

Original Investigation

Association Between Atrial Fibrillation and Dementia in the General Population

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IMPORTANCE Atrial fibrillation (AF) has been suggested as a risk factor for dementia since it may lead to chronic cerebral hypoperfusion and stroke. However, longitudinal studies assessing the association between AF and dementia have shown inconsistent results.

OBJECTIVE To determine the effect of AF on the risk of developing dementia during 20 years of follow-up.

DESIGN, SETTING, AND PARTICIPANTS The association of prevalent and incident AF with incident dementia was assessed from July 6, 1989, to February 4, 2010, in 6514 dementia-free participants in the prospective population-based Rotterdam Study. Data analysis was conducted from September 18, 2014, to April 17, 2015. Cox proportional hazards regression models adjusting for age, sex, and cardiovascular risk factors; censored for stroke; and stratified by median age were used. In addition, we investigated whether the association between incident AF and dementia varied according to the duration of exposure, categorized in 6-year time bands.

EXPOSURES Prevalent and incident AF.

MAIN OUTCOMES AND MEASURES Incident dementia, determined according to the *Diagnostic and Statistical Manual of Mental Disorders* (Third Edition Revised) and the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association criteria.

RESULTS At baseline, 318 of 6514 participants (4.9%) had prevalent AF, and during 81 483 person-years of follow-up, 994 participants (15.3%) developed incident dementia. With findings presented as adjusted hazard ratio (95% CI), prevalent AF was related to an increased risk of dementia (1.33; 1.02-1.73). Among 6196 participants without prevalent AF during 79 003 person-years of follow-up, 723 participants (11.7%) developed incident AF and 932 individuals (15.0%) developed incident dementia. Incident AF was associated with an increased risk of dementia in younger participants (<67 years: 1.81; 1.11-2.94 vs ≥67 years: 1.12; 0.85-1.46; $P = .02$ for interaction). The risk of dementia was strongly associated with duration of exposure to AF in the younger participants (in the highest stratum: 3.30; 1.16-9.38; $P = .003$ for trend) but not in the elder participants (0.25; 0.04-1.86; $P = .94$ for trend).

CONCLUSIONS AND RELEVANCE Atrial fibrillation is associated with an increased risk of dementia, independent of clinical stroke. This association was strongest for younger participants with the longest duration of AF. Future studies should investigate whether optimal treatment of AF can prevent or postpone dementia.

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Worldwide, approximately 40 million people have dementia, and this number is expected to increase owing to aging of the population.¹ Although the pathophysiologic mechanisms of dementia are largely unknown, there is abundant evidence implicating cardiovascular disease and its risk factors.² Atrial fibrillation (AF) is a common cardiovascular disease in the elderly population and might be related to dementia via various pathways.^{3,4} First, the most feared complication of AF is stroke, a well-known risk factor for dementia. Second, lower cardiac output in AF leads to chronic cerebral hypoperfusion, which in turn causes damage to the brain. Third, a noncausal explanation is shared etiology because of overlapping risk factors.

Within the Rotterdam Study, Ott et al⁵ showed that AF is more prevalent in people with dementia. However, the cross-sectional design of this study precluded conclusions regarding a causal relationship. Since then, several longitudinal studies⁶⁻¹⁷ have investigated the association between AF and incident dementia, but the results have been inconsistent: some studies found that AF was associated with an increased risk of cognitive decline or dementia, whereas others found no association. These inconsistencies might be the result of methodologic variation across studies. For example, some studies had relatively small samples or short follow-up periods, which might have limited their statistical power. In addition, the age ranges differed substantially among studies, as did the assessment of AF and dementia.

Therefore, within the population-based Rotterdam Study, we investigated the association between AF and dementia during a follow-up period of 20 years. We assessed the associations between prevalent AF and dementia, as well as incident AF and dementia. Furthermore, we evaluated whether these associations were independent of stroke and varied with age.

Methods

Setting and Study Population

This study was embedded within the Rotterdam Study, a prospective population-based cohort study that investigates chronic diseases in the elderly. The Rotterdam Study has been approved by the medical ethics committee of the Erasmus Medical Center and by the Ministry of Health, Welfare and Sports of the Netherlands, implementing the Population Study Act Rotterdam Study. Written informed consent was obtained from all participants; no financial compensation was provided. The Rotterdam Study started on July 6, 1989, among inhabitants aged 55 years or older residing in Ommoord, a district of Rotterdam, the Netherlands. Of the 10 215 invited inhabitants, 7983 agreed to participate in the baseline examinations. Follow-up examinations take place every 3 to 4 years. Data analysis for the present study was conducted from September 18, 2014, to April 17, 2015. Details regarding the objective and design of the Rotterdam Study are described elsewhere.¹⁸

For this study, we excluded 455 participants because they were not properly screened for dementia, 482 individuals because they had prevalent dementia, and 43 participants for lack

of follow-up information on the dementia diagnosis. In addition, 489 people were excluded owing to missing data on AF. Finally, for the analyses of the association with prevalent AF, 6514 participants were included. For the analyses with incident AF, we excluded the 318 participants with prevalent AF and 2 participants owing to lack of follow-up data on incident AF, resulting in a total of 6194 participants for these analyses. After additionally censoring for stroke, we excluded 195 participants who had a stroke at baseline and 5 participants for lack of follow-up information on incident stroke. In the analysis with incident AF, only 175 participants with prevalent stroke were excluded because 25 were already omitted owing to prevalent AF.

Assessment of AF

Prevalent and incident AF was assessed using 3 methods.¹⁹ Electrocardiography (ECGs) was performed at baseline and at each follow-up examination. These ECGs were stored digitally and analyzed by the Modular ECG Analysis System (MEANS), which has a high sensitivity and specificity in coding cardiac arrhythmias.^{20,21} To verify the diagnosis of AF, every ECG with any rhythm disorder identified by the MEANS program was coded independently by 2 research physicians who were masked to the MEANS diagnosis. In case of disagreement between the research physicians, a cardiologist decided on the final diagnosis. In addition, information for all participants concerning the presence of AF and the date of onset was obtained from family physicians and physician specialists. Finally, information on all hospital discharges from a nationwide medical registry (Landelijke Medische Registratie) was collected. The date of incident AF was defined as the date of first occurrence of symptoms with subsequent ECG verification. We did not differentiate between AF and atrial flutter when identifying cases since these conditions are very similar with regard to risk factors and consequences.^{22,23} Follow-up for incident AF was completed February 4, 2010.

Assessment of Dementia

Participants were screened for dementia at baseline and follow-up examinations using a 3-step protocol. Screening was done using the Mini-Mental State Examination²⁴ and the Geriatric Mental State Schedule²⁵ organic level. Screen-positives (Mini-Mental State Examination score <26 or Geriatric Mental State Schedule organic level >0) subsequently underwent an examination and informant interview with the Cambridge Examination for Mental Disorders of the Elderly.²⁶ Participants with suspected dementia underwent further neuropsychological testing if necessary. In addition, the total cohort was continuously monitored for dementia through computerized linkage of the study database and digitized medical records from family physicians and the Regional Institute for Outpatient Mental Health Care. When clinical neuroimaging was required and available, it was used for decision making on the diagnosis. A consensus panel, led by a neurologist (P.J.K.), decided on the final diagnosis in accordance with the *Diagnostic and Statistical Manual of Mental Disorders* (Third Edition Revised)²⁷ and National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and

Related Disorders Association criteria.²⁸ Follow-up evaluation for dementia was completed on February 4, 2010.

Measurement of Risk Factors

Weight and height were measured at the Rotterdam Study research center, and body mass index was calculated as weight in kilograms divided by height in meters squared. Blood pressure was measured in the sitting position on the right arm and calculated as the mean of 2 measurements using a random-zero sphygmomanometer. Diabetes mellitus was defined as a fasting serum glucose level of 126.1 mg/dL or more (to convert to millimoles per liter, multiply by 0.0555), nonfasting serum glucose level of 200.0 mg/dL or more, or use of anti-diabetic medication. Serum glucose, total cholesterol, and high-density lipoprotein cholesterol levels were acquired by an automated enzymatic procedure (Boehringer Mannheim System). Information on blood pressure-lowering medication, lipid-lowering medication, educational level, and smoking habits were assessed by interview. Information on ever use of oral anticoagulant medication was collected using all prescriptions on file from the pharmacies for all participants. Smoking habits were categorized as current, former, and never smoking. Information on apolipoprotein E (*APOE*, NM_000041) genotype, coded as 1 or 2 ϵ 4 alleles, was obtained using polymerase chain reaction on coded DNA samples. History of stroke, coronary heart disease (myocardial infarction or revascularization procedure), and heart failure was evaluated using home interviews and confirmed by review of medical records.^{29,30} Incident stroke was assessed continuously through automatic linkage of physicians' medical records with the study database. In addition, family physicians' medical records on participants who moved out of the Ommoord district and nursing home physicians' medical records were checked on a regular basis. Of all potential strokes, information from family physicians and hospital discharge letters were collected and reviewed by research physicians. An experienced neurologist (P.J.K.) verified the stroke diagnoses.²⁹

Statistical Analysis

Baseline characteristics of people with and without prevalent AF were compared using logistic regression models, adjusting for age and sex where appropriate. We assessed the association between AF and incident dementia using Cox proportional hazards regression models. The underlying time scale in these models was the follow-up time. Follow-up started on the date that participants entered the Rotterdam Study. Participants were censored at the date of dementia diagnosis, date of death, or end of the study period, defined as the last date of follow-up or February 4, 2010, whichever came first. In sensitivity analyses, we additionally censored at date of stroke if a stroke occurred before the end of the follow-up period. We investigated both prevalent and incident AF in separate analyses. Prevalent AF was entered dichotomously into the models, whereas incident AF was entered into the models as a time-varying factor. In the latter analyses, participants with prevalent AF were excluded because we were not aware of the duration of the arrhythmia. The basic model (model I)

was adjusted for age and sex. The extended model (model II) was additionally adjusted for diabetes mellitus, smoking, total cholesterol level, high-density lipoprotein cholesterol level, use of lipid-lowering medication, systolic and diastolic blood pressure, use of blood pressure-lowering medication, body mass index, educational level, coronary heart disease, heart failure, *APOE* ϵ 4 carrier status, and ever use of oral anticoagulant medication. We separately investigated Alzheimer disease.

We studied potential effect modification by age using an interaction term and by stratifying analyses at the median age. In addition, we investigated whether the association between AF and dementia differed according to duration of AF by stratifying follow-up time from onset of AF until the censor date (ie, date of dementia diagnosis or end of follow-up, whichever came first) into 3 categories: greater than 0 and 6 years or less, greater than 6 and 12 years or less, and greater than 12 years. Cutoff times were chosen to equally divide the follow-up time for AF, which was highest at 18.8 years.

Missing data on covariates (<4.0%) were imputed using multiple imputations. Analyses were performed using SPSS, version 20.0 (IBM Corp).

Results

At baseline, 318 participants (4.9%) had prevalent AF. These participants were older, used blood pressure-lowering medication more often, had lower high-density lipoprotein cholesterol levels, and more frequently had diagnoses of diabetes mellitus, coronary heart disease, and heart failure compared with participants without prevalent AF (Table 1). Conversely, people without prevalent AF had higher total cholesterol levels. In analyses with prevalent AF, 994 participants (15.3%) developed incident dementia (with 787 [79.2%] having Alzheimer disease) during 81 483 person-years of follow-up. In analyses with incident AF, 723 participants (11.7%) developed incident AF and 932 (15.0%) developed dementia (with 741 [79.5%] having Alzheimer disease) during 79 003 person-years.

As measured by age- and sex-adjusted hazard ratio (HR) (95% CI), we found that people with prevalent AF had an increased risk of dementia (1.34; 1.03-1.74). Results were similar after additional adjustments. For incident AF, the adjusted HR was 1.23 (0.98-1.56) (Table 2). For both prevalent and incident AF, associations slightly attenuated when separately investigating Alzheimer disease. Censoring for stroke did not significantly change the results (Table 2).

We found that the association of both prevalent and incident AF with dementia differed with age ($P = .04$ and $.02$, respectively, for interaction), with the strongest association in persons younger than the median age of the population (Table 3). In this younger group, the association of incident AF and dementia was statistically significant (Table 3). Furthermore, among younger participants, we found that the risk of dementia was higher when the duration of AF increased ($P = .003$ for trend) (Figure). For instance, in the stratum with follow-up time exceeding 12 years, the adjusted HR (95% CI) in participants younger than the median age was 3.30 (1.16-

Table 1. Baseline Characteristics

Characteristic	Atrial Fibrillation, No. (%) ^a		P Value for Difference ^b
	Not Prevalent (n = 6196)	Prevalent (n = 318)	
Age, mean (SD), y	68.3 (8.5)	75.7 (8.1)	<.001
Female, sex	3678 (59.4)	161 (50.6)	<.001
BMI, mean (SD)	26.3 (3.7)	26.0 (3.6)	.48
Blood pressure, mm Hg, mean (SD)			
Systolic	139 (22)	142 (25)	.40
Diastolic	74 (11)	73 (13)	.52
Blood pressure-lowering medication	1367 (22.1)	109 (34.9)	<.001
Diabetes mellitus	609 (9.9)	64 (20.1)	<.001
Cholesterol, mean (SD), mg/dL			
Total	258.7 (46.3)	239.4 (46.3)	<.001
HDL	54.1 (15.4)	46.3 (11.6)	<.001
Lipid-lowering medication	151 (2.4)	9 (2.8)	.09
Smoking			
Former	2548 (42.2)	136 (44.3)	.74
Current	1429 (23.3)	56 (18.2)	.35
Apolipoprotein E ε4 carrier	1646 (27.8)	82 (26.5)	.95
Educational level			
Primary	2235 (36.6)	126 (40.8)	1 [Reference]
Lower vocational	1006 (16.5)	51 (16.5)	.08
Lower secondary	673 (11.0)	29 (9.4)	.68
Intermediate vocational	1463 (24.0)	80 (25.9)	.09
General secondary	198 (3.2)	6 (1.9)	.54
Higher vocational	470 (7.7)	16 (5.2)	.63
University	64 (1.0)	1 (0.3)	.32
Ever use of oral anticoagulant medication	1386 (22.4)	87 (27.4)	<.001
Coronary heart disease	468 (7.9)	53 (18.0)	<.001
Heart failure	152 (2.5)	58 (18.8)	<.001

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); HDL, high-density lipoprotein.

SI conversion factor: To convert cholesterol to millimoles per liter, multiply by 0.0259.

^a Percentages were calculated without missing data.

^b Differences were calculated using logistic regression models.

Table 2. Atrial Fibrillation and the Risk of Dementia

Characteristic	Dementia			Alzheimer Disease		
	Cases, No. (%)	HR (95% CI)		Cases, No. (%)	HR (95% CI)	
		Model I ^a	Model II ^b		Model I ^a	Model II ^b
Including Stroke						
Atrial fibrillation						
Prevalent (n = 6514)	994 (15.3)	1.34 (1.03-1.74)	1.33 (1.02-1.73)	787 (12.1)	1.30 (0.96-1.75)	1.29 (0.95-1.75)
Incident (n = 6194)	932 (15.0)	1.13 (0.90-1.41)	1.23 (0.98-1.56)	741 (12.0)	1.09 (0.85-1.40)	1.18 (0.91-1.54)
Censored for Stroke						
Atrial fibrillation						
Prevalent (n = 6314)	844 (13.4)	1.35 (1.01-1.81)	1.33 (0.99-1.78)	705 (11.2)	1.31 (0.94-1.81)	1.28 (0.93-1.78)
Incident (n = 6019)	793 (13.2)	1.14 (0.89-1.49)	1.24 (0.96-1.61)	665 (11.0)	1.08 (0.82-1.42)	1.15 (0.87-1.54)

Abbreviation: HR, hazard ratio.

^a Model I was adjusted for age and sex.

^b Model II was additionally adjusted for diabetes mellitus, smoking, total cholesterol and high-density lipoprotein cholesterol levels, lipid-lowering

medication, systolic and diastolic blood pressure, blood pressure-lowering medication, body mass index, educational level, ever use of oral anticoagulant medication, coronary heart disease, heart failure, and apolipoprotein E ε4 carrier status.

9.38). No such trend with exposure time was seen in participants older than the median age (0.25; 0.04-1.86; *P* = .94 for trend). These results were similar for younger vs older participants with Alzheimer disease (1.49; 1.11-2.01 vs 0.99; 0.81-1.21) and non-Alzheimer dementia (1.44; 0.88-2.36 vs 1.08; 0.70-1.66).

Discussion

In this population-based study, we found that individuals with AF had an increased risk of dementia. This association was similar for Alzheimer disease and independent of stroke. The

Table 3. Atrial Fibrillation and the Risk of Dementia, Stratified for Age at Median^a

Characteristic	Dementia, HR (95% CI)			
	No./Total No. (%) ^b	Age, <67 y	No./Total No. (%) ^b	Age, ≥67 y
Atrial fibrillation				
Prevalent	213/3096 (6.9)	1.91 (0.85-4.26)	781/3418 (22.8)	1.28 (0.97-1.70)
Incident	206/3049 (6.8)	1.81 (1.11-2.94)	726/3145 (23.1)	1.12 (0.85-1.46)

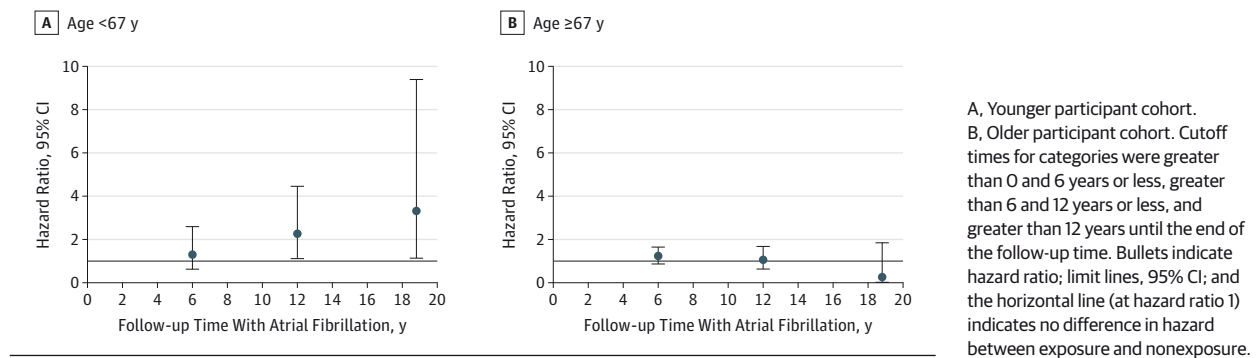
Abbreviations: HR, hazard ratio.

^a Model was adjusted for age, sex, diabetes mellitus, smoking, total cholesterol and high-density lipoprotein cholesterol levels, lipid-lowering medication, systolic and diastolic blood pressure, blood pressure-lowering medication,

body mass index, educational level, ever use of oral anticoagulant medication, coronary heart disease, heart failure, and apolipoprotein E ε4 carrier status.

^b Number of cases/number of participants.

Figure. Hazard Ratios for Dementia per Category of Follow-up of Time With Atrial Fibrillation



risk of dementia was highest in younger participants (<67 years), particularly if they had a longer period of AF.

Before these results can be interpreted, several methodologic considerations need to be discussed. Strengths of the study are the population-based and prospective design, the relatively long follow-up period, and the case-finding procedure used to identify dementia. In addition, we assessed both the associations of prevalent and incident AF with incident dementia, alleviating methodologic limitations of previous cross-sectional analyses of the Rotterdam Study data.⁵ There are also several limitations to our study. First, we could not distinguish between persistent and paroxysmal AF. Second, AF can occur without symptoms, and although numerous ECG measurements were performed at the research center, we might have missed some participants with asymptomatic AF. Third, with the exception of oral anticoagulant use, other potential confounders were assessed only at baseline. This limitation might have led to residual confounding. Fourth, we did not have information regarding treatment following AF. It is possible that the risk of dementia for people with AF attenuates after successful treatment. Finally, the Rotterdam Study population is relatively homogeneous, consisting mostly of white individuals who live in a middle-income district, limiting generalizability of results.

The increased risk of cognitive decline or dementia in people with AF has been reported by some studies^{6-10,17} but not others.¹¹⁻¹⁶ Methodologic variability is a likely explanation for these inconsistent findings. For example, smaller sample size or shorter follow-up periods might have hampered the possibility of finding an association in some studies. Other studies relied on registries, which increases the possibility of misclassification. Another important differ-

ence across studies was the age of the participants. Participants tended to be older in studies that did not find an association. In line with this notion, we found that incident AF was a risk factor for dementia only in younger participants. Since dementia develops gradually over many years, AF probably needs to occur at a younger age to contribute to the onset of dementia. Similarly, associations of other dementia risk factors, such as hypertension, hypercholesterolemia, and obesity, also appear to differ with age, with a stronger effect earlier in life.³¹⁻³³ In line with this reasoning, if AF is a causal factor in the etiology of dementia, one would expect that the longer a person has this condition, the higher the risk for dementia. We demonstrated that the risk of dementia was highest for people with the longest history of AF. However, this dose-response association was present only in younger participants. In contrast to our findings, a recent study⁶ concluded that the presence of AF at midlife was not a risk factor of dementia, whereas late-life AF was a risk factor. However, survival bias might have influenced those results because only participants who survived until a reexamination in late life were analyzed.

Several mechanisms could explain the association between AF and dementia. First, the association might be caused by stroke. Although our results remained similar after censoring for stroke, it remains possible that asymptomatic strokes explain the link between AF and dementia. Such asymptomatic strokes are often lacunes, which are related to an increased risk of dementia.³⁴ Imaging studies with long-term follow-up may aid in resolving this potential underlying mechanism. Second, the brain is vulnerable to changes in blood flow. Hence, cerebral hypoperfusion due to lower cardiac output in AF could cause damage to nerve cells.³⁵⁻³⁷ Third, a non-

causal explanation is shared etiology because AF and dementia share many risk factors, such as hypertension, diabetes mellitus, and hypercholesterolemia. However, adjustment of cardiovascular risk factors did not attenuate our results. Furthermore, we found a dose-response association between AF and the risk for dementia in younger participants, which is also more suggestive of a causal association.

Our finding that AF is a risk factor for dementia has important clinical implications. Given that this arrhythmia has treatment options, the risk for dementia could potentially be reduced by optimal treatment of AF.³⁸ The primary treatment option to prevent stroke is anticoagulant medication. Although we adjusted for ever use of anticoagulants, we were not able to adjust for the effectiveness of the treatment. Such adjustment is important because oral anticoagulant drugs have a narrow therapeutic range. A previous study³⁹ has shown that, in patients receiving anticoagulants, time outside the therapeutic range is associated with an increased risk of dementia.

Furthermore, we did not have any information on treatment options for AF, such as antiarrhythmic medication, cardioversion, or catheter ablation. To our knowledge, only one previous study⁴⁰ suggested that patients with AF who underwent catheter ablation had a lower risk of dementia compared with patients who did not receive treatment. More studies are needed to investigate whether optimal treatment of AF can prevent or delay the onset of dementia.

Conclusions

We found that AF was associated with an increased risk for dementia. Furthermore, there appeared to be a dose-response association with the duration of AF. However, this association was confined to the younger cohort of our population. Future studies should determine whether optimal treatment of AF can prevent or postpone dementia.

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