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Atrial Fibrillation and Risk of Dementia: A Prospective Cohort study

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Abstract

Background/Objectives—Atrial fibrillation may increase dementia risk, but prior studies yielded conflicting results. Many had low power or limited measures of dementia. We investigated whether atrial fibrillation is associated with increased risk of incident dementia or Alzheimer disease, beyond its effect on stroke.

Design—A prospective cohort study

Setting—An integrated healthcare delivery system

Participants—A population-based sample of 3,045 community-dwelling adults age 65 and older without dementia or clinical stroke, followed from 1994-2008.

Measurements—Atrial fibrillation was identified from health plan electronic data using International Classification of Diseases, version 9, codes from inpatient and outpatient encounters. Covariates came from self-report, study measures, and health plan data. Participants were screened every 2 years with the Cognitive Abilities Screening Instrument (score range, 0-100), with detailed neuropsychological and clinical assessment of those scoring less than 86. The outcomes of all-cause dementia and possible or probable Alzheimer disease were determined by a multidisciplinary consensus committee using standard research criteria.

Results—Atrial fibrillation was present in 132/3,045 (4.3%) participants at baseline and was diagnosed in 370 (12.2%) more over a mean of 6.8 years of follow-up. 572 participants (18.8%) developed dementia (449 with Alzheimer disease). The adjusted hazard ratio for all-cause dementia associated with atrial fibrillation was 1.38 (95% CI 1.10-1.73) and for possible or probable Alzheimer disease, 1.50 (95% CI 1.16-1.94). Results were similar for participants with or without clinically recognized stroke during follow-up and in sensitivity analyses examining only probable Alzheimer disease.

Conclusion—Atrial fibrillation is associated with higher risk of developing Alzheimer disease and dementia. Future studies should examine whether specific treatments including optimal anticoagulation can decrease this risk.

Keywords

atrial fibrillation; cardiac arrhythmia; dementia; Alzheimer disease; epidemiology

Introduction

By 2030, nearly 1 in 5 Americans (71.5 million) will be 65 or older.[1] Worldwide, the number of people age 65 and older is projected to reach 1.3 billion by 2040.[2] Cognitive impairment is one of the most feared conditions associated with aging. In the United States, the estimated costs of Alzheimer disease (AD) are 172 billion dollars each year.[3] Most of the known risk factors for dementia are not modifiable, including the most robust risk factor currently known, APOE genotype.

Evidence is emerging that atrial fibrillation (AF), a common heart arrhythmia, may contribute to dementia risk.[4-8] AF affects 3 million people in the United States, including more than 10% of people age 80 and older.[9] AF increases the risk of stroke,[10] which is known to increase dementia risk.[11, 12] Beyond its effect on clinically recognized stroke, AF could increase dementia risk via other mechanisms such as decreased cerebral perfusion[13, 14] or thromboembolism causing silent cerebral infarction.[15] Such insults may act in concert with other neuropathologic processes such as neuritic plaques and

neurofibrillary tangles, which are common in older individuals, to lower cognitive reserves and hasten the onset of dementia. It is also possible that AF and dementia are associated because they share underlying risk factors or pathophysiologic mechanisms such as inflammation. The potential association between AF and dementia has important implications because the best approach to treating AF is not known. If there were a causal relationship between AF and the development of dementia, then different treatment strategies for AF might have differing effects on dementia risk.

Prior studies of AF and dementia have yielded conflicting results. Of eight longitudinal studies,[6-8, 16-20] three found that AF was associated with increased risk of dementia[6-8], while five found no association (please see online appendix).[6-8, 16-20]. Most studies were small, with less than 700 subjects,[7, 8, 17-20] and length of follow-up was relatively short,[7, 16-18, 20] limiting their power. The largest study relied on solely administrative data to identify dementia,[6] which likely led to poor measurement of this outcome. All but one prior study identified AF only at baseline, which likely led to substantial misclassification since participants may have developed AF during follow-up. A recent meta-analysis combined results across seven prospective studies and reported an overall odds ratio of 1.6 (95% confidence interval [CI], 1.0-2.7) for the association between AF and dementia, but there was substantial heterogeneity across studies, and all were rated as having moderate to high risk of bias.[21]

We examined the association between AF and dementia within the Adult Changes in Thought (ACT) study, a prospective, population-based cohort study of risk factors for dementia in older adults. Strengths of ACT include long follow-up and rigorous ascertainment of dementia outcomes. Our objective was to determine whether AF is associated with increased risk of incident all-cause dementia or AD in older adults, independent of its effect on clinically-recognized stroke.

Methods

Study Design and Setting

ACT is a population-based cohort study set within Group Health (GH), an integrated healthcare delivery system. GH maintains extensive electronic data including International Classification of Diseases, version 9 (ICD-9) codes from inpatient and outpatient encounters, laboratory data, and pharmacy data. Participants gave informed consent, and all study procedures were approved by GH's Human Subjects Review Committee, in accordance with ethical rules for human experimentation stated in the Declaration of Helsinki.

Population

Study methods have been described in detail elsewhere.[22] Briefly, ACT recruited community-dwelling, non-demented adults age 65 and older from among GH members living in or near Seattle, Washington beginning in 1994. The original cohort of 2581 people was enrolled between 1994-6 and an expansion cohort of 811 participants between 2000 and 2002. In 2004, the study began ongoing enrollment to replace people who die or drop out. In all phases, the sample was randomly selected. For these analyses, we required at least 1 year of GH enrollment prior to study entry (to ensure adequate availability of data about AF) and at least one ACT follow-up visit (needed to detect the outcome) (Figure). Because our aim was to examine the association of AF with dementia apart from AF's known effect on stroke, we excluded participants with a history of clinically-recognized stroke at study entry (based on either self-report or ICD-9 codes from inpatient or outpatient encounters). These analyses include follow-up through September 30, 2008.

Study Measures

AF was considered present if there were at least 2 encounters with ICD-9 codes for AF or atrial flutter (427.31 or 427.32) on different days within a 12 month period. We required two encounters to increase the likelihood that people classified with AF truly had this arrhythmia. We previously reported that at GH, for the elderly population, administrative data have sensitivity of 95% and specificity of 99% for AF.[23] The date of AF onset was defined as the date of the second encounter. Because we did not have additional information about the duration or persistence of AF, once a person qualified as having AF, we considered him or her to have AF from that time forward.

Primary outcomes were incident all-cause dementia and possible or probable AD identified through ACT study procedures.[22] Every 2 years, participants are screened with the Cognitive Abilities Screening Instrument.[24] People scoring below 86 undergo detailed evaluation including neurological and neuropsychological assessment. Results of recent cranial imaging are also reviewed, if available. If no recent images are available but they would be useful in the differential diagnosis of dementia, then imaging scans are requested. All available data are then reviewed by a multidisciplinary consensus committee, which uses *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition)[25] criteria to identify cases of dementia. National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria[26] are used to classify possible and probable AD. The date of dementia onset is defined by convention as the date halfway between the study visit which triggered the dementia evaluation and the prior visit. Age-specific incidence rates for dementia and AD in the ACT study are consistent with those from similar studies around the world.[22]

Biennial ACT interviews provided information about demographics, self-reported health status, smoking, and exercise. Participants were asked whether a physician had ever told them they had hypertension, diabetes mellitus, angina, congestive heart failure (CHF), heart attack, stroke, small strokes or transient ischemic attack (TIA), and whether they had ever had coronary bypass surgery or angioplasty. Prior studies have found excellent agreement between self-report and medical records for coronary artery bypass grafting and angioplasty (kappa of 0.79-0.90)[27] and substantial agreement for diabetes, hypertension, stroke, and myocardial infarction (0.64-0.80).[27, 28] Agreement is worse for CHF and angina.[27, 28] Height, weight and blood pressure were measured at ACT study visits, and blood samples were obtained for APOE genotyping.[29, 30] Depressive symptoms were measured using a modified version of the Center for Epidemiologic Studies Depression scale.[31] GH automated pharmacy data provided information about use of warfarin and antihypertensive medications. GH computerized laboratory data provided information about estimated glomerular filtration rate (eGFR) and hemoglobin levels from tests performed as part of routine clinical care. To assess study subjects' baseline eGFR and hemoglobin levels, we calculated the average of all measures obtained in the 2 years prior to study entry.

Incident strokes were determined from self-report and from inpatient and outpatient ICD-9 codes. Coronary heart disease (CHD) was defined as angina, heart attack, angioplasty, or coronary bypass surgery. For self-reported CHD, CHF, or stroke during follow-up, the date of onset was defined as halfway between the study visit at which this condition was first reported and the prior visit. We classified hypertension status by cross-classifying self-report of hypertension at baseline and receipt of antihypertensive medications from GH pharmacy data. Results of APOE genotyping were dichotomized as any vs. no copies of the APOE ε4 allele.

Statistical Analyses

We performed descriptive analyses examining characteristics of the cohort, overall and for subgroups based on whether AF was present at study entry. We calculated proportions for categorical variables and medians and interquartile ranges for continuous variables. To determine whether differences between groups were statistically significant, we used the chi-squared test for categorical variables and the Wilcoxon rank-sum test for continuous variables. We used Cox proportional hazards modeling to estimate adjusted hazard ratios (HRs) and 95% CIs for the association between AF and all-cause dementia or possible/probable AD. Age was the time scale, ensuring thorough adjustment for age, and people were censored when they died, disenrolled from GH, or withdrew from ACT, or on September 30, 2008. For analyses in which AD was the outcome, people were censored if they developed another form of dementia. In all cases, censoring occurred at the time of the last ACT visit prior to the censoring event, since this was the last time at which incident dementia could have been detected. Analyses were stratified by ACT cohort (original, expansion or replacement).

The following covariates were selected for inclusion in final models a priori based on review of the literature and clinical plausibility: education, sex, diabetes, hypertension, systolic and diastolic blood pressure, CHD, incident stroke, and CHF. CHD, incident stroke, and CHF were time-dependent, with all other covariates defined at the time of study entry. For time-dependent variables, once a person was identified as having the condition, he or she was classified as affected from that time forward. Blood pressure measures were included as continuous variables, centered at the population means. Because we hypothesized that the association between AF and dementia might differ based on whether people experienced a stroke during follow-up, we initially included an interaction term for AF and incident stroke. Because the interaction was not statistically significant and risk estimates were similar for people with and without incident stroke, the primary results we present are from models without an interaction term.

In sensitivity analyses planned a priori, we examined the effect of additional adjustment for APOE genotype, smoking, and depressive symptoms (limited to people with no missing values). We explored the effect of using a broader definition for stroke that included additional ICD-9 codes and self-reported TIA. The latter analysis excluded an additional 264 people who, based on the broader definition, had a history of stroke or TIA at baseline (Figure). The goal was to probe more assiduously the possibility that any association between AF and dementia in fact reflected an association between stroke and dementia. Post hoc sensitivity analyses explored the impact of defining AF as present based on one or more AF ICD-9 codes, rather than two or more, and of limiting the outcome to probable AD, to increase the likelihood that participants with the outcome truly had neuropathologic AD.

Analyses were carried out in Stata, version 11 (College Station, TX: StataCorp LP).

Results

These analyses included 3,045 ACT participants. The median age at study entry was 74.3 years, 60% were female, 91% were white, and 38% had completed college (Table 1). 132 people (4.3%) had AF at study entry, and an additional 370 (12.2%) were diagnosed with AF over a mean of 6.8 years of follow-up. At baseline, people with AF were more likely to have cardiovascular risk factors and diseases than people without AF (Table 1). Use of warfarin was rare and was predominantly seen in people with AF.

Total follow-up was 20,806 person-years, including 2,150 person-years with AF and 18,656 person-years without AF. During follow-up, 391 people (12.8%) experienced a stroke,

including 112 people who had AF. 572 participants (18.8%) developed dementia, including 449 (14.7%) with possible or probable AD. People with AF were at higher risk of dementia than people without AF (Table 2). The adjusted HR for all-cause dementia associated with AF was 1.38 (95% CI, 1.10-1.73), adjusted for gender, education, diabetes, hypertension, systolic and diastolic blood pressure, incident stroke, CHD, and CHF. The risk of possible or probable AD was also higher in people with AF compared to people without AF (adjusted HR 1.50, 95% CI 1.16-1.94). Models including an interaction term between AF and incident stroke showed no significant interaction, and risk estimates for the association between AF and dementia or AD were very similar for people who experienced a stroke during the study and people who did not. For example, the HR for dementia associated with AF was 1.32 (95% CI 0.85-2.07) in people who experienced a stroke during follow-up compared to 1.40 (95% CI 1.08-1.82) in those who did not.

Results from sensitivity analyses were very similar. With additional adjustment for APOE genotype, smoking, and depressive symptoms, the adjusted HR for dementia in relation to AF was 1.34 (95% CI 1.05-1.71), and for possible or probable AD, 1.41 (95% CI 1.07-1.86). For the analyses using a more liberal definition of stroke, the adjusted HR for all-cause dementia in relation to AF was 1.43 (95% CI 1.12-1.82), and for possible or probable AD, 1.46 (1.10-1.92). Results changed little when AF was defined based on the presence of at least one ICD-9 code for AF, rather than two, or when the outcome was limited to probable AD.

Discussion

In this population-based study of older adults, AF was associated with a 40 to 50% higher risk of both AD and all-cause dementia, independent of stroke. This elevated risk persisted after adjustment for many cardiovascular risk factors and diseases and in numerous sensitivity analyses. Because we followed participants prospectively, screened them routinely for cognitive impairment, and ascertained dementia using sensitive and valid methods, our findings provide more rigorous information than many prior studies of this question. We made considerable efforts to identify and account for clinically recognized stroke, and so our estimates reflect the associations of AF with dementia beyond its known association with clinical stroke.

Several biologic mechanisms may underlie the association of AF with dementia and AD. AF leads to incomplete atrial emptying which may lead to thrombus formation in the left atrial appendage. This can result in systemic embolization, including to the brain. In addition to clinically recognized stroke, people with AF experience silent cerebral emboli.[15] We have previously reported that cerebral microinfarcts are an important neuropathological predictor of clinical dementia.[32] It is not known whether AF increases the risk of cerebral microinfarcts. Second, AF is associated with increased beat-to-beat heart rate variability, which may lead to cerebral hypoperfusion.[13] Either or both of these mechanisms may be associated with other neuropathological entities associated with dementia, such as neurofibrillary tangles, Lewy bodies, and hippocampal sclerosis. Our findings are consistent with Fortuhi's “dynamic polygon” hypothesis,[33] which posits that multiple processes and risk factors act together to produce late-life dementia. People with late-life dementia and AD commonly have multiple neuropathologic findings, e.g. vascular pathology and/or Lewy bodies in addition to AD lesions.[34] It may be that in people with levels of AD pathology insufficient to produce dementia on their own, additional insults from AF decrease cognitive reserves to hasten the onset of dementia or AD.

In addition to the mechanisms described above, there are other possible explanations for the association we observed between AF and dementia. First, AF and dementia may share

underlying risk factors or pathophysiologic processes, such as inflammation. It may be that despite our efforts to control for cardiovascular risk factors and clinical cardiovascular disease, AF is serving as a marker for the overall burden of cardiovascular disease. Second, subtle changes in the brain may affect autonomic input to the heart, changing cardiac conduction and leading to AF. However, we studied the outcome of incident dementia, and so we expect that autonomic changes should have been minimal in these cases with early AD.

Our findings are consistent with prior cross-sectional studies[4, 35] and with some[6-8] but not all[16-20] longitudinal studies (for more information, please see summary table provided as an online appendix). Three of eight longitudinal studies reported that people with AF were at higher risk of dementia than people without AF,[6-8] although one study found this association only in people with mild cognitive impairment[7] and another found an association at 5 years of follow-up but not 1 or 10 years.[8] Five longitudinal studies found no association.[16-20] In general, the studies that found an association examined a younger population than those that found no association, but there were other important differences. The methods used to detect both AF and dementia varied widely. Only one prior study[6] presented data about AF diagnosed during follow-up; other studies ascertained AF only at baseline. Because we identified AF diagnosed during follow-up, we likely have more complete ascertainment than most prior studies, improving our accuracy and power. Some studies used measures of dementia that have poor sensitivity and/or specificity, such as ICD-9 codes from administrative data[6] or Mini-Mental State Examination scores less than 24.[16] Our study included the largest number of dementia cases identified using sensitive and rigorous methods of any study to date. Only one prior study included more dementia cases,[6] but it relied on purely administrative data to identify dementia, which likely led to substantial misclassification. This probably led to bias, the direction of which cannot be predicted.

Our study has limitations. Diagnoses of dementia and AD were based on clinical criteria, and while neuroimaging studies were available for many dementia cases, research-quality neuroimaging was not performed. Cases of vascular or mixed dementia may have been misclassified as AD. We do not feel this detracts from our findings, because prior work has established that in late-life dementia, people who meet neuropathologic criteria for AD commonly have additional coexisting neuropathologic findings, often vascular lesions.[34] The association between AF and AD remained present when we limited the outcome to probable AD, a group that is very likely to meet neuropathologic criteria for AD.[34]

We likely missed some cases of AF that did not come to clinical attention, particularly those that were transitory or asymptomatic. It is difficult to predict how this misclassification would have affected our results. If this misclassification were nondifferential, then the true association between AF and dementia may be stronger than we observed. We lacked information about AF duration and persistence, so we could not examine these aspects of AF in relation to dementia. The timing of dementia onset and similarly the onset of self-reported CHD, stroke and CHF was subject to error because the exact date of onset was not known and so it was estimated as occurring halfway between ACT study visits. Covariates including CHD and CHF were measured from self-report, which may be inaccurate. We did not have information about valvular heart disease nor echocardiographic findings such as left atrial dilatation and impaired systolic function, which are associated with development of AF.[10] All of these limitations could have led to residual confounding. Our study population is predominantly white and well-educated, which may limit generalizability. Participants who died or withdrew from ACT may have differed from those who remained in the study in terms of both their likelihood of having AF and of developing dementia, which may have led to bias.

Our findings have important clinical implications. AF is common and its prevalence is increasing.[36] It is not known whether specific treatments for AF could modify the elevated risk of dementia we observed. If such treatment could delay the onset of dementia by even a few years, this could have a substantial impact on the burden of dementia in the population. Although one recent observational study reported that people with AF who underwent catheter ablation had lower risk of dementia than those who did not,[37] these results may have been biased because treatment was not randomly assigned. Additional research is needed to examine the relationship of various treatments for AF with cognitive outcomes. Clinical trials and comparative effectiveness studies examining AF treatments will surely continue to study stroke and mortality but should also use sensitive and rigorous measures to ascertain cognitive decline and incident dementia so that these important outcomes can be evaluated. Future research seeking ways to avert the increasing burden of dementia should aim to determine the extent to which AF might be a modifiable risk factor.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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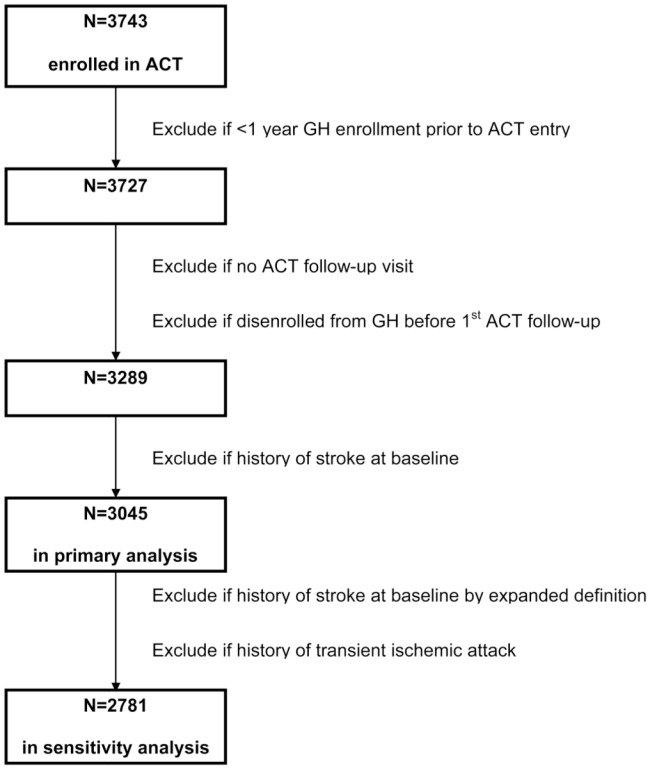

Figure. Selection of Study Subjects
Abbreviations: ACT, Adult Changes in Thought; GH, Group Health.

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Table 1

Baseline Characteristics of the Cohort, Overall and by Atrial Fibrillation Status

		Atrial Fibrillation at Baseline		
Characteristics	**Total N=3045***	**Without AF n=2913**	**With AF n=132**	**p-value†**
Age in years, median (IQR)	74.3 (70.3 - 79.5)	74.2 (70.3 – 79.4)	76.5 (71.6 – 82.6)	<0.01
Age 65-69	705 (23.2)	682 (23.4)	23 (17.4)	<0.01
70-74	949 (31.2)	914 (31.4)	35 (26.5)	
75-79	679 (22.3)	652 (22.4)	27 (20.5)	
80-84	466 (15.3)	442 (15.2)	24 (18.2)	
85+	246 (8.1)	223 (7.7)	23 (17.4)	
Female	1827 (60.0)	1756 (60.3)	71 (53.8)	0.14
Self-reported white race	2766 (90.9)	2640 (90.6)	126 (95.5)	0.06
Education				
< High school	393 (12.9)	377 (12.9)	16 (12.1)	0.71
Completed high school	713 (36.3)	687 (23.6)	26 (19.7)	
Some college	781 (25.7)	746 (25.6)	35 (26.5)	
Completed college	1158 (38.0)	1103 (37.9)	55 (41.7)	
Coronary heart disease	571 (18.8)	523 (18.0)	48 (36.4)	<0.01
Congestive heart failure	102 (3.4)	78 (2.7)	24 (18.2)	<0.01
Treated hypertension	976/3028 (32.2)	924/2901 (31.9)	52/127 (40.9)	0.03
Systolic BP, median (IQR)	138 (125 – 154) (N=3005)	138 (126 – 154) (N=2875)	135 (121 – 149) (N=130)	0.02
Diastolic BP, median (IQR)	75 (69 – 82) (N=3002)	75 (69 – 82) (N=2872)	71 (63 – 80) (N=130)	<0.01
Diabetes mellitus	285/3044 (9.4)	270/2913 (9.3)	15/131 (11.5)	0.40
Body mass index, median (IQR)	26.6 (24.0 – 30.1)	26.6 (24.0 – 30.1)	26.5 (24.1 – 29.3)	0.43
Obese (BMI ≥ 30 kg/m^2)	762/2994 (25.5)	735/2867 (25.6)	27/127 (21.3)	0.27
Fair or poor health status	443/3044 (14.6)	418/2913 (14.4)	25/131 (19.1)	0.13
Exercise ≥ 3 times/week	2183/3042 (71.8)	2085/2911 (71.6)	98/131 (74.8)	0.43
Ever smoker	1576/3038 (51.9)	1501/2908 (51.6)	75130 (57.7)	0.18
Any APOE ε4 allele	673/2631 (25.6)	653/2524 (25.9)	20/107 (18.7)	0.10

Characteristics	Total N=3045*	Atrial Fibrillation at Baseline: Without AF n=2913	Atrial Fibrillation at Baseline: With AF n=132	p-value†
Missing	414 (13.6)	389 (13.4)	25 (18.9)	
Modified CESD-10 score ≥ 10‡	314/3029 (10.4)	300/2897 (10.4)	14/132 (10.6)	0.93
Any warfarin fill in prior 12 mo.	137 (4.5)	83 (2.9)	54 (40.9)	<0.01
At least 3 warfarin fills in prior 12 mo.	106 (3.5)	62 (2.1)	44 (33.3)	<0.01
Estimated GFR, median (IQR)§	65.8 (56.6 – 75.2) (N=2427)	65.8 (56.6 – 75.1) (N=2298)	65.5 (55.2 – 75.8) (N=129)	0.93
Hemoglobin, median (IQR)§	13.8 (12.9 – 14.6) (N=2376)	13.8 (12.9 – 14.6) (N=2263)	13.7 (12.7 – 14.6) (N=113)	0.32

Abbreviations: APOE, apolipoprotein E; BMI, body mass index; BP, blood pressure; CESD-10, Center for Epidemiologic Studies – Depression scale, 10-question version (scale range, 0 to 30); GFR, glomerular filtration rate (normal range, ; IQR, interquartile range; mmHg, millimeters mercury;

*For continuous variables, the median and interquartile range are presented. Data were missing for <5% of subjects for all variables except APOE genotype, estimated GFR, and hemoglobin level.

†p-values are for the comparison of people with vs. without AF at the time of entry into the study and were calculated based on the chi-squared test (for categorical variables) or Wilcoxon rank-sum test (for continuous variables).

‡CESD-10 range, 0 to 30; recommended cut-off for depression, ≥10.[31]

§Values represent the average of all available measures obtained during the 2 years prior to study entry.

Table 2

Hazard Ratios for Risk of Incident Dementia and Alzheimer Disease Associated with Atrial Fibrillation

	Follow-up, person-years	Events, No.	Incidence (per 1000 per year)	Minimally adjusted HR (95% CI)*	Fully adjusted HR (95% CI)†
Dementia‡					
No AF	18,656	469	25.1	1.00 (Ref.)	1.00 (Ref)
AF	2,150	103	47.9	1.28 (1.03-1.59)	1.38 (1.10-1.73)
Possible or probable AD‡					
No AF	18,656	367	19.7	1.00 (Ref.)	1.00 (Ref)
AF	2,150	82	38.1	1.33 (1.04-1.69)	1.50 (1.16-1.94)

Abbreviations: AD, Alzheimer disease; AF, atrial fibrillation; CHD, coronary heart disease; CHF, congestive heart failure; CI, confidence interval; HR, hazard ratio.

*HR from Cox proportional hazards regression model, with age as the time scale, adjusted for incident stroke and stratified by study cohort (original, expansion or replacement.)

†Further adjusted for gender, education, diabetes, hypertension, systolic and diastolic blood pressure, CHD, and CHF. AF, incident stroke, CHD, and CHF were time-dependent variables. All other covariates were assessed at baseline.

‡Participants were screened every 2 years with the Cognitive Abilities Screening Instrument (score range, 0-100), with detailed assessment of those scoring below 86. Dementia and possible or probable Alzheimer disease were determined by a multidisciplinary consensus committee using standard research criteria.

¶Atrial fibrillation was ascertained from health plan electronic data (International Classification of Diseases, version 9, codes for inpatient and outpatient encounters.)

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