Journal of the American Heart Association

ORIGINAL RESEARCH

Risk of Dementia Associated With Atrial Cardiopathy: The ARIC Study

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BACKGROUND: The contribution of atrial cardiopathy to dementia risk is uncharacterized. We aimed to evaluate the association of atrial cardiopathy with incident dementia and potential mediation by atrial fibrillation (AF) and stroke.

METHODS AND RESULTS: We conducted a prospective cohort analysis of participants in the ARIC (Atherosclerosis Risk in Communities) study attending visit 5 (2011–2013). We used Cox regression to determine the association between atrial cardiopathy and risk of dementia. Structural equation modeling methods were used to determine potential mediation by AF and/or stroke. Atrial cardiopathy was defined if ≥1 of the following at visit 5: P-wave terminal force >5000 mV·ms in ECG lead V1, NT-proBNP (N-terminal pro–brain natriuretic peptide) >250 pg/mL or left atrial volume index ≥34 mL/m^2 by transthoracic echocardiography. We repeated our analysis necessitating ≥2 markers to define atrial cardiopathy. The prevalence of atrial cardiopathy was 34% in the 5078 participants (mean age 75 years, 59% female, 21% Black adults), with 763 participants developing dementia. Atrial cardiopathy was significantly associated with dementia (adjusted HR, 1.35 [95% CI, 1.16–1.58]), with strengthening of the effect estimate when necessitating ≥2 biomarkers (adjusted HR, 1.54 [95% CI, 1.25–1.89]). There was an increased risk of dementia among those with atrial cardiopathy when excluding those with AF (adjusted HR, 1.31 [95% CI, 1.12–1.55]) or stroke (adjusted HR, 1.28 [95% CI, 1.09–1.52]). The proportion of the effect mediated by AF was 4% (P=0.005), and 9% was mediated by stroke (P=0.048).

CONCLUSIONS: Atrial cardiopathy was significantly associated with an increased risk of dementia, with only a small percent mediation of the effect by AF or stroke.

Key Words: atrial cardiopathy ■ dementia ■ left atrium ■ population study

Atrial fibrillation (AF) is associated with the development of cognitive impairment independent of clinical stroke[1,2] including data from a meta-analysis with >80 000 participants with AF, suggesting that AF, even in the absence of stroke, may contribute independently to cognitive impairment.[3–5]

Atrial cardiopathy, characterized by abnormality in left atrial (LA) structure or function, is increasingly recognized as an important contributor to ischemic stroke.[6] Since atrial cardiopathy is associated with an increased risk of stroke and AF,[7,8] and both stroke and AF are associated with an increased dementia risk,[9] it is important to determine whether a link exists between atrial cardiopathy and dementia, and if present, whether it is independent of AF and stroke. The link between atrial cardiopathy and dementia risk, and mediation of any potential association by AF and stroke have not been previously characterized.

Given that atrial cardiopathy has been suggested as another explanation of LA embolization (than AF alone), clinical trials and other research efforts have begun to incorporate measures of LA size and alternate biomarkers of cardiac function into their work. We have previously demonstrated an association between atrial cardiopathy, defined using the criteria set forth in a major ongoing clinical trial,[10] and florbetapir positron

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Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.121.025646

For Sources of Funding and Disclosures, see page 8.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- Among community-dwelling older adults, atrial cardiopathy was associated with an increased risk of dementia, even after controlling for known vascular risk, and this association was only minimally mediated by either atrial fibrillation or stroke.

What Are the Clinical Implications?

- Our findings suggest that abnormalities in left atrial structure or function may be an independent risk factor for incident dementia.

Nonstandard Abbreviations and Acronyms

ARIC	Atherosclerosis Risk in Communities Study

emission tomography markers of beta-amyloid in the ARIC-positron emission tomography ancillary study.[11] That work, however, excluded individuals with dementia, and although it suggests an association with a major mechanism of dementia, it is important to understand the overall role in dementia risk.

The aim of this study was to define the association of atrial cardiopathy, classified by an established definition based on different components of LA function (LA size, serum NT-proBNP (N-terminal pro–brain natriuretic peptide) and P-wave terminal force on electrocardiography), with incident dementia in a community-based cohort. We hypothesized that there would be an association between atrial cardiopathy and incident dementia independent of vascular risk factors and even among participants without a diagnosis of AF. We also hypothesized that if an association between atrial cardiopathy and incident dementia was found it would not be completely mediated by AF or stroke.

METHODS

Study Population

The study was approved by the Institutional Review Board at all institutions involved and informed consent was obtained. Data that support the findings of this study are available per ARIC (Atherosclerosis Risk in Communities) study policies.

The ARIC study is a community-based cohort study of 15 792 participants originally recruited from 1987 to 1989 from four US communities: Washington County, Maryland; Forsyth County, North Carolina; northwestern suburbs of Minneapolis, Minnesota; and Jackson, Mississippi. More detailed methods about the ARIC study have been previously described.[12] More than 20 years after the initial study visit, participants returned for visit 5 (2011–2013). At visit 5 participants underwent cognitive testing previously detailed.[13,14] Our study population includes participants who did not have dementia up to, and including, the time of evaluation of visit 5 and had echocardiography, electrocardiography, and serum amino NTproBNP performed or collected at visit 5, which was considered this study's baseline. Inclusion criteria also necessitated complete information on important potential confounders of interest, and non-Black participants from Jackson and non-White participants from Washington County or Minneapolis were also excluded attributable to the small numbers, as this is standard practice in ARIC. Two more study visits occurred after visit 5 (this study's baseline), specifically visit 6 (2016–2017) and visit 7 (2018–2019), with ongoing surveillance between study visits. Visit 7, or the last date of surveillance serves as this study's end of follow-up.

Atrial Cardiopathy

The primary independent variable was study-defined atrial cardiopathy. Atrial cardiopathy was defined using 3 different biomarkers that capture different aspects of left atrial structure and function. These criteria were adapted based on our prior work as well as that of ARCADIA (Atrial Cardiopathy and Antithrombotic Drugs In Prevention After Cryptogenic Stroke), a national ongoing clinical trial randomizing patients with ischemic stroke to either anticoagulation or antiplatelet medication based on specific criteria that indicates a state of atrial cardiopathy.[10,11] Specifically ARIC participants were considered to have atrial cardiopathy if ≥1 of the following were present: P-wave terminal force >5000 mV·ms in ECG lead V1, NTproBNP >250 pg/mL, and left atrial volume index ≥34 mL/m^2 by transthoracic echocardiography.[15] Sex specific cut-offs were not used for LA volume index as guidelines have stated that indexing by body surface area accounts for differences in LA size by sex.[16] P-wave terminal force was calculated by multiplying amplitude by duration of the P-wave in lead V1 from a 12-lead ECG. The full ARIC echocardiography protocol, and cardiac evaluation that is performed has been previously described, and a condensed version is provided (Data S1, Supplemental Methods).[17] In a secondary analysis, the definition of atrial cardiopathy was adjusted so that participants had to have at least 2 out of the 3 biomarkers present to meet criteria.

Dementia

The primary dependent variable, or outcome, was dementia onset after visit 5 (participants excluded if dementia at time of visit 5) through the latest date of dementia surveillance (December 31, 2019) or censoring because of death. Dementia determination in ARIC is extensive. Participants who were seen in person at visits 5 through 7 received a comprehensive neuropsychological battery, and an informant interview in a subset of participants. A diagnosis of dementia was generated based on testing results by a computer diagnostic algorithm and then adjudicated by an expert based on the Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition) and the criteria outlined by the National Institutes of Health/National Institute on Aging.[18] In additional to dementia diagnoses determined in person, dementia was also determined by participant telephone cognitive testing as well as informant interview as previously described.[14,19] Finally, additional dementia cases were identified by hospital discharge codes (*International Classification of Diseases, Ninth Revision* [*ICD-9*] codes 331.0, 290.4, 290.0, 290.1, 290.2, 290.3, 290.9, 294.1, 294.2, 294.8, 294.9, 331.1, 331.2, 331.8, and 331.9) or death certificates. When using these methods, the date of dementia diagnosis was given a 6-month lead time recognizing that the true onset was likely before the date listed.

Covariates and Statistical Analysis

The covariates chosen for this analysis were determined based on the potential to either mediate or confound the relationship between atrial cardiopathy and incident dementia. Most variables were assessed at visit 5, with the exception of race, sex, and education level which were all assessed at the baseline visit. The following variables were considered as potential confounders: age, current smoking, hypertension (defined as systolic >140 mm Hg, or diastolic >90 mm Hg, or use of hypertension medication), diabetes (defined as a hemoglobin A1c ≥6.5%), low-density lipoprotein cholesterol (mg/dL), and apolipoprotein E (apoE) genotype (APOEε4 present versus absent). Prevalent stroke, prevalent heart failure, and prevalent coronary heart disease were also determined according to ARIC definitions and adjudication practices,[20] and were considered as potential confounders, except when excluding those with prevalent stroke or when evaluating mediation. Anticoagulation medication use was defined as any anticoagulant type medication (such as heparins/heparinoids, warfarin, direct oral anticoagulants) used in the past 4 weeks, and was considered a time-varying covariate. Hypertension and current smoking were in addition, also considered as time-varying covariates. Mild cognitive impairment was defined as has been previously described.[14]

Cox proportional hazards regression models were used to determine the association atrial cardiopathy and incident dementia. The time to onset of dementia analysis required the participants to attend visit 5 and was not conditional on attending visit 6 or 7 to minimize bias related to competing risk of death after visit 5 or attrition. Participants without the outcome of interest (dementia) were censored at the latest date of the visit 7 assessment, or the last telephone assessment, or death. The analysis was adjusted using nested adjustment models for the covariates just described, which were chosen based on the literature and a prior knowledge about the potential for them to confound the hypothesized association. Specifically, the adjustment models included age, race*enrollment center variable, sex, education level (Model 1), then adding hypertension, diabetes, low-density lipoprotein cholesterol, current smoking status, APOEε4 (Model 2), then finally prevalent stroke, prevalent coronary heart disease, and prevalent heart failure (Model 3). The final model (Model 4) includes the covariates from Model 3, although it includes time-varying hypertension, time-varying current smoking instead, plus adds time-varying anticoagulation medication use. An additional analysis included an interaction term in a separate model to determine the potential for effect measure modification by sex. A sensitivity analysis also included prevalent and incident AF during time of follow-up in Model 3 (Table S1). In sensitivity analyses, we also considered competing risk of death (Table S2). Finally, we performed a sensitivity analysis that excluded participants with mild cognitive impairment (Table S3).

Recognizing that AF might be on the causal pathway between a state of atrial cardiopathy and the development of dementia, a formal mediation analysis was performed using structural equation modeling with estimation of indirect and total effects. The primary analysis used adjudicated AF through the end of visit 5, with a supplemental analysis adding reported cases of AF (not adjudicated) through the end of surveillance. Similarly, recognizing that stroke might be on the causal pathway between a state of atrial cardiopathy and the development of dementia, a formal mediation analysis was similarly performed to isolate the indirect and total effects. Stroke was defined as adjudicated prevalent stroke by the end of visit 5 and/or adjudicated stroke that occurred between visit 5 and the end of surveillance, but before onset of dementia, if dementia occurred. The mediation models were adjusted for age, race, sex, and education level.

Finally, we conducted sensitivity analyses by excluding participants who did not have prevalent AF and/or prevalent stroke at visit 5.

RESULTS

Participant demographics are provided in Table 1. Of 5952 participants, 209 were excluded because of

prevalent dementia by the end of visit 5, 37 were excluded because of being neither Black, or White, or non-Black participants from Jackson, or non-White participants from Washington County or Minneapolis because of small numbers, and 358 were excluded because of lack of dementia surveillance data after visit 5. Covariate data were missing in 270 resulting in a final study population of 5078, of whom 1709 participants met study criteria for atrial cardiopathy (Figure 1); 478 participants had atrial cardiopathy when necessitating at least 2 biomarkers were present. There were several statistically significant differences between participants with and without atrial cardiopathy, such as higher rates of prevalent AF (17.5% versus 2.6%) and prevalent stroke (5.2% versus 2.3%) in those with versus without cardiopathy (Table 1).

Atrial Cardiopathy and Incident Dementia

A total of 763 participants progressed to dementia after visit 5 through the end of follow-up, with a mean time at risk of 2236 days or 6.12 years. Absolute incidence rates of dementia were higher among those with atrial cardiopathy (3.69 per 1000 person-years) than in those without atrial cardiopathy (1.86 per 1000 person-years). In the primary analysis of the entire visit 5 sample that met inclusion criteria, study-defined atrial cardiopathy was significantly associated with increased risk of dementia (HR, 1.35 [95% CI, 1.16–1.58], Model 3) compared with those who did not have atrial cardiopathy after adjusting for confounders (Table 2). There was a larger difference in the cumulative dementia free survival between those with atrial cardiopathy and no evidence of atrial cardiopathy in the unadjusted model (Figure 2A), than in the adjusted model (Figure 2B) with the second curve demonstrating the anticipated dementia free survival of a non-smoking 75-year-old White male with a low-density lipoprotein of 100, without hypertension, diabetes, or an APOEε4 allele.

The results were similar when accounting for time-varying hypertension, smoking, and anticoagulation medication use (HR, 1.35 [95% CI, 1.16–1.58], Table 2, Model 4). The association was stronger when using a stricter definition in which participants had to have at least 2 out of the 3 biomarkers to meet a diagnosis of atrial cardiopathy with strengthening of the effect estimate (HR, 1.54 [95% CI, 1.25–1.89], Model 4).

When including AF (both prevalent and incident cases during follow-up) in the final adjustment model, the results remained nearly unchanged (Table S1). There was no difference in the association between atrial cardiopathy and dementia among men versus women (p-interaction=0.55). After excluding those with mild cognitive impairment (n=1039) from the study population, there was a strengthening of the effect estimate with a slight widening of the confidence interval due to loss of participants (HR, 1.47 [95% CI, 1.20–1.81]; Table S3).

Atrial Cardiopathy and Incident Dementia Among those Without AF

Similar findings were seen among the cohort of participants without a history of AF at visit 5 (n=4691).

Table 1. Participant Demographics, By Atrial Cardiopathy Status, At ARIC Visit 5 (2011–2013)

Participant demographic	Without Atrial Cardiopathy (n=3428)	With Atrial Cardiopathy (n=1735)	*P* value
Age, mean (SD)	74 y (4.6)	77 y (5.2)	<0.001
Female sex	2026 (60.1%)	955 (56.0%)	0.004
Black race	759 (22.5%)	334 (19.5%)	0.014
Education level (years of school)			<0.001
Basic education (≤11)	384 (11.4%)	246 (14.4%)	
Intermediate education (12–16)	1401 (41.6%)	739 (43.2%)	
Advanced education (>17)	1584 (47.0%)	724 (42.4%)	
Current cigarette smoker	193 (5.7%)	93 (5.4%)	0.68
Hypertension	2372 (70.4%)	1389 (81.3%)	<0.001
Diabetes	917 (27.2%)	466 (27.3%)	0.97
Low-density lipoprotein, mean (SD)	106mg/dL (34.0)	101mg/dL (34.5)	<0.001
Prevalent atrial fibrillation/flutter	88 (2.6%)	399 (17.5%)	<0.001
Prevalent stroke	77 (2.3%)	89 (5.2%)	<0.001
Prevalent coronary heart disease	328 (9.7%)	406 (23.8%)	<0.001
Anticoagulation use in the past 4 wks	83 (2.5%)	236 (13.8%)	<0.001
Mild cognitive impairment	641 (19%)	398 (23.3%)	<0.001

Hypertension defined as systolic >140 mm Hg, or diastolic >90 mm Hg, or use of hypertension medication. Diabetes defined as a hemoglobin A1c ≥6.5%. Two-sided *P*<0.05 was considered statistically significant. Presented as n (%) unless otherwise noted. ARIC indicates Atherosclerosis Risk in Communities Study.

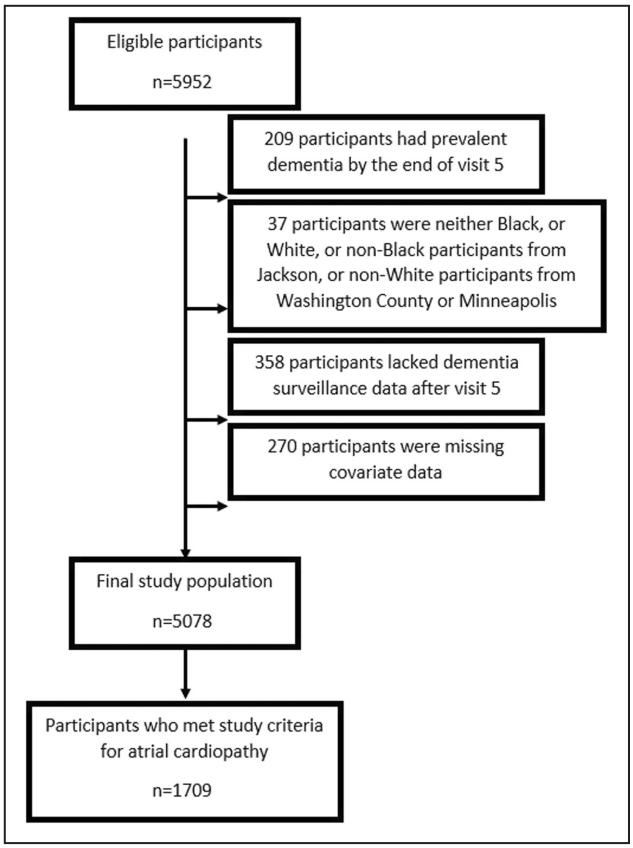

Figure 1. Participant flow diagram.

Specifically, there was a significantly increased risk of dementia among those with atrial cardiopathy (adjusted HR, 1.30 [95% CI, 1.10–1.53]), but with an attenuation of effect and slight widening of the CIs when excluding those with prevalent AF. The results were similar when accounting for time-varying covariates (Table 3). There was again a statistically significant increased risk of dementia seen when necessitating that participants have at least 2 out of 3 biomarkers to meet atrial cardiopathy criteria (adjusted HR, 1.53 [95% CI, 1.21–1.95], Model 4).

Atrial Cardiopathy and Incident Dementia among those Without AF or Stroke

When excluding both those with prevalent AF or prevalent stroke (n=4559), there was still a significant association with an increased risk of dementia among those with atrial cardiopathy (adjusted HR, 1.28 [95% CI, 1.09–1.52], Table 4) with similar magnitude of effect to our primary analysis, which was also reflected when using the stricter definition of atrial cardiopathy (adjusted HR, 1.52 [95% CI, 1.19–1.95]).

Mediation Analyses

In the model where atrial cardiopathy might impact incident dementia through AF (mediator), we tested the (1) effect of atrial cardiopathy on AF, (2) the effect of AF on incident dementia, (3) the effect of atrial cardiopathy on incident dementia, (4) the total effect of atrial cardiopathy on incident dementia, adjusted for AF. The mediation model was adjusted for age, race, sex, and education level. The association between atrial cardiopathy and incident dementia was significantly mediated by AF (P=0.008). The proportion of effect mediated by prevalent AF as well as accounting for incident AF cases during the period of follow-up but before the time of dementia diagnosis, defined as the indirect effect/total effect, was 4% (0.0076/0.2017).

In the model where atrial cardiopathy might impact incident dementia through stroke (mediator), we constructed a similar model as used for AF, except considering adjudicated stroke through the end of surveillance (n=244) as the potential mediator. Participants with prevalent AF were excluded for this analysis. The mediation model was again adjusted for age, race, sex, and education level. The proportion of effect mediated by stroke was 9% (0.0015/0.0160, P=0.048).

Competing Risk Analysis

When considering the possibility of competing risk from death in the association between atrial cardiopathy and dementia, the subhazard ratio for atrial cardiopathy is 1.33 (95% CI, 1.14–1.55; Table S2) in the final adjustment model, which is similar to the effect estimate from the primary analysis. When considering the definition of atrial cardiopathy that only necessitated 2 biomarkers, the effect estimate only slightly attenuated (subhazard ratio, 1.49 [95% CI, 1.21–1.85]) when accounting for competing risk of death (other models not shown).

Table 2. Adjusted Hazard Ratios (95% CIs) for Atrial Cardiopathy (2 Definitions) and Incident Dementia

	Model 1		Model 2		Model 3		Model 4	
(n=5078)	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Atrial cardiopathy	1.46	1.26–1.70	1.45	1.25–1.68	1.35	1.16–1.58	1.35	1.16–1.58
Atrial cardiopathy*	1.65	1.36–1.99	1.69	1.39–2.05	1.54	1.27–1.88	1.54	1.25–1.89

Model 1: Age, race, sex, education level. Model 2: Model 1 + hypertension, diabetes, low-density lipoprotein cholesterol, current smoker, Apoe4. Model 3: Model 2 + prevalent stroke, prevalent heart failure, prevalent coronary heart disease. Model 4: Model 3 except with time-varying hypertension, time-varying smoking status and time-varying anticoagulation use. HR indicates hazard ratio.

*Definition of atrial cardiopathy necessitates at least 2 out of 3 biomarkers.

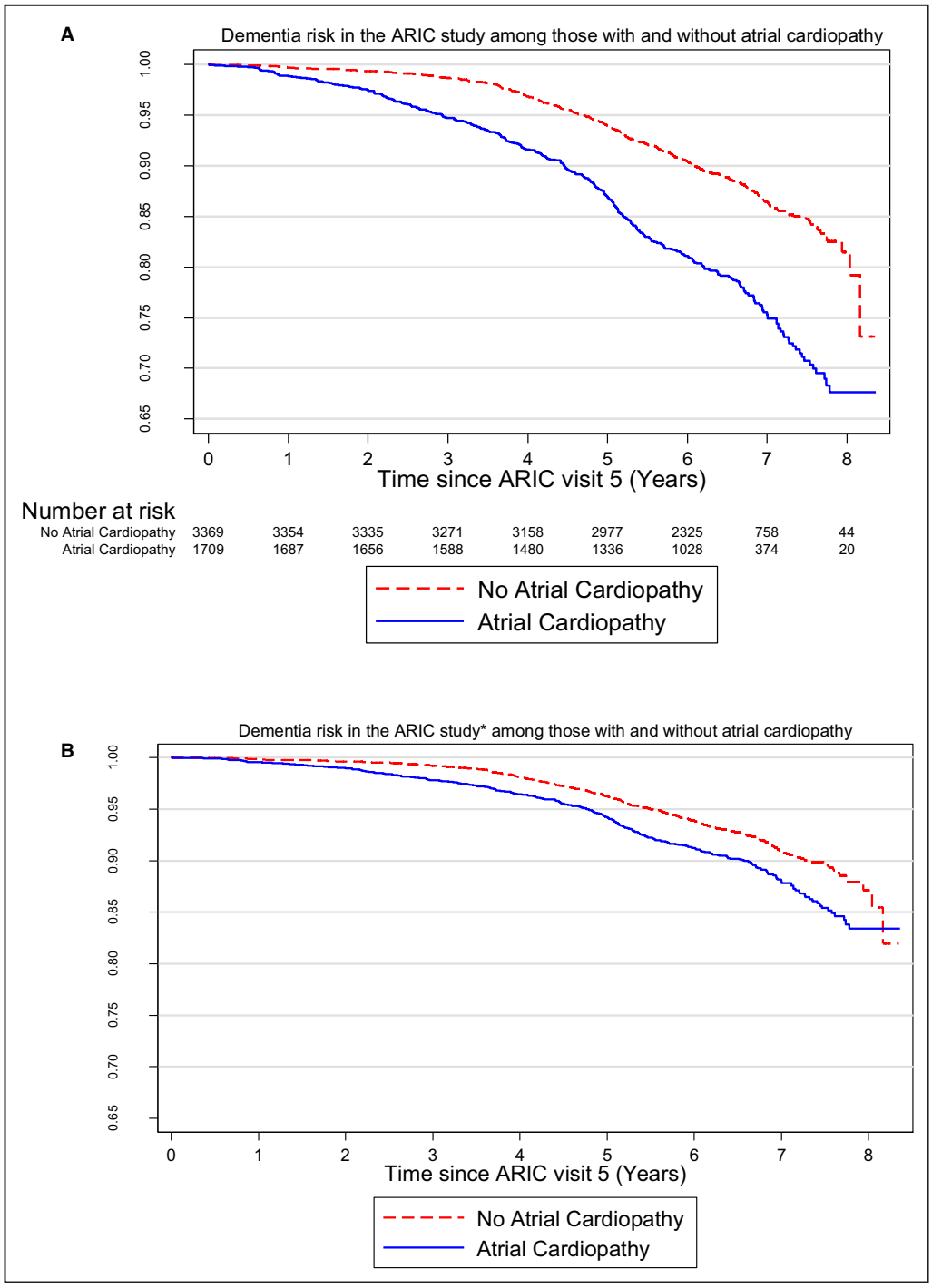

Figure 2. Kaplan–Meier curve demonstrating the cumulative dementia free survival of those with and without study defined atrial cardiopathy unadjusted (A) and adjusted (B)*.
B, Analysis is for a nonsmoking 75 year-old White male with a low-density lipoprotein level of 100 without hypertension, diabetes, or an Apoe4 allele.

DISCUSSION

In our analysis of 5078 community-dwelling, older adults, we found that the presence of atrial cardiopathy was significantly associated with an increased risk of dementia, which remained statistically significant, with strengthening of the effect estimate, when applying more stringent criteria to the definition of atrial cardiopathy. Based on the mediation analysis, we found that both AF and stroke mediated some of the effect

Table 3. Adjusted Hazard Ratios (95% CIs) for Atrial Cardiopathy (2 Definitions) and Incident Dementia Among People Without a Diagnosis of AF

	Model 1		Model 2		Model 3		Model 4	
(n=4691)	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Atrial Cardiopathy	1.39	1.18–1.62	1.38	1.18–1.62	1.30	1.10–1.53	1.31	1.12–1.55
Atrial Cardiopathy*	1.53	1.21–1.94	1.61	1.27–2.04	1.52	1.19–1.92	1.53	1.21–1.95

Model 1: Age, race, sex, education level. Model 2: Model 1 + hypertension, diabetes, low-density lipoprotein cholesterol, current smoker, ApoE4. Model 3: Model 2 + prevalent heart failure, prevalent coronary heart disease. Model 4: Model 3 except with time-varying hypertension, time-varying smoking status and adding time-varying anticoagulation use. AF indicates atrial fibrillation; and HR, hazard ratio.

*Defined atrial cardiopathy necessitates at least 2 out of 3 biomarkers.

between atrial cardiopathy and dementia, but that the relative contributions was <10%. These findings reveal that a state of atrial cardiopathy, which precedes AF and stroke, contributes to the risk of dementia, independent of AF and stroke. We cautiously suggest that an understanding of this relationship might provide a basis for new interventional strategies to help thwart the development of dementia.

Although existing studies have investigated the association between both AF and incident dementia, and stroke and incident dementia,[1,21,22] including work from our own group,[2] to our knowledge, this is the first manuscript to demonstrate the potential relationship between a state of atrial cardiopathy and incident dementia in an asymptomatic cohort, among those without stroke or AF.

Vascular contributions to cognitive impairment and dementia are a growing field, and the emphasis on this area of research is needed as the overlap between athero- and arteriolosclerotic cerebrovascular disease and Alzheimer's Disease (AD) pathology is incompletely understood. While the cerebral pathology behind AD is classically described as amyloid plaques and neurofibrillary tangles, post-mortem analysis has revealed the presence of ischemic type changes co-occurring with this AD pathology, suggesting the potential for overlap between the 2 entities previously considered distinct.[23–25]

There are numerous mechanisms that could result in the neurovascular unit being insulted, and over time potentially failing and thereby leading to cognitive decline. Mechanisms such as a hypercoagulable state, hypoperfusion, inflammation, or genetic interactions could account for the commonality of atrial cardiopathy and cognitive decline, as have been suggested in the setting of AF,[26] although still speculative, emphasizing the need for a more specific link.

It is now understood that a diagnosis of AF should lie more along a continuum, rather than simply considered a binary entity.[27,28] Atrial cardiopathy has been defined as a state of atrial abnormality, at an anatomical, mechanical, or endothelial level, and can occur either in conjunction with or completely independent from AF.[29,30] Given this understanding, we previously considered the association between atrial cardiopathy and the presence of an imaging marker of amyloid beta on florbetapir positron emission tomography in the ARIC study. We found that left atrial volume index and a state of atrial cardiopathy was associated with increased uptake, suggestive of an imaging marker of AD pathology.[11] It is plausible that similar mechanisms that might lead to dementia in patients with AF would occur in participants with atrial cardiopathy.

We report a prevalence of atrial cardiopathy in this study of 33.6% at baseline, which is similar to other estimates, although the majority of the data describing patients with atrial cardiopathy have been done in patients with ischemic stroke. In an analysis of the Columbia University database of unexplained stroke, 35% of those patients without AF met criteria for atrial cardiopathy using NTproBNP, LA enlargement, and P-wave terminal force.[31] Other work in adults without stroke found that 19% of the ARIC population had an abnormal P-wave terminal force, apart from AF, which was also found to be associated with a greater decline in global cognition.[32] We also found that 30% of the ARIC cohort had a LA volume index greater about 35 ml/m^2 (enlarged) which was associated with a higher incidence of dementia compared with those with an LA volume index in the lowest quartile.[33] Determining the prevalence of atrial cardiopathy apart from AF in the general population will be important in advancing research in this area.

While this analysis certainly does not imply causality, it is interesting to consider the ramifications of this association between atrial cardiopathy and dementia. Given that there is no evidence to initiate anticoagulation,[34] as is the case if AF is discovered in patients meeting criteria, it re-emphasizes the potential importance of the prevention of development of atrial cardiopathy. Prevention of sustained vascular risk, particularly in middle-aged adults, may be the best strategy to prevent development of both atrial cardiopathy and incident dementia.

We recognize that there are limitations in our analysis. First, asymptomatic AF or silent cerebral infarction may have been missed by the ARIC adjudication process. Second, another definition of atrial cardiopathy may be superior to the one chosen for this manuscript, but it is a definition that has been used in other

Table 4. Adjusted Hazard Ratios (95% CIs) for Atrial Cardiopathy (2 Definitions) and Incident Dementia Among People Without a Diagnosis of AF or Stroke

	Model 1		Model 2		Model 3		Model 4	
n=4559	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Atrial Cardiopathy	1.35	1.15–1.59	1.35	1.14–1.60	1.26	1.07–1.50	1.28	1.09–1.52
Atrial Cardiopathy*	1.51	1.19–1.94	1.58	1.24–2.03	1.50	1.17–1.93	1.52	1.19–1.95

Model 1: Age, race, sex, education level. Model 2: Model 1 + hypertension, diabetes, low-density lipoprotein cholesterol, current smoker, ApoE4. Model 3: Model 2 + prevalent heart failure, prevalent coronary heart disease. Model 4: Model 3 except with time-varying hypertension, time-varying smoking status and adding time-varying anticoagulation use. AF indicates atrial fibrillation; and HR, hazard ratio.

*Defined atrial cardiopathy necessitates at least 2 out of 3 biomarkers.

research, and by ongoing clinical trials and will therefore offer the ability to compare our findings to other's work. We also used a stricter definition in a sensitivity analysis, necessitating 2 biomarkers with strengthening of our effect estimates. Third, despite the methods used to ascertain the outcome, some participants who died without having dementia may have been censored before dementia was observed. We did however perform a competing risk assessment for death and found that the association remained essentially unchanged. Fourth, dementia is usually a slow process so it may have been that we did not capture some participants with milder symptoms during our follow-up period. We did exclude participants with mild cognitive impairment in a sensitivity analysis to attempt to account for this, and found that our described association strengthened, suggesting that the association found is even more important among those without signs or symptoms of cognitive impairment at study baseline. Fifth, as in all observational studies, there may be residual confounding from some unmeasured variables that we did not consider in our analysis. Sixth, there may be the possibility of survival bias in that participants in our study had to survive to visit 5 to be included. However, this would actually lead to dilution of effect as those who had more extensive underlying cardiac disease, or those who might meet criteria for atrial cardiopathy, would have died so it is encouraging that we still found significant associations among those with potentially milder cardiac changes. Finally, it may be that our findings would not be applicable, or generalizable, among a different population than ARIC, given that it only represents 4 US communities, although it used population-based sampling. It would also not change the internal validity of our results.

In conclusion, among community-dwelling older adults, atrial cardiopathy was associated with an increased risk of dementia, even after controlling for known vascular risk, and this association was only minimally mediated by either AF or stroke.

ARTICLE INFORMATION

Received March 23, 2022; accepted May 25, 2022.

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Acknowledgments

We thank the ARIC staff and participants for their important contributions.

Sources of Funding

The ARIC study is performed as a collaborative study supported by National Heart, Lung, and Blood Institute contracts (HHSN268201700001I, HHSN268201700002I, HHSN268201700003I, HHSN268201700004I, HHSN268201700005I). Neurocognitive data are collected by U01 2U01HL096812, 2U01HL096814, 2U01HL096899, 2U01HL096902, 2U01HL096917 from the National Institutes of Health (National Heart, Lung, and Blood Institute [NHLBI], National Institute of Neurological Disorders and Stroke [NINDS], National Institute on Aging, and National Institute on Deafness and Other Communication Disorders [NIDCD]), and with previous brain magnetic resonance imaging examinations funded by R01-HL70825 from the NHLBI. Dr Johansen receives funding from the NINDS (K23NS112459). Dr Gottesman is supported by the NINDS Intramural Research Program. Dr Chen receives funding from the NHLBI (R01 HL141288, R01 HL126637, K24 HL155813).

Disclosures

Dr Knopman serves on a Data Safety Monitoring Board for the Dominantly Inherited Alzheimer Network (DIAN) Observational Study. He serves on a Data Safety Monitoring Board for a tau therapeutic for Biogen but receives no personal compensation. He is an investigator in clinical trials sponsored by Biogen, Lilly Pharmaceuticals, and the University of Southern California. He serves as a consultant for Roche, Samus Therapeutics, Third Rock, and Alzeca Biosciences but receives no personal compensation.

Supplemental Material

Data S1
Tables S1–S3

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SUPPLEMENTAL MATERIAL

Data S1. Supplemental Methods

Between 2011 and 2013, ARIC participants returned for a 5th study visit during which comprehensive doppler, tissue doppler, 2-dimensional (2D) and speckle tracking echocardiography was performed. All echocardiograms were performed using dedicated Philips iE33 Ultrasound systems with Vision 2011 and X5-1 xMatrix transducer for 2D, Doppler, and 3D data acquisition, purchased specifically for use in the ARIC study. LA size was assessed with 2D echocardiography. Size measurement was performed at the end of systole using biplane disk summation and indexed to body surface area to derive an LA volume index per American Society of Echocardiography guidelines.

Table S1. Adjusted hazard ratios (95%CIs) for atrial cardiopathy (two definitions) and incident dementia adding time-varying atrial fibrillation as a covariate

(N=5078)	HR	95% CI
Atrial Cardiopathy	1.33	1.13-1.55
Atrial Cardiopathy*	1.49	1.20-1.83

*This definition of atrial cardiopathy necessitates at least 2 out of 3 biomarkers
Atrial fibrillation represents both prevalent atrial fibrillation at visit 5 and incident cases during follow-up
Abbreviations: HR: Hazard Ratio, CI: Confidence Interval
Adjustment model: Age, race, sex, education level, time-varying hypertension, diabetes, LDL cholesterol, time-varying smoker, Apoe4, prevalent stroke, prevalent heart failure, prevalent coronary heart disease, time-varying anticoagulation use, time-varying atrial fibrillation

Table S2. Adjusted hazard ratios (95%CIs) for atrial cardiopathy and incident dementia, accounting for competing risk of death								
(N=5078)	Model 1		Model 2		Model 3		Model 4	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Atrial Cardiopathy	1.42	1.23-1.66	1.42	1.22-1.65	1.33	1.14-1.55	1.33	1.14-1.56

Abbreviations: HR: Hazard Ratio, CI: Confidence Interval

Model 1: Age, race, sex, education level

Model 2: Model 1 + hypertension, diabetes, LDL cholesterol, current smoker, Apoe4

Model 3: Model 2 + prevalent stroke, prevalent heart failure, prevalent coronary heart disease

Model 4: Model 3 except with time-varying hypertension, time-varying smoking status and time-varying anticoagulation use

Table S3. Adjusted hazard ratios (95%CIs) for atrial cardiopathy and incident dementia, excluding those with mild cognitive impairment (N=1039)								
(N=4039)	Model 1		Model 2		Model 3		Model 4	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Atrial Cardiopathy	1.58	1.30-1.93	1.55	1.28-1.90	1.45	1.18-1.78	1.47	1.20-1.81

Abbreviations: HR: Hazard Ratio, CI: Confidence Interval

Model 1: Age, race, sex, education level

Model 2: Model 1 + hypertension, diabetes, LDL cholesterol, current smoker, Apoe4

Model 3: Model 2 + prevalent stroke, prevalent heart failure, prevalent coronary heart disease

Model 4: Model 3 except with time-varying hypertension, time-varying smoking status and time-varying anticoagulation use