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Sex Differences and Similarities in Atrial Fibrillation Epidemiology, Risk Factors and Mortality in Community Cohorts: Results from the BiomarCaRE Consortium

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Abstract

Background—Atrial fibrillation (AF) is a common cardiac disease in aging populations with high comorbidity and mortality. Sex differences in AF epidemiology are insufficiently understood.

Methods—In N=79,793 individuals without AF diagnosis at baseline (median age 49.6 years, age range 24.1-97.6 years, 51.7% women) from four community-based European studies (FINRISK, DanMONICA, Moli-sani, Northern Sweden) of the BiomarCaRE consortium, we examined AF incidence, its association with mortality, common risk factors, biomarkers and prevalent cardiovascular disease, and their attributable risk by sex. Median follow-up time was 12.6 (to a maximum of 28.2) years.

Results—Fewer AF cases were observed in women, N=1,796 (4.4%) than in men, N=2,465 (6.4%). Cardiovascular risk factor distribution and lipid profile at baseline were less beneficial in men compared to women and cardiovascular disease was more prevalent in men. Cumulative incidence increased markedly after the age of 50 years in men and after 60 years in women. The lifetime risk was similar (more than 30%) for both sexes. Subjects with incident AF had a 3.5-fold risk of death compared to those without AF. Multivariable-adjusted models showed sex differences for the association of body mass index (BMI) and AF, hazard ratio (HR) per standard deviation (SD) increase 1.18, 95% confidence interval (CI) 1.12 to 1.23 in women versus 1.31, 95% CI 1.25 to 1.38 in men; interaction P value 0.001. Total cholesterol was inversely associated with incident AF with a greater risk reduction in women, HR per SD 0.86, 95% CI 0.81 to 0.90 versus 0.92, 95% CI 0.88 to 0.97 in men, interaction P value 0.023. No sex differences were seen for C-reactive protein and N-terminal pro B-type natriuretic peptide.

The population attributable risk of all risk factors combined was 41.9% in women and 46.0% in men. About 20% of the risk was observed for BMI.

Conclusions—Lifetime risk of AF was high and AF was strongly associated with increased mortality both in women and men. BMI explained the largest proportion of AF risk. Observed sex differences in the association of BMI and total cholesterol with AF need to be evaluated for underlying pathophysiology and relevance to sex-specific prevention strategies.

Keywords

atrial fibrillation; sex; epidemiology; cohort; biomarkers risk assessment; mortality

Introduction

Atrial fibrillation (AF) is a common cardiac disease that increases the risk of morbidity and mortality in aging women and men.1–3 Considerable sex differences in prevalence, incidence, and mortality have been reported.2,4 AF prevalence in middle-aged and older community cohorts is almost twice as high in men than in women.5–7 The increasing prevalence of AF and subsequent public health and economic burden require research efforts to understand sex differences in disease distribution and risk factor associations.5 The onset of AF diminishes the survival advantage in women.8 Risk of adverse outcomes in AF also appears to differ by sex, e.g. stroke risk is higher in women with AF.9 Consistently reported risk factors for AF such as obesity, arterial hypertension, blood lipid profile, diabetes,

smoking, alcohol consumption, and prevalent cardiovascular diseases, show differential distributions by sex and thus need to be considered as possible explanations for observed differences in AF epidemiology.10 Furthermore, biomarkers related to the disease such as C-reactive protein (CRP) and B-type natriuretic peptide (Nt-proBNP) are known to differ by sex,11,12 and may be differentially associated with AF risk.

Despite the increasing public health importance of AF, sex-specific disease distributions and associations of clinical risk factors and cardiac biomarkers with AF have received limited attention. Our study comprises a subset of the BiomarCaRE (Biomarker for Cardiovascular Risk Assessment in Europe) consortium, which provides information on the epidemiology of AF and its risk factors in European community cohorts.13 Our objective was to systematically examine sex differences in AF incidence, and in the association of AF with mortality, classical cardiovascular risk factors and biomarkers in Europe. We also examined sex differences in population attributable risks for AF derived from the classical risk factors.

Methods

Study Sample

The present study is a substudy of the BiomarCaRE consortium.13 Current analyses include BiomarCaRE cohorts with available information on AF status at baseline and follow-up (DanMONICA, FINRISK, Moli-sani and Northern Sweden), totaling N=79,793 individuals. All individuals gave informed consent prior to study inclusion. The cohorts were based on representative population samples with baseline examinations between 1982 and 2010. Individuals with self-reported and/or physician-diagnosed history of AF/atrial flutter and/or prior ICD-10 coding for AF/atrial flutter and/or AF/atrial flutter on the baseline electrocardiogram (ECG) were defined as having prevalent AF and excluded from all analyses (N=687). Details on the enrolment and follow-up procedures of each study are provided in the Supplemental Material. Missing data were handled by available case analyses.

Risk Factors and Follow-Up

Risk factor information was available from the baseline visits. Body mass index (BMI), systolic blood pressure, and total cholesterol were measured locally by routine methods, and along with daily smoking, prevalent diabetes, anti-hypertensive medication, history of stroke, and myocardial infarction centrally harmonized in the MORGAM (MONICA Risk, Genetics, Archiving and Monograph) project.14 These clinical variables have consistently been related to AF and are part of risk prediction schemes.15 Average alcohol consumption was assessed in grams per day and according to the WHO average volume drinking categories (http://www.who.int/publications/cra/en/). As ‘abstainers’ could not be separated from the ‘average drinking category I’, we merged these two categories. The diagnosis of AF was based on study ECG tracings, questionnaire information, national hospital discharge registry data, including data on ambulatory visits to specialized hospitals. Additionally, causes of death registry data were screened for incident AF as a comorbidity of individuals that died for other causes. Mortality data were derived from central death registries. The last follow-up was between 2010 and 2011 in the various cohorts.

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Biomarker measurement

Biomarker measurements from stored blood samples were available for some of the cohorts (Supplementary Table 1). In N=37,902 individuals, CRP was determined by latex immunoassay CRP16 (Abbott, Architect c8000), with intraassay and interassay coefficients of variation of 0.93 and 0.83.16 In N=29,038 participants Nt-proBNP was measured on the ELECSYS 2010 platform using an electrochemiluminescence immunoassay (ECLIA, Roche Diagnostics). The analytical range is given as 5–35.000 ng/L. Intra- and interassay coefficients of variation were 2.58 and 1.38.

Local Ethics Committees have approved all participating studies. The authors had full access to the data and take responsibility for its integrity. All authors have read and agreed to the manuscript as written.

Statistical Analysis

Continuous variables were presented as median (25^{th}, 75^{th} percentile) and binary variables as absolute and relative frequencies. Cumulative incidence curves for AF and death without AF as competing risks were computed using the Aalen-Johansen estimator.17 To examine the association of AF and all-cause mortality a sex and cohort stratified Cox regression for all-cause mortality with AF during follow-up as a time dependent covariate was computed. Total cholesterol, BMI, daily smoking, diabetes, systolic blood pressure and antihypertensive medication were used as time fixed covariates as they are only available at baseline. For these covariates and AF, a sex interaction was included in the model to allow for the effect of the covariate to vary by sex. Age was used as the time scale in all models.18

To study the associations of AF risk factors with time to AF for women and men, sex and cohort stratified Cox regressions were performed. First, for each risk factor a Cox model was computed. Then a model including simultaneously BMI, systolic blood pressure, total cholesterol, diabetes, daily smoking, and antihypertensive medication was fitted. Finally, each of the variables alcohol consumption, history of stroke, history of myocardial infarction, CRP, and Nt-proBNP were added in turn to this last model. For all covariates a sex interaction was included in each model. If a model included systolic blood pressure, then antihypertensive medication was included in the model. Relative risk ratios (RRR) for the women:men ratio of hazard ratios and population attributable risks (PARs) for incident AF were calculated.

For the PAR calculations, categorization of the continuous variables BMI (<25 kg/m^2, 25 to < 30 kg/m^2, ≥30kg/m^2), systolic blood pressure (<120 mm Hg, 120 to <140 mm Hg, 140 to <160 mm Hg, ≥160 mm Hg), and total cholesterol (cut-off 200 mg/dL=5.17 mmol/L) were performed. Average daily alcohol consumption was categorized based on calculated alcohol intake as follows: category I: for women 0-19.99g alcohol daily, for men 0-39.99 g; category II: for women 20-39.99 g, for men 40-59.99 g; category III: for women ≥40 g, for men ≥60 g.

In secondary analyses we evaluated the association of waist-to-hip ratio and the height and weight component of BMI, with time-to-AF following similar Cox modelling protocols.

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All statistical methods were implemented in R statistical software version 3.3.3 (www.R-project.org). A more detailed description of the statistical methods is provided in the Supplemental Material.

Results

Our study sample had an overall median age of 49.6 years, age range 24.1 to 97.6 years at baseline, about half of the participants (48.3%) were men. Median age was similar for women and men (49.2 versus 50.0 years) The baseline characteristics of the sample by sex are provided in Table 1. Risk factor distributions were more favorable in women who had lower BMI and systolic blood pressure than men. Women smoked less, consumed lower amounts of alcohol, and had lower levels of diabetes than men. Total cholesterol and CRP levels were similar in both sexes. Median Nt-proBNP concentrations were higher in women than in men. Study characteristics by cohort are shown in Supplemental Table 1.

Over a median follow-up of 12.4 years, range 0-29 years, fewer incident AF cases occurred in women, N=1,796 (4.4%) than in men, N=2,465 (6.4%) (P< 0.001) (for follow-up information by cohort see Supplemental Table 2). Cumulative incidence curves with death as a competing risk are shown in Figure 1 and Supplemental Figure 1 (and by cohort in Supplemental Figure 2). The curves differed by sex. After the age of 50 years, AF incidence in men increased steeply, while in women this increase occurred after the age of 60 years. Both curves converged at the age of 90. AF incidence was very low before the age of 50.

In age-adjusted and risk factor adjusted models, incident AF was associated with more than a 3.5-fold increased risk of death in both sexes (Figure 2).

Multivariable-adjusted HRs for AF by sex and the respective interaction P values are shown in Table 2. All cardiovascular risk factors (except for diabetes), history of stroke and myocardial infarction, and Nt-proBNP were associated with new onset AF in both sexes. Alcohol consumption and CRP were not associated with AF in women. We observed significant interactions by sex in the association between incident AF, BMI and total cholesterol. BMI was more strongly related to new onset AF in men, HR per standard deviation increase 1.31, 95% confidence interval (CI) 1.25 to 1.38, compared to women, HR 1.18, 95% CI 1.12 to 1.23, with a RRR of 0.89, 95% CI 0.84 to 0.96. Total cholesterol was inversely associated with incident AF with a stronger risk reduction in women (HR 0.86, 95% CI 0.81 to 0.90 versus 0.92, 95% CI 0.88 to 0.97 in men), RRR 0.93, 95% CI 0.87 to 0.99. The association persisted after accounting for cholesterol lowering medication in an exploratory analysis (Supplemental Table 3). Age-adjusted Cox regression models are provided in Supplemental Table 4. Additional interactions for Nt-proBNP and daily alcohol consumption lost statistical significance after multivariable adjustment.

In secondary analyses waist-to-hip ratio showed a stronger association with AF in men compared to women. The interaction did not reach statistical significance. Height revealed a stronger association with AF in women than in men, interaction P value <0.001 (Supplemental Table 5).

PARs for 5-year incident AF resulting from the classical risk factors are presented in Table 3. PARs of most classical risk factors were similar in both sexes. A higher PAR was observed for total cholesterol in women (PAR 8.6%, 95% CI 5.4 to 12.0) compared to men (PAR 3.8%, 95% CI 0.2 to 7.3). Alcohol consumption produced a higher PAR in men versus women in whom the PAR was very low with 0.2% in average volume drinking category II. The PAR of a history of myocardial infarction was higher in men (PAR 6.1%, 95% CI 4.2 to 8.2) compared to women (PAR 3.0%, 95% CI 1.5 to 4.5). Obesity accounted for a PAR of 13.3% in men and 14.4% in women. In total, the examined risk factors (BMI, systolic blood pressure, total cholesterol, daily smoking, diabetes, alcohol consumption, history of myocardial infarction and history of stroke) and cardiovascular diseases accounted for 41.9% and 46.0% of the PAR in women and in men, respectively.

Discussion

In a pooled analysis of community cohorts across Europe, the cumulative risk of developing AF was higher in men than in women over most of the lifespan but became similar at older age with a comparable lifetime risk. Incident AF was associated with more than a 3.5-fold increased mortality risk with no significant sex difference. Among the classical risk factors, higher BMI and lower total cholesterol were associated with a higher risk of AF in men than in women. PAR resulting from classical risk factors were largely comparable.

The age-dependency of AF is well known.7,19,20 We confirmed an increase in incidence of AF with age in women and men. Cumulative incidence was low in middle age. Women lagged about a decade behind men, but reached the cumulative incidence of men by the age of 90. Overall, a third of women and men were estimated to develop AF during their lifetime. A considerable lifetime risk of AF between one fifth and one fourth has been reported in studies with usually comparatively small numbers in the older age groups.20–6 With a broader age range, our data estimate the risk to be even higher. The risk of mortality related to AF onset as described earlier8,23 remains high. In both, women and men, AF was associated with more than a 3.5-fold increased risk of death with no evidence for a sex difference. Thus, AF poses a significant risk for premature mortality.

BMI and obesity are established risk factors for AF.7,24,25 Prior studies have found sex differences in the association of obesity with long-term incidence of AF. While no statistically significant interactions were reached in the Framingham Heart Study, the effect estimates showed a higher magnitude of association in men.26 In the Danish Diet, Cancer, and Health Study, obese women had a 2-fold higher risk of AF compared to men (HR of 2.35 in multivariable-adjusted analyses).27 An Australian study in more than 4,000 individuals reported a possible sex interaction of BMI with incident AF.28 Body fat distribution differs by sex and additional adiposity measures may need to be examined. For example, in a subsample of our cohorts, waist-to-hip ratio showed a stronger association with AF in men than in women but the interaction did not reach statistical significance. However, BMI has remained the strongest validated predictor of incident AF.29

Further secondary analyses in our sample revealed differential associations of height with AF in women and men. That, in part, may help to explain the observed sex differences for

BMI. Increased height is related to higher risk of AF.30 This may be linked to a greater susceptibility to arrhythmia through larger cardiac dimensions and higher excitability of the conduction system.31,32 In our data the association appears to be stronger in women, which requires further examination to clarify possible mechanisms. Despite the role of height in our findings, BMI remains a central risk factor. Elevated BMI may be a sign of insufficient risk factor control.10 But the proportionality of weight gain and increased AF risk within short periods of follow-up33,34 and the close correlation of weight and weight fluctuations with AF patterns suggest a possible direct relationship with AF.35 Evidence suggests that the effects of obesity on cardiac structural remodeling and function differ by sex,36–38 which increases the predisposition to AF. Irrespective of the underlying mechanisms, BMI is a modifiable risk factor in AF.35,40 Its population attributable risk has significantly increased5 and has been reported to account for up to 18% of risk for incident AF in women. 33 In our current sample the attributable risk was similar, about 20% if overweight and obese individuals were combined. Thus, BMI provides an opportunity for possible risk reduction in both sexes.

Women and men show well established differences in plasma lipid profiles.40 The counterintuitive inverse association of total cholesterol and other pro-atherogenic lipoproteins has been reported earlier.41,42 This observation has been explained by membrane stabilizing characteristics of cholesterol, although the exact pathophysiology remains unclear. Importantly, this inverse association was observed in both sexes in our study, with a borderline higher effect size in women.

The inflammatory biomarker CRP was associated with AF in men, but did not reach statistical significance in women. The HRs were relatively small as described in prior investigations.11 For the cardiac biomarker Nt-proBNP, an interaction by sex in age-adjusted models with a higher relative risk in women became non-significant after adjustment for clinical covariates. Sex and BMI are among the strongest correlates of Nt-proBNP concentrations. Female sex and obesity are correlated with higher natriuretic peptides.43,44 Thus, confounding, the small sample size with available information on Nt-proBNP or more complex interactions may explain the observations, which need to be elucidated in further studies.

Sex differences for risk factor associations have consistently been reported for diabetes and smoking in relation to coronary heart disease and stroke, with a higher relative risk of developing disease in women.45–47 In contrast to coronary heart disease and stroke, diabetes was not associated with incident AF in our cohorts and no interaction by sex was observed. Smoking usually carries a higher risk for cardiovascular disease in women.45,46 We could not extend this knowledge towards AF where the association appeared to be similar in both sexes. Differences in sex for prior cardiovascular disease prevalence are well established major risk factors for incident AF.48,49 Our study indicates that previous myocardial infarction or stroke are associated with similar risk of developing AF in women and men and are therefore comparable risk indicators in both sexes.

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Limitations and strengths

Our data are restricted to epidemiological observations that cannot reveal potential mechanisms explaining the differential associations by sex. Data on the pathophysiological pathways potentially underlying sex-specific differences are needed. Furthermore, our results on cardiovascular risk factors are not sufficient to examine potential sex disparities. Unfortunately, baseline ECGs were not available systematically in all cohorts, which may have led to an underdiagnosis of AF and introduced bias. Follow-up information on AF derived from hospital discharge data, including data on ambulatory visits to specialized hospitals may lead to misclassification of AF cases, in particular intermittent AF. This possible misclassification may have led to a lower incidence and a weakening of the associations of classical risk factors with incident AF and mortality. In the past, the specificity of administrative registry data has been proven to be good with limitations in sensitivity.50,51 In addition, biomarker information was only available in a subgroup of the study sample. The relating results are hypothesis-generating and have thus to be interpreted with caution.

The strength of the study is the population-based and longitudinal study design. Furthermore, we used harmonized data on classical cardiovascular risk factors and biomarker measurements in large studies with long-term follow-up information with sufficient power to examine sex interactions.

In conclusion, our data provide evidence that differences in AF incidence observed by sex may be explained by the sex-specific distribution of risk factors and by differential associations of classical risk factors. A substantial proportion of the AF burden can be explained by classical cardiovascular disease risk factors in both sexes. While blood pressure, smoking, alcohol consumption, Nt-proBNP, and prevalent cardiovascular disease are largely similar predictors of incident AF in both sexes, total cholesterol concentrations may show sex differences. A higher BMI and obesity are stronger risk factors for the development of AF in men and require better awareness and targeted intervention.

Understanding the sex differences in AF risk and risk factors is essential for developing long-term preventive measures to reduce mortality, public health burden and healthcare costs related to AF in both women and men.

Supplemental Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

AF	atrial fibrillation
BMI	body mass index
CI	confidence interval
CRP	C-reactive protein
FU	follow-up
HR	hazard ratio
Nt-proBNP	N-terminal pro B-type natriuretic peptide
PAR	population attributable risk
RRR	relative risk ratio
SD	standard deviation

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Clinical Perspective

What is new?

- In European community cohorts, life-time risk of atrial fibrillation (AF) was more than 24% by the age of ninety in both sexes.
- Men developed AF a decade earlier.
- Interim AF was associated with more than a 3.5-fold increased mortality risk.
- Among the classical risk factors, body mass index (BMI) explained the largest proportion of AF risk.
- Sex interactions were seen for risk associations of BMI and total cholesterol.

What are the clinical implications?

- AF is a frequent disease and is related to high mortality.
- AF risk factors are similar in both sexes.
- Observed sex differences for BMI and total cholesterol need to be evaluated for their relevance in sex-specific prevention strategies.

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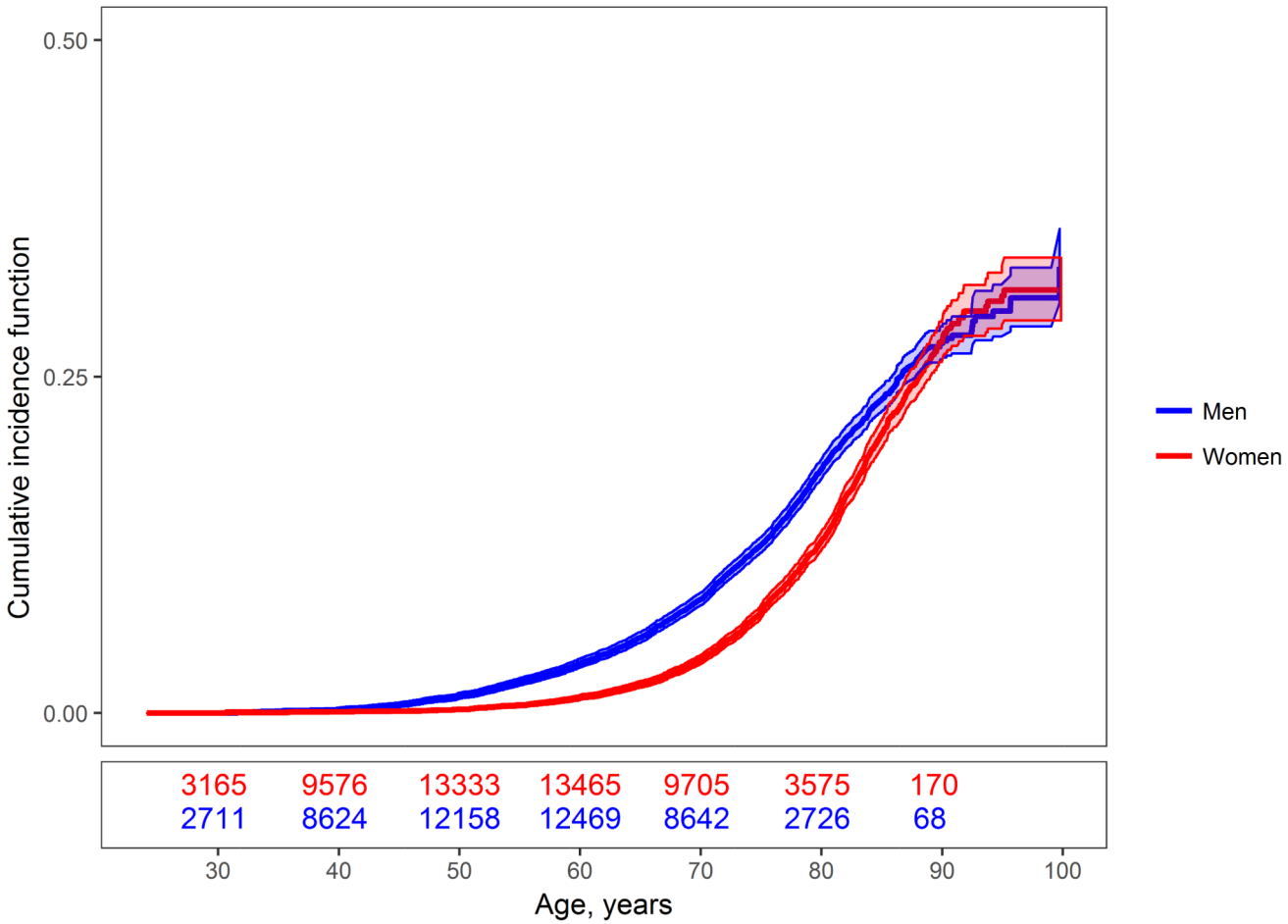

Figure 1.

Cumulative incidence curves and 95% confidence intervals for atrial fibrillation in women and men with death as a competing risk are shown. The numbers of individuals at risk are provided under the figure. Testing for the equality of the cumulative incidence curves produces a P value <0.001.

	Sex	Hazard Ratio (95% Confidence Interval)	Hazard Ratio P value	Interaction P value
Model 1	Men	3.57 (3.32, 3.84)	<0.001	0.28
	Women	3.81 (3.47, 4.18)	<0.001	
Model 2	Men	3.51 (3.26, 3.78)	<0.001	0.70
	Women	3.59 (3.27, 3.95)	<0.001	

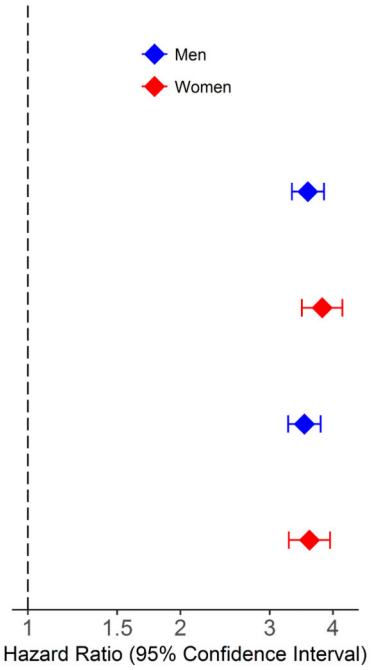

Figure 2.

Cox regression analyses for all-cause mortality with atrial fibrillation as time-dependent covariate, model 1. Model 2 is additionally adjusted for body mass index, systolic blood pressure, diabetes, daily smoking, antihypertensive medication, total cholesterol. The x-axis is shown on a log-scale.

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Table 1

Baseline characteristics of the sample by sex.

Variable	Women N=41,226	Men N=38,567	P value
Age at examination (years)	49.2 (39.5, 59.0)	50.0 (39.9, 59.9)	<0.001
BMI (kg/m^2)	25.7 (22.8, 29.5)	26.7 (24.3, 29.4)	<0.001
Systolic blood pressure (mmHg)	130 (118, 147)	136 (125, 150)	<0.001
Diabetes No. (%)	1818 (4.4)	2075 (5.4)	<0.001
Daily smoking No. (%)	8527 (20.8)	10947 (28.6)	<0.001
Antihypertensive medication No. (%)	6718 (17.0)	6198 (16.9)	0.49
Total cholesterol (mmol/L)	5.6 (4.9, 6.4)	5.6 (4.9, 6.4)	<0.001
Average daily alcohol consumption (g)	1.0 (0, 6.0)	8.0 (1.0, 23.0)	<0.001
Average drinking category I No. (%)	37886 (94.7)	32827 (88.1)	<0.001
Average drinking category II No. (%)	1781 (4.5)	2791 (7.5)	<0.001
Average drinking category III No. (%)	342 (0.9)	1663 (4.5)	<0.001
History of stroke No. (%)	445 (1.1)	668 (1.7)	<0.001
History of myocardial infarction No. (%)	484 (1.2)	1567 (4.1)	<0.001
C-reactive protein (mg/L)	1.4 (0.7, 3.2)	1.4 (0.7, 2.9)	0.51
Nt-proBNP (ng/mL)	59 (35, 100)	37 (20, 76)	<0.001

Continuous variables are presented as median (25^{th}, 75^{th} percentile), binary variables as absolute and relative frequencies. The P value given is for the Mann-Whitney test or the Chi-square test. N incident AF: All=4,261 (5.3%), women=1,796 (4.4%), men=2,465 (6.4%).

Average drinking categories based on pure alcohol intake: category I, for women 0-19.99 g/day, for men 0-39.99 g/day; category II, for women 20-39.99 g/day, for men 40-59.99 g/day; category III, for women ≥40 g/day, for men ≥60 g/day.

BMI stands for body mass index, Nt-proBNP for N-terminal pro B-type natriuretic peptide.

Table 2

Multivariable-adjusted atrial fibrillation hazard ratios by sex and interaction P values for atrial fibrillation risk factors in the overall sample.

Variable	Interaction P value	Sex	Hazard Ratio (95% Confidence Interval)	P value	Relative Risk Ratio (95% Confidence Interval)
Body mass index (kg/m^2)	0.001	Women	1.18 (1.12, 1.23)	<0.001	0.89 (0.84, 0.96)
		Men	1.31 (1.25, 1.38)	<0.001	
Systolic blood pressure (mm Hg)	0.90	Women	1.09 (1.04, 1.15)	<0.001	1.00 (0.93, 1.07)
		Men	1.10 (1.05, 1.15)	<0.001	
Diabetes	0.68	Women	1.15 (0.96, 1.38)	0.14	1.05 (0.83, 1.34)
		Men	1.09 (0.93, 1.28)	0.28	
Daily smoking	0.27	Women	1.34 (1.17, 1.55)	<0.001	1.10 (0.93, 1.30)
		Men	1.22 (1.11, 1.35)	<0.001	
Antihypertensive medication	0.077	Women	1.65 (1.47, 1.85)	<0.001	1.15 (0.99, 1.34)
		Men	1.43 (1.29, 1.59)	<0.001	
Total cholesterol (mmol/L)	0.023	Women	0.86 (0.81, 0.90)	<0.001	0.93 (0.87, 0.99)
		Men	0.92 (0.88, 0.97)	<0.001	
Alcohol consumption	0.12	Women	1.07 (0.99, 1.15)	0.072	0.93 (0.85, 1.02)
		Men	1.15 (1.10, 1.20)	<0.001	
History of stroke	0.57	Women	1.42 (1.07, 1.88)	0.014	1.11 (0.77, 1. 61)
		Men	1.28 (1.01, 1.62)	0.042	
History of myocardial infarction	0.55	Women	1.93 (1.55, 2.40)	<0.001	1.08 (0.84, 1.40)
		Men	1.78 (1.55, 2.05)	<0.001	
C-reactive protein (mg/L)	0.40	Women	1.05 (0.96, 1.16)	0.28	0.95 (0.84, 1.07)
		Men	1.11 (1.03, 1.12)	0.006	
Nt-proBNP (ng/mL)	0.16	Women	2.19 (1.95, 2.47)	<0.001	1.11 (0.96, 1.28)
		Men	1.98 (1.83, 2.14)	<0.001	

Nt-proBNP stands for N-terminal pro B-type natriuretic peptide.

The first six variables represent our base model, the others are separately added on top to the base model. All models include body mass index, systolic blood pressure, total cholesterol, daily smoking, diabetes, and antihypertensive medication. Biomarker information was available in a subgroup only (Supplemental Table 1).

Hazard ratios for continuous variables are for one standard deviation (SD) increase, body mass index: 4.67 kg/m², systolic blood pressure: 21 mm Hg, total cholesterol: 1.17 mmol/L, log(C-reactive protein, mg/L): 1.1, log(Nt-proBNP, ng/mL): 0.98, transformed alcohol consumption: 1.36. Standard deviations were computed using all observations regardless of sex.

C-reactive protein, Nt-proBNP and alcohol consumption were log-transformed. Since alcohol consumption can equal zero, one was added before applying the transformation.

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Table 3

Population attributable risk (%) for 5-year atrial fibrillation incidence by sex.

Variable	PAR (95% Confidence Interval) Women	PAR (95% Confidence Interval) Men
Body mass index 25 to <30 kg/m^2	4.2 (0.1, 8.4)	6.9 (2.0, 11.2)
Body mass index ≥30kg/m^2	14.4 (10.0, 19.0)	13.3 (9.9, 17.0)
Systolic blood pressure 120 to <140 mm Hg	0.5 (-3.8, 4.4)	4.7 (0.9, 8.8)
Systolic blood pressure 140 to <160 mm Hg	5.2 (-1.7, 10.7)	5.0 (-0.1, 9.9)
Systolic blood pressure ≥160 mm Hg	9.0 (2.4, 14.2)	8.7 (4.7, 13.1)
Diabetes	1.1 (-1.1, 3.4)	0.5 (-1.4, 2.5)
Daily smoking	3.0 (1.2, 4.8)	3.0 (0.8, 5.2)
Total cholesterol <5.17 mmol/L	8.6 (5.4, 12.0)	3.8 (0.2, 7.3)
Average drinking category II	0.2 (-1.3, 2.0)	2.1 (0.1, 4.2)
Average drinking category III	0.4 (-0.2, 1.3)	1.6 (0.3, 3.1)
History of myocardial infarction	3.0 (1.5, 4.5)	6.1 (4.2, 8.2)
History of stroke	1.1 (0.0, 2.5)	0.5 (-0.5, 1.6)
Total PAR (%)	41.9 (29.4, 51.9)	46.0 (38.2, 55.2)

The cause-specific Cox models used include body mass index, systolic blood pressure, total cholesterol, daily smoking, diabetes, alcohol consumption, history of myocardial infarction, history of stroke and antihypertensive medication. Age was used as the time scale. The models were stratified by sex and cohort.

Average drinking categories are based on pure alcohol intake: category II, for women 20-39.99 g/day, for men 40-59.99 g/day; category III, for women ≥40 g/day, for men ≥60 g/day.

PAR stands for population attributable risk.