Atrial fibrillation increases the risk of dementia among older adults even in the absence of stroke

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Abstract

Background: Atrial fibrillation increases risk of stroke, and thus risk of cognitive impairment and dementia. Emerging evidence suggests an association also in the absence of stroke. We aimed to examine the association between atrial fibrillation and incident dementia, with and without exclusion of individuals with stroke, and to examine if sex and genetic factors modify the possible association.

Methods: In 2000-2001, a population-based sample of 70-year-olds (N=561) underwent comprehensive somatic and neuropsychiatric examinations and genotyping, as part of the Gothenburg H70 Birth Cohort Study in Sweden. Participants were followed-up at age 75 and 79. Atrial fibrillation at baseline was identified through ECG, proxy informant interviews, and the National Patient Register (NPR). Stroke at baseline and follow-up was identified through self-reports, proxy informant interviews, and the NPR. Dementia at baseline and follow-up was diagnosed according to the DSM-III-R criteria based on neuropsychiatric examinations, proxy informant interviews, and the NPR.

Results: Individuals with atrial fibrillation had an almost threefold increased risk of dementia during 12 year follow-up (HR 2.8; 95% CI 1.3-5.8;p=0.006), and this risk remained after excluding individuals with stroke at baseline and follow-up. After stratification for sex, the association was only found among men (HR 4.5; 95%CI 1.9-11.0;p=0.001, interaction sex*atrial fibrillation; p=0.163) and non-carriers of the *APOE* ε4 allele (HR 4.5; 95%CI 1.8-11.2;p=0.001, interaction APOE*atrial fibrillation;p=0.267). Population attributable risk for dementia resulting from atrial fibrillation was 13%.

Conclusion: It is important to detect atrial fibrillation to prevent dementia. Also, patients with atrial fibrillation should be screened for cognitive symptoms.

Keywords: Atrial fibrillation; Dementia; Alzheimer Disease; Epidemiology

Introduction

The prevalence of dementia increases with age, with almost 25% of the population affected by age 85 [1]. The total number living with dementia worldwide is expected to increase from 46.8 million in 2015 to 131.5 million in 2050 due to an aging population [2]. Atrial fibrillation is also a common disease among older adults with prevalence figures in Europe of around 4% at age 60–70 years, and 10%–17% above age 80 [3]. Atrial fibrillation is a risk factor for stroke, which may cause cognitive impairment and dementia. However, emerging evidence suggests an association between atrial fibrillation and dementia also in the absence of stroke [4].

In 1998, the population-based Rotterdam study found a cross-sectional association between atrial fibrillation and dementia both in the presence and absence of stroke [5]. Since then, a number of prospective studies have shown associations between atrial fibrillation and incidence of dementia [6-16], with some exceptions [17-20]. Many studies adjust for stroke or exclude participants with stroke at baseline [7, 9, 12, 13, 21]. However, few studies have adjusted for or excluded participants with stroke during the whole study period.

In addition, the moderating effect of sex and genetic factors on the association between atrial fibrillation and dementia has not been evaluated in detail. When studying risk factors for dementia, many studies adjust for sex without investigating sex interactions, making more research needed to determine the modifying effect of sex on risk factors for dementia [22, 23]. Among the few studies examining sex as a modifier on risk factors for dementia, the apolipoprotein E (*APOE*) ε4 allele [24], overweight/obesity, and low physical activity have been reported to have higher impact on dementia risk in women compared to men [23]. Sex differences regarding the association between atrial fibrillation and cognitive impairment and dementia, independent of stroke, has been proposed as a knowledge gap [25].
Genes may also modify the effect of risk factors for dementia. One well-known genetic risk factor for AD pathology is the *APOE* ε4 allele. However, the few studies investigating the modifying effect of the *APOE* ε4 allele on the association between atrial fibrillation and dementia show conflicting results [9, 16]. Another gene of possible importance for dementia is the angiotensin-converting enzyme (*ACE*) gene, which is important for the renin-angiotensin-aldosterone system (RAAS) [26]. Our research group has recently reported an association

between the *ACE* rs1799752 (In/Del) polymorphism and age of dementia onset, where individuals with the *ACE* D/D genotype had higher risk to develop dementia [27, 28]. In addition, atrial fibrillation has been associated with RAAS and the *ACE* In/Del polymorphism. However, contrary to the association between the *ACE* D/D genotype and dementia, the *ACE* I/I genotype has been found to be associated to atrial fibrillation [29]. To our knowledge, few studies have examined if the association between atrial fibrillation and dementia is modified by genetic risk factors for dementia, such as variants in the *APOE* and *ACE* genes.

The aim of this study was to examine the association between atrial fibrillation and incident dementia in a population sample of older adults followed over 12 years, with and without exclusion of participants with stroke at baseline and during follow-up.
We also aimed to examine if sex and genetic factors (the *APOE* ε4 allele, the *ACE* rs1799752 (In/Del) polymorphism) modified the possible association between atrial fibrillation and dementia.

Materials and methods

Participants

Data was obtained from the population-based Gothenburg H70 Birth Cohort Study, where men and women were selected from the population register based on birth-dates. The present study includes participants born in 1930, examined at age 70, 75, and 79. A total number of 896 individuals were invited at baseline in 2000, 13 died before they could be examined, 15 had moved out of Sweden, 12 could not speak Swedish and five could not be traced, leaving an effective sample of 851 individuals. A total of 604 individuals accepted to participate (response rate 71%). Of those, 579 individuals took part in the psychiatric examination. All individuals with dementia at baseline (n=16), or missing information on atrial fibrillation (n=2) were excluded, leaving a sample of 561 individuals. Of the 561 individuals examined at age 70, 433 individuals participated at the follow-up examination at age 75 (response rate among survivors: 80%) and 364 individuals participated at the follow-up examination at age 79 (response rate among survivors: 77%).

The study was approved by the Regional Ethics Committee for Medical Research at the University of Gothenburg. Informed consent was obtained from all participants, their relatives or both.

Data collection

Medical history was obtained by medical doctors or research nurses using semi-structured interviews including questions regarding disorders, symptoms, and medication use. Physical examinations included measurements of blood pressure, anthropometry (e.g. height and weight) and ECG. Blood pressure was measured in the right arm after five minutes rest in the seated position with a manual sphygmomanometer. The 12-lead ECG was coded according to the Minnesota Code (MC) by a biomedical analyst working at the cardiac laboratory at Sahlgrenska University Hospital.

Trained psychiatric research nurses performed the neuropsychiatric examinations using semi-structured interviews that comprised questions about psychiatric disorders and symptoms, and cognitive tests. The neuropsychiatric examinations included assessments of psychiatric symptoms, signs of dementia, tests of mental functioning (e.g. memory, proverbs, language, visuospatial and executive abilities, apraxia, construction, agnosia), the Mini Mental State Examination (MMSE) [30], and the Alzheimer's Disease Assessment Scale – ADAS [31].

All participants were asked to provide contact information for a proxy-informant. The proxy-informant interviews were semi-structured and performed by telephone by a research nurse or a psychologist and included questions about medical history, changes in behaviour and intellectual function, as well as questions about age of onset and course of dementia when appropriate.

All individuals who took part in the study were invited to brain-CT examination in 2000-01. A total number of 420 individuals participated. The CT-scans were performed without contrast and with eight millimetres thick slices. The scans were first evaluated by a radiologist for clinical relevant findings. Then, a neurologist blind to clinical data assessed brain infarcts, grouped as watershed/territorial infarcts or lacunar infarcts. This information was used as additional information for exclusion of stroke at baseline.

DNA was extracted from blood samples according to standard procedures. Genotyping of *ACE* rs1799752 was conducted according to Olsson et al. [32]. *APOE* genotyping was performed by mini-sequencing as previously described in detail [33]. Genotypes were obtained for the two SNPs rs7412 and rs429358, which are used to unambiguously define ε2, ε3, and ε4 alleles.

The inpatient part of the National Patient Register (NPR) contains information about hospital discharge diagnoses and received full national coverage in 1978. All Swedish citizens have access to health care and could therefore be included in the register. The NPR is coded according to the Swedish version of the International Statistical Classification of Diseases and Related Health Problems (ICD-SE). Death dates were obtained from the Swedish Tax Agency.

Diagnoses of dementia and atrial fibrillation

Dementia diagnoses at each examination were based on the Diagnostic and Statistical Manual of Mental Disorders, third edition revised (DSM-III-R), using information from psychiatric examinations and proxy-informant interviews, as described in detail previously [34]. Dementia diagnoses for individuals lost to follow-up were based on information from the in-patient part of the National Patient Register (NPR) according to the International Classification of Diseases (ICD) Tenth Edition (ICD-10-SE codes: F00-03, G30) [35]. Incident dementia up to the end of 2012 was also based on information from the NPR. Dementia was classified as Alzheimer's disease according to the NINCDS-ADRDA-criteria [36], vascular dementia similar to the NINDS-AIREN-criteria (i.e. when there was a temporal connection, within one year, between the first symptoms of dementia and a history of stroke/TIA) [37], mixed dementia when there was a history of stroke/TIA without clear temporal connection with dementia onset, and other causes when there was a temporal connection with other disorders, e.g., normal pressure hydrocephalus and Parkinson's disease. Age of dementia onset was estimated based on information from proxy-informants, the NPR, and the psychiatric examinations.

Atrial fibrillation was identified at baseline from ECG (MC 8-3), the NPR (ICD-8-SE code 427.92; ICD-9-SE code 427D; ICD-10-SE code I48) or from a proxy-informant interview. The question in the proxy-informant interview was phrased "Has he/she or has he/she had atrial fibrillation?".

Comorbidities

Stroke was identified at baseline and at follow-up from self- and proxy-reports, the NPR (ICD8-SE codes 431, 433, 434; ICD9-SE codes 431, 432, 434, 438???; ICD10-SE codes I61-I63, I69.1-I69.4), and hospital medical records, as described previously [38]. The interviews included question about sudden onset of focal symptoms or acute aphasia, duration of symptoms, age at onset, and admission to hospital due to stroke. The criteria for a stroke diagnosis, based on self- and proxy-reports, were rather strict, only including participants with a clear history of acute focal symptoms (e.g. hemiparesis or aphasia) lasting for more than 24 hours. We also diagnosed stroke from the NPR up to 2012. At baseline, stroke was also diagnosed if watershed or territorial infarcts were present on CT-brain scan.

The diagnosis of myocardial infarction was based on self-report, presence of major or intermediate Q-waves on ECG (MC 1-1-X or 1-2-X) as suggested by Ammar et al [39], or the NPR (ICD-8-SE codes 410, 412.01, 412.09; ICD-9-SE codes 410, 411A, 411C, 412; ICD10-SE codes I21-I23, I24.1, I25.2, I25.6, U98).

The diagnosis of heart failure was based on the NPR (ICD8-SE codes: 427.00, 428.99; ICD9-SE codes: 428; ICD10-SE codes I11.0, I13.0, I13.2, I50, K76.1).

Hypertension was defined as systolic blood pressure ≥ 150 or diastolic blood pressure ≥ 90, as suggested by the Eighth Joint National Committee (JNC 8) in 2014 [40], or the use of antihypertensive medication.

Diabetes mellitus was defined as present treatment with insulin or antidiabetic drugs.

Statistics

To compare baseline characteristics in the total sample grouped by atrial fibrillation status, Fisher's exact test for proportions and t-test for MMSE and BMI were performed. To analyse the association between atrial fibrillation at baseline and incident dementia during follow-up, Cox-regression analyses were performed. Participants were censored at the time of death, emigration out of Sweden, or time of dementia onset. Cox-regression analyses were also performed after excluding participants with stroke at baseline and during follow-up.

Sex, education, smoking, BMI, myocardial infarction, heart failure, hypertension, diabetes mellitus, *APOE* ε4 status, and *ACE* rs1799752 status at baseline were considered as possible

covariates. In this study, we applied a machine learning variable selections procedure called the best subset selection [41]. All different subset combinations of our predictors were explored according to the Bayesian Information Criteria (BIC), the coefficient of determination (Adjusted R-Square) and the Mallow's Cp statistics. Covariates were selected based on average performance on these tests.

Interactions with atrial fibrillation and sex, *APOE*, and *ACE* were tested in the Cox-regression analyses. Stratified analyses were performed if the p-value was below 0.2 for the interaction term, as suggested previously [42]. To calculate the proportion of dementia cases that could be attributed to atrial fibrillation in the population, Population Attributable Risk (PAR) was calculated. The calculations of PAR included the adjusted hazard ratios (HR) from the Cox-regression analyses in the total sample and the subsample free from stroke. To perform the statistical analyses, we used R programming version 3.4.3, the leap package was used for variable selection and the attribrisk package was used for the calculation of PAR.

Results

Sample characteristics at baseline for the total sample (n=561), grouped by atrial fibrillation are shown in table 1. Male sex and a history of myocardial infarction and heart failure were more common in the atrial fibrillation group. Other baseline characteristics, i.e. BMI, MMSE, diabetes mellitus, hypertension, *APOE* ε4 status, *ACE* In/Del status, and educational level did not differ between those with and without atrial fibrillation. Atrial fibrillation was found in 54 individuals (38 men, 16 women) at baseline. Among these, 17 were diagnosed from ECG, 26 from NPR, and 37 from proxy informants, and 22 were diagnosed from at least two sources.

The mean follow-up time was 10.4 years (SD 2.8). In total, 53 (9.4%) individuals, 22 men and 31 women, developed dementia during 6133 person years of follow-up. The mean age of dementia onset was 76.6 years (SD 3.1).

Atrial fibrillation and dementia

The HR for dementia was increased in individuals with atrial fibrillation in the total sample after adjustments for sex, education, baseline myocardial infarction and heart failure (HR 2.8; 95%CI 1.3-5.8; p=0.006), see table 2. The associations remained after excluding participants with stroke at baseline or during follow-up. The PAR for dementia resulting from atrial fibrillation was 13% in the total sample and 12% in the subsample free from stroke.

The HR for AD was increased in the total sample (HR 2.7; 95% CI 1.1-6.6; p=0.032) and the subsample free from stroke (HR 2.9; 95% CI 1.2-7.2; p=0.021) after adjustments for education, APOE, baseline myocardial infarction, smoking status, and BMI.

Since the interaction term atrial fibrillation*sex had a p-value below 0.2 both in the total sample (p=0.100) and the subsample free from stroke (p=0.163), see table 3, stratified analyses based on sex were performed. After stratification, the HR for dementia was increased in men with baseline atrial fibrillation, but not in women, see table 4. The interaction term atrial fibrillation**APOE* had a p-value below 0.2 in the total sample (p=0.083), but not in the subsample free from stroke (p=0.267), see table 3. However, stratified analyses based on *APOE* ε4 status were performed in both the total sample and the subsample free from stroke for illustrative purpose. The HR for dementia was increased in those not carrying the *APOE* ε4 allele, but not in carriers of the allele, see table 5. No stratifications were performed based on the *ACE* gene since the interaction term had a p-value above 0.2, both in the total sample (p=0.530) and the subsample free from stroke (p=0.312).

Discussion

We found an association between atrial fibrillation and incident dementia in a population based sample followed from age 70 to 82. This risk remained after exclusion of individuals with stroke at baseline and follow-up. However, the increased risk was only observed in men and in persons without the *APOE* ε4 allele. PAR for dementia resulting from atrial fibrillation was 13%, showing the possible public health benefit of treating atrial fibrillation.

Previous studies also report an increased risk of dementia in individuals with atrial fibrillation. In a meta-analysis of prospective studies from 2011, Kwok et al found an association between atrial fibrillation and dementia in stroke patients, but the relationship was less strong in studies on other populations [43]. In a meta-analysis from 2012 (including the same studies as Kwok et al for the general population and two more recent studies), Santangeli et al showed an association in participants who had normal cognitive function and no history of stroke at baseline [4]. Heterogeneity between studies included in these meta-analyses was substantial. One reason for disparate results could be length of follow-up, since all negative studies had a mean follow-up of less than four years [17-20]. Moreover, the studies included in these meta-analyses had a wide range of study designs, including community and population-based samples, clinical samples, register studies, and one randomized controlled trial. Further, only one of the included studies adjusting for stroke during follow-up [11].

We found a somewhat higher risk (HR 2.7; 95% CI: 1.1-6.5) in our stroke-free sample than the Whitehall II study, which also excluded participants with incident stroke (HR 1.67; 95% CI: 1.17, 2.38) [11]. Other community or population based studies, taking incident stroke into account by censoring participants at the time of a clinical stroke [8, 15] or adjusting for incident stroke [6, 16], have shown similar results as the Whitehall II study (HR 1.23-1.48).

Atrial fibrillation and dementia share common risk factors such as old age, diabetes, hypertension, coronary heart disease, and heart failure [44]. In the absence of manifest stroke and in addition to shared risk factors, there are several possible explanations for the association between atrial fibrillation and dementia. First, atrial fibrillation may cause silent brain infarctions, i.e. infarcts visible on CT or MRI scans with no history of stroke-like symptoms [45]. Second, atrial fibrillation is suggested to be initiated and perpetuated by systemic inflammation but also to trigger the release of CRP and inflammatory cytokines, causing platelet activation [44]. A third mechanism regarding the association between atrial fibrillation and dementia could be cerebral hypoperfusion due to irregular heart beat and reduced cardiac output [44].

We found that atrial fibrillation was associated with dementia in men, but not in women. In contrast to our study, one register based study from Taiwan found similar risk for dementia in men and women with atrial fibrillation [7]. However, these results are difficult to compare with our findings due to methodological differences (register based versus examination based) as well as different settings. Also in contrast to our study, the Swedish Kungsholmen study found that the increased risk of incident dementia in individuals with atrial fibrillation (after stratifying by sex) only was present among women [16]. Possible reasons for the sex differences found in our study include the relatively small sample of women with atrial fibrillation. One other reason could be the young age of our sample. It has been suggested that men have higher incidence of dementia in younger age groups [24], while women have higher incidence and prevalence among the oldest old [22]. However, the proportion developing dementia in our study did not differ between men and women (data not shown). It has also been shown that atrial fibrillation is presented on average 5 years earlier in men than women [46]. There are also sex-differences regarding frequency of atrial fibrillation. Our finding that atrial fibrillation was more common in men is in line with other studies from North America and Europe [47]. However, it has been reported that male sex no longer predict the development of atrial fibrillation when the height of the participants and risk factors for atrial fibrillation are taken into account [48]. Cardiac structural and electrical differences, as well as hormone differences, has been suggested to play a role in observed sex differences in frequency and outcomes of atrial fibrillation [25].

The association between atrial fibrillation and dementia was only present in individuals without the *APOE* ε4 allele. This result is in concordance with the population-based CAIDE study from Finland [9] but in contrast to the population-based Swedish Kungsholmen study [16]. The *APOE* ε4 allele has been suggested to have several pathological pathways to AD, such as affecting the metabolism, aggregation and deposition of beta-amyloid, activity in brain networks, regulation of synaptic plasticity, lipid metabolism, neurogenesis, and neuroinflammation [49]. A synergistic effect between the *APOE* ε4 allele and risk factors for dementia could be explained by the *APOE* ε4 allele causing defects in neuronal repair systems, making *APOE* ε4 carriers less resilient to damages [49]. Another explanation could be that several risk factors together cause dementia. Shared pathways for the *APOE* ε4 allele and atrial fibrillation in the pathogenesis of dementia could be one reason why atrial fibrillation did not increase dementia risk among *APOE* ε4

carriers. Other reasons include that older adults with atrial fibrillation and at least one *APOE* ε4 allele are a selected survival group, or that there are differences in the underlying cause(s) of dementia in *APOE* ε4 carriers than in non-carriers. For example, the results of a recent biomarker-based study suggest that *APOE* ε4-negative prodromal AD patients have more non-amnestic cognitive impairment, more rapid cognitive decline, higher cerebrospinal fluid levels of Aβ peptides and neuronal injury biomarkers, increased white matter pathology, and cortical atrophy compared to *APOE* ε4-positive prodromal AD patients [50]. Since there are few studies to support the differential effect of *APOE* ε4 on the association between atrial fibrillation and dementia, these findings need to be further explored.

Among the strengths of this study are the population-based sample and the long follow up time of 12 years. In addition, the comprehensive examinations were conducted by health professionals and included questionnaires, physical examinations (including ECG), biological markers as well as register data. We also had the possibility to exclude participants with a history of stroke at baseline as well as incident stroke during follow-up. There are also limitations. First, the question about atrial fibrillation was only asked to the proxy informants and not to the participants. However, we had the possibility to include both register data and information from ECG. Second, we were only able to diagnose clinical stroke at follow-up. Since stroke may go without clinical symptoms, the inclusion of MRI brain scans at both baseline and follow-up would have been useful to detect silent strokes. Third, the sample size limits the possibility to perform subgroup analyzes. Fourth, only individuals living in Gothenburg, Sweden were included, which limit generalizability to other age groups and settings. Fifth, although response rates during follow-up were relatively high, we cannot exclude the possibility of selective attrition. This was to some extent alleviated by using register data to diagnose dementia in those lost to follow-up. However, register data misses a large proportion of cases with dementia.

Conclusion

Our study suggests that atrial fibrillation is a risk factor for dementia also in the absence of stroke. In addition, we found higher risk in men than in women regarding the association between atrial fibrillation and dementia, and that atrial fibrillation only increased risk of dementia among non-carriers of the *APOE* ε4 allele. Since atrial fibrillation is common and prevalence figures are suggested to increase further, it is important to continue studying the association between atrial fibrillation and dementia as well as possible mechanisms of the association. Our findings may be important in relation to prevention, and further emphasizes the importance to detect atrial fibrillation in the population. Also, patients with atrial fibrillation should be screened for cognitive symptoms.

Conflict of interests

Ingmar Skoog has given talks for Takeda,

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Table 1. Baseline characteristics and longitudinal outcomes for participants grouped by atrial fibrillation

	Atrial fibrillation	No Atrial fibrillation	p-value
	n=54	***n=507***	
Men, n (%)	38 (70.4)	186 (36.7)	<0.001
Education, more than mandatory, n (%)[a]	28 (51.9)	192 (38.1)	0.057
Smoking, n (%)			
Never	19 (32.2)	246 (48.5)	
Former	23 (42.6)	187 (36.9)	
Current	12 (22.2)	74 (14.6)	0.128
BMI, mean (sd)	27.2 (4.6)	27.0 (4.1)	0.765
MMSE, mean (sd)[b]	28.0 (1.4)	28.2 (1.5)	0.284
Myocardial infarction, n (%)	15 (27.8)	43 (8.5)	<0.001
Heart failure, n (%)	7 (13.0)	11 (2.2)	0.001
Diabetes, n (%)[c]	6 (11.1)	32 (6.4)	0.248
Hypertension, n (%)	42 (77.8)	421 (83.0)	0.346
APOE, n %[d]			
ε4	14 (26.4)	141 (28.6)	
no ε4	39 (73.6)	352 (71.4)	0.873
ACE, n %[e]			
DD	11 (22.4)	138 (28.5)	
ID	21 (42.9)	230 (47.5)	
II	17 (34.7)	116 (24.0)	0.241
Longitudinal outcomes	***n=53***	***n=507***	
Incident dementia, n %	10 (18.5)	43 (8.5)	0.025
Vascular dementia	1 (1.9)	4 (0.8)	
Alzheimer	6 (11.1)	28 (5.5)	
Mixed	2 (3.7)	11 (2.2)	
Other	1 (1.9)	0 (0.0)	
Incident stroke, n %	9 (16.7)	57 (11.2)	0.264

Data is missing for:
[a] three individuals
[b] five individuals
[c] four individuals
[d] 15 individuals
[e] 28 individuals

Table 2. Risk of dementia associated with atrial fibrillation.

Total sample	**HR (95% CI) unadjusted**	**p**	**HR (95% CI) adjusted [a]**	**p**	**PAR % (95% CI)**
Atrial fibrillation	2.6 (1.3-5.3)	0.006	2.8 (1.3-5.8) [a]	0.006	12.9 (1.0-25.9)
Stroke- free subsample					
Atrial fibrillation	2.9 (1.3-6.5)	0.011	2.7 (1.1-6.5)	0.027	12.1 (0.4-25.3)

[a] Adjusted for sex, education, and baseline myocardial infarction and heart failure

Table 3. Risk of dementia associated with atrial fibrillation and interactions with sex and genetic factors in the total sample and the subsample free from stroke

	Total sample		**Stroke- free subsample**	
	HR (95% CI) adjusted[a]	**p**	**HR (95% CI) adjusted[a]**	**p**
Atrial fibrillation	4.5 (1.9-10.9)	0.001	4.6 (1.6-13.2)	0.005
Sex	1.5 (0.7-2.9)	0.267	1.3 (0.6-2.7)	0.517
Atrial fibrillation*Sex	0.2 (0.0-1.4)	0.100	0.2 (0.0-1.9)	0.163
Atrial fibrillation	4.8 (2.0-11.3)	<0.001	4.0 (1.4-11.9)	0.012
APOE	2.9 (1.5-5.3)	0.001	2.6 (1.3-5.2)	0.008
Atrial fibrillation**APOE*	0.2 (0.0-1.2)	0.083	0.4 (0.1-2.2)	0.267
Atrial fibrillation	4.2 (1.2-14.9)	0.028	6.0 (1.2-28.9)	0.026
ACE	1.0 (0.7-1.6)	0.896	0.9 (0.6-1.5)	0.785
Atrial fibrillation**ACE*	0.7 (0.3-1.9)	0.530	0.5 (0.1-1.8)	0.312

[a] Adjusted for sex (except in the model including atrial fibrillation*sex interaction), education, baseline myocardial infarction and heart failure

Table 4. Risk of dementia associated with atrial fibrillation after stratification by sex.

Total sample	**HR (95% CI) unadjusted**	**p**	**HR (95% CI) adjusted[a]**	**p**
Atrial fibrillation, men	4.2 (1.8-9.7)	0.001	4.5 (1.9-11.0)	0.001
Atrial fibrillation, women	0.7 (0.1-5.4)	0.759	0.6 (0.1-5.1)	0.660
Stroke- free subsample				
Atrial fibrillation, men	4.8 (1.7-13.3)	0.002	5.0 (1.7-14.7)	0.003
Atrial fibrillation, women	0.9 (0.1-6.7)	0.917	0.7 (0.1-5.7)	0.698

[a] Adjusted for education, baseline myocardial infarction and heart failure

Table 5. Risk of dementia associated with atrial fibrillation after stratification by *APOE*

Total sample	**HR (95% CI) unadjusted**	**p**	**HR (95% CI) adjusted[a]**	**p**
Atrial fibrillation, *APOE* ε4	1.1 (0.3-4.6)	0.929	1.2 (0.3-5.1)	0.846
Atrial fibrillation, no *APOE* ε4	4.2 (1.9-9.5)	0.001	4.5 (1.8-11.2)	0.001
Stroke- free subsample				
Atrial fibrillation, *APOE* ε4	1.4 (0.3-6.0)	0.668	1.1 (0.2-5.3)	0.873
Atrial fibrillation, no *APOE* ε4	4.5 (1.6-12.2)	0.004	4.3 (1.4-13.2)	0.012

[a] Adjusted for education, baseline myocardial infarction and heart failure

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