Auricchio[8], Adriana Anesini[8], Cristina Camporini[8], Maria Luce Caputo[8], Rebecca Peronaci[8], Francois Regoli[8], Martina Ronchi[8]. Local Principal Investigator: Giulio Conte[8]

Kantonsspital St. Gallen: Roman Brenner[7], David Altmann[7], Karin Fink[7], Michaela Gemperle[7], Jessica Meier[7]. Local Principal Investigator: Peter Ammann[7]

Hôpital Cantonal Fribourg: Mathieu Firmann[21], Sandrine Foucras[21], Daniel Hayoz[21], Martine Rime[21]. Local Principal Investigator: Michael Kühne[1,2]

Luzerner Kantonsspital: Benjamin Berte[9], Kathrin Bühler[9], Amir Jadidi[9], Virgina Justi[9], Frauke Kellner-Weldon[9], Richard Kobza[9], Melanie Koch[9], Brigitta Mehmann[9], Sonja Meier[9], Myriam Roth[9], Andrea Ruckli-Kaeppeli[9], Ian Russi[9], Kai Schmidt[9], Mabelle Young[9]. Local Principal Investigator: Michael Kühne[1,2]

Ente Ospedaliero Cantonale Lugano: Elia Rigamonti[8], Carlo Cereda[8], Alessandro Cianfoni[8], Maria Luisa De Perna[8], Jane Frangi-Kultalahti[8], Patrizia Assunta Mayer Melchiorre[8], Anica Pin[8], Serena Staglianò[8], Tatiana Terrot[8], Luisa Vicari[8]. Local Principal Investigator: Giorgio Moschovitis[8].

University Hospital Geneva: Georg Ehret[10], Hervé Gallet[10], Elise Guillermet[10], Francois Lazeyras[10], Karl-Olof Lovblad[10], Patrick Perret[10], Philippe Tavel[10]. Local Principal Investigator: Dipen Shah[10]

University Hospital Lausanne: Nathalie Lauriers[22], Marie Méan[22], Alessandra Pia Porretta[22], Sandrine Salzmann[22], Jürg Schläpfer[22]. Local Principal Investigator: Michael Kühne[1,2]

Bürgerspital Solothurn: Andrea Grêt[23], Jan Novak[23], Sandra Vitelli[23]. Local Principal Investigator: Frank-Peter Stephan[23], Michael Kühne[1,2]

Ente Ospedaliero Cantonale Bellinzona: Jane Frangi-Kultalahti[8], Augusto Gallino[8], Luisa Vicari[8]. Local Principal Investigator: Marcello Di Valentino[8]

University of Zurich/University Hospital Zurich: Helena Aebersold[15], Fabienne Foster[15], Matthias Schwenkglenks[15,16].

Medical Image Analysis Center AG Basel: Marco Düring[18], Tim Sinnecker[18], Anna Altermatt[18], Michael Amann[18], Petra Huber[18], Manuel Hürbin[18], Esther Ruberte[18], Alain Thöni[18], Jens Würfel[18], Vanessa Zuber[18].

Department Clinical Research, University of Basel/University Hospital Basel: Michael Coslovsky[3], Pia Neuschwander[3], Patrick Simon[3].

Schiller AG Baar: Ramun Schmid[24], Christian Baumann[24], Nico Ruckstuhl[24]

[21] Department of Cardiology, Hôpital Cantonal Fribourg, Fibourg, Switzerland. [22] Department of Cardiology, University Hospital Lausanne, Lausanne, Switzerland. [23] Department of Cardiology, Bürgerspital Solothurn, Solothurn, Switzerland. [24] Schiller AG Baar, Baar, Switzerland

Table 2 Summaries of linear regression models for the association of atrial fibrillation and presence of lesion (predictors; separate models for each lesion type) with MoCA (outcomes).

	Unadjusted				**Adjusted**			
	Est	**95%**	**p-**	**p for**	**Est**	**95%**	**p-value**	**p for**
LNCCI/SNCI	-	(-0.98;	8.22e-	0.07	-	(-0.69;	1.750e-	0.13
AF	-	(-1.21;	7.54e-		-	(-1.28;	9.89e-	
LNCCI	-	(-1.03;	3.93e-	0.04	-	(-0.76;	4.22e-	0.03
AF	-	(-1.26;	1.09e-		-	(-1.32;	4.12e-	
SNCI	-	(-1.00;	5.88e-	0.23	-	(-0.70;	0.004	0.44
AF	-	(-1.24;	1.02e-		-	(-1.29;	7.71e-	
Mb	-	(-0.44;	0.22	0.58	0.06	(-0.20;	0.65	0.53
AF	-	(-1.32;	3.26e-		-	(-1.30;	8.51e-	
WMH (Faz	-	(-1.02;	5.87e-	0.74	-	(-0.57;	0.004	0.62
AF	-	(-1.21;	4.94e-		-	(-1.27;	1.33e-	
Any lesion	-	(-1.03;	2.88e-	0.18	-	(-0.57;	0.009	0.21
AF	-	(-1.22;	1.67e-		-	(-1.30;	6.54e-	

Adjusting variables included age, sex, BMI, smoking status (active vs. non-smoker), history of hypertension, history of diabetes, education level (basic: ≤6 years, middle: 6 to ≤12 years, advanced: >12 years) and use of oral anticoagulation. n=2434 for LNCCI and/or SNCI; n=2378 for Mb; n=2433 for WMH (Fazekas ≥2); n=2439 for any lesion. AF = atrial fibrillation; LNCCI = large non-cortical and cortical infarcts; Mb = microbleeds; SNCI = small non-cortical infarcts; WMH = white matter hyperintensities.

Table 1 Baseline characteristics stratified by presence or absence of atrial fibrillation.

	Atrial Fibrillation	**No atrial fibrillation**	**P-value**
	n=1,480	**n=959**	
Age, years	75.0 (6.1)	74.2 (6.0)	0.002
Female sex	424 (28.6)	354 (36.9)	2.30E-05
BMI, kg/m^2	27.5 (4.7)	26.2 (4.3)	7.82E-12
Highest education			8.10E-06
Basic	176 (11.9)	64 (6.7)	
Middle	722 (48.8)	450 (46.9)	
Advanced	582 (39.3)	445 (46.4)	
Active smoker	91 (6.1)	63 (6.6)	0.74
AF type			n.a.
Paroxysmal	666 (45.0)	n.a.	
Non-paroxysmal	814 (55.0)	n.a.	
Time since AF diagnosis, years	3.16 [0.79, 7.96]	n.a.	n.a.
Systolic blood pressure, mmHg	136.2 (18.8)	136.5 (16.9)	0.67
Diastolic blood pressure, mmHg	78.2 (12.1)	75.9 (9.6)	9.10E-08
Pulse pressure, mmHg	58.0 (15.4)	60.6 (14.5)	1.31E-05
CHA_2DS_2-VASc, points	3.7 (1.6)	3.5 (1.4)	0.0031
Diabetes mellitus	248 (16.8)	178 (18.6)	0.28

Sleep apnoea	186 (12.6)	98 (10.2)	0.09
Arterial hypertension	1064 (71.9)	643 (67.0)	0.01
Prior stroke or TIA	327 (22.1)	126 (13.1)	3.59E-08
Prior heart failure	338 (22.9)	147 (15.3)	6.71E-06
Coronary heart disease	432 (29.2)	337 (35.2)	0.002
Peripheral vascular disease	118 (8.0)	88 (9.2)	0.33
Prior renal failure	297 (20.1)	142 (14.8)	0.001
Anticoagulation			0
None	125 (8.4)	874 (91.1)	
VKA	585 (39.5)	13 (1.4)	
NOAC	770 (52.0)	72 (7.5)	
Antiplatelet therapy	280 (18.9)	568 (59.2)	3.51E-92
Beta-blockers	1052 (71.1)	297 (31.0)	5.17E-84
ACE-inhibitors	449 (30.3)	257 (26.8)	0.07
Angiotensin II receptor blockers	495 (33.4)	290 (30.2)	0.1
Aldosterone antagonists	152 (10.3)	38 (4.0)	2.14E-08
Calcium-channel blockers	350 (23.6)	238 (24.8)	0.54

Continuous variables are shown as means (standard deviation). Categorical variables are shown as counts (percentages). ACE = angiotensin-converting enzyme; AF = atrial fibrillation; BMI = body mass index; NOAC = non-Vitamin K antagonists; TIA = transient ischemic attack; VKA = Vitamin K antagonists.

Editorial summary:
Krisai et al. compare brain structure and cognitive function in elderly patients with and without atrial fibrillation using brain MRI and cognitive testing. They find that atrial fibrillation is associated with more brain lesions and lower cognitive function, but the cognitive impairment occurs primarily through direct effects of the arrhythmia rather than through brain damage.

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Ischemic brain infarcts, white matter hyperintensities, and cognitive impairment are increased in patients with atrial fibrillation

Multicenter population based cross-sectional analysis in 2'439 patients

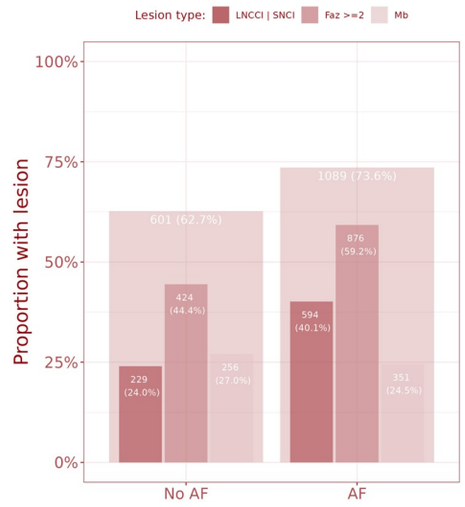
Comparison of MRI findings and cognitive function in patients with / without AF

Mean age 75 years
Female sex 32%

Comparison of 1'480 (61%) AF patients vs. 959 (39%) non-AF patients

Brain lesions

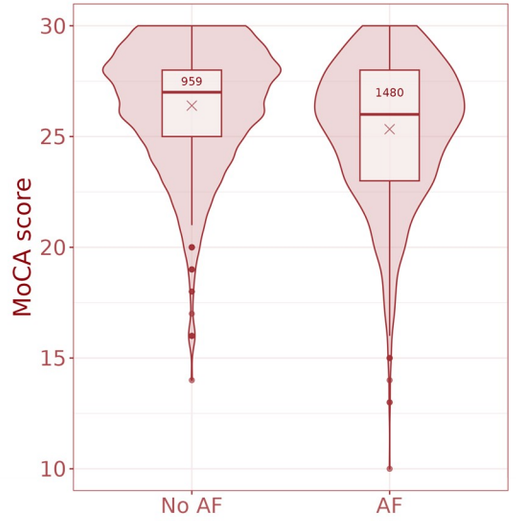
OR 1.79 (95% CI 1.30, 2.45), p=0.0003



Brain lesions are more frequent in AF patients

Cognition

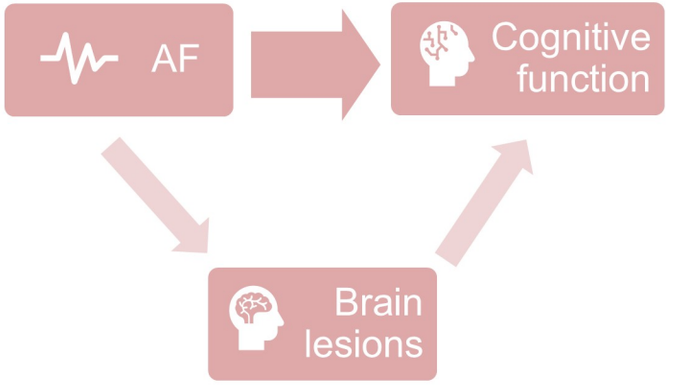
β -0.93 (95% CI -1.33; -0.54), p=3.44e-06



Cognitive function is lower in AF patients

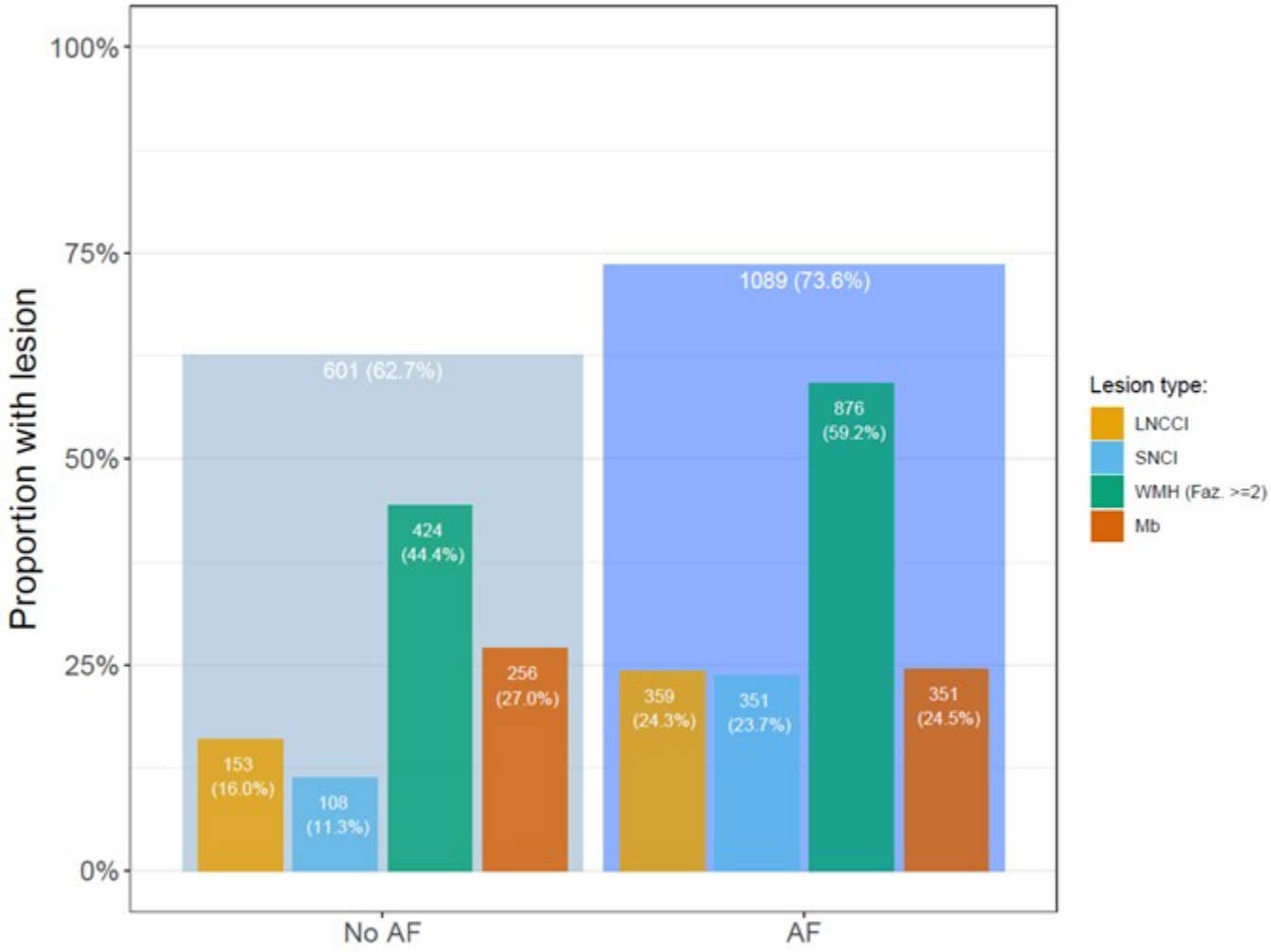
Effect of AF

Direct effect
-0.99 (95% CI -1.32; -0.63)

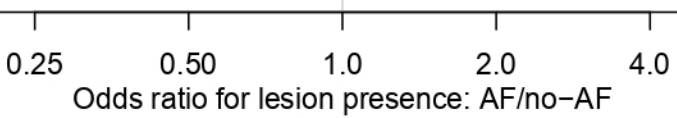


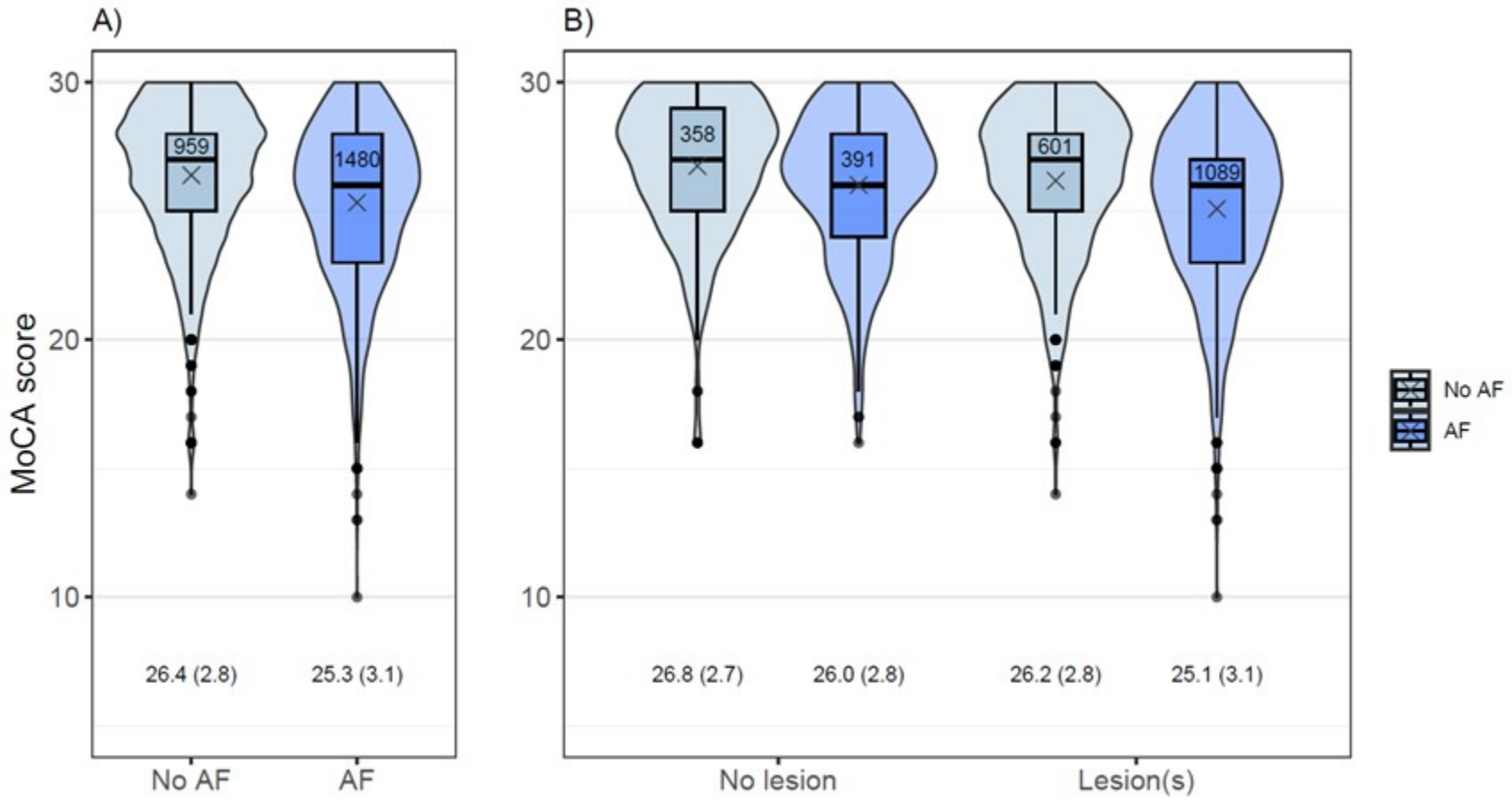
Indirect effect
-0.06 (95% CI -0.10; -0.02)

Effect of AF on cognition is direct and not mediated by brain lesions


100%
75%
50%
25%
0%
Proportion with lesion
601 (62.7%)
153 (16.0%)
108 (11.3%)
424 (44.4%)
256 (27.0%)
1089 (73.6%)
359 (24.3%)
351 (23.7%)
876 (59.2%)
351 (24.5%)
No AF
AF
Lesion type:
LNCCI
SNCI
WMH (Faz. >=2)
Mb

Outcome	Model	N	OR	95% CI	p
LNCCI and/or SNCI	Unadjusted	2434	2.12	(1.77; 2.55)	8.92e−17
	Adjusted	2434	1.78	(1.30; 2.45)	0.0003
LNCCI	Unadjusted	2434	1.68	(1.36; 2.07)	8.54e−07
	Adjusted	2434	1.29	(0.89; 1.86)	0.177
SNCI	Unadjusted	2434	2.44	(1.93; 3.09)	4.27e−15
	Adjusted	2434	2.11	(1.43; 3.13)	0.000166
Mb	Unadjusted	2378	0.88	(0.73; 1.06)	0.171
	Adjusted	2378	0.72	(0.51; 1.01)	0.0579
WMH (Faz. >=2)	Unadjusted	2433	1.82	(1.54; 2.14)	9.18e−13
	Adjusted	2433	2.03	(1.50; 2.77)	4.38e−06
Any lesion	Unadjusted	2439	1.66	(1.39; 1.98)	1.36e−08
	Adjusted	2439	1.52	(1.11; 2.09)	0.00953




A)
B)
30
20
10
MoCA score
959
1480
358
391
601
1089
26.4 (2.8)
25.3 (3.1)
26.8 (2.7)
26.0 (2.8)
26.2 (2.8)
25.1 (3.1)
No AF
AF
No lesion
Lesion(s)
No AF
AF

Mediator	Effect	Estimate	95% CI
LNCCI and/or SNCI	Natural direct effect	−0.98	(−1.36; −0.63)
	Natural indirect effect	−0.04	(−0.09; −0.01)
	Total causal effect	−1.02	(−1.39; −0.68)
LNCCI	Natural direct effect	−0.99	(−1.34; −0.64)
	Natural indirect effect	−0.04	(−0.08; −0.00)
	Total causal effect	−1.03	(−1.38; −0.68)
SNCI	Natural direct effect	−1.01	(−1.37; −0.67)
	Natural indirect effect	−0.01	(−0.04; 0.02)
	Total causal effect	−1.02	(−1.37; −0.68)
Mb	Natural direct effect	−1.02	(−1.40; −0.67)
	Natural indirect effect	−0.00	(−0.03; 0.03)
	Total causal effect	−1.02	(−1.40; −0.67)
WMH (Faz. >=2)	Natural direct effect	−0.98	(−1.34; −0.63)
	Natural indirect effect	−0.05	(−0.09; −0.01)
	Total causal effect	−1.03	(−1.39; −0.68)
Any lesion	Natural direct effect	−0.99	(−1.32; −0.63)
	Natural indirect effect	−0.06	(−0.10; −0.02)
	Total causal effect	−1.04	(−1.38; −0.69)