# Sex Differences and Similarities in Atrial Fibrillation Epidemiology, Risk Factors, and Mortality in Community Cohorts

## Results From the BiomarCaRE Consortium (Biomarker for Cardiovascular Risk Assessment in Europe)

**Christina Magnussen, MD et al**

**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 4 community-based European studies (FINRISK, DanMONICA, Molisani Northern Sweden) of the BiomarCaRE consortium (Biomarker for Cardiovascular Risk Assessment in Europe), 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=1796; 4.4%), than in men (N=2465; 6.4%). Cardiovascular risk factor distribution and lipid profile at baseline were less beneficial in men than in 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 (>30%) for both sexes. Subjects with incident AF had a 3.5-fold risk of death in comparison with those without AF. Multivariable-adjusted models showed sex differences for the association of body mass index and AF (hazard ratio per standard deviation increase, 1.18; 95% confidence interval [CI], 1.12–1.23 in women versus 1.31; 95% CI 1.25–1.38 in men; interaction *P* value of 0.001). Total cholesterol was inversely associated with incident AF with a greater risk reduction in women (hazard ratio per SD, 0.86; 95% CI, 0.81–0.90 versus 0.92; 95% CI, 0.88–0.97 in men; interaction *P* value of 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 body mass index.

**CONCLUSIONS:** Lifetime risk of AF was high, and AF was strongly associated with increased mortality both in women and men. Body mass index explained the largest proportion of AF risk. Observed sex differences in the association of body mass index and total cholesterol with AF need to be evaluated for underlying pathophysiology and relevance to sex-specific prevention strategies.

The full author list is available on page 1594.

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Sources of Funding, see page 1595

**Key Words:** atrial fibrillation ■ biomarkers ■ cohort studies ■ epidemiology ■ mortality ■ risk assessment ■ sex

## Clinical Perspective

### What Is New?

- In European community cohorts, lifetime risk of atrial fibrillation (AF) was >24% by the age of 90 years in both sexes.
- Men developed AF a decade earlier.
- Interim AF was associated with >3.5-fold increased mortality risk.
- Among the classic risk factors, body mass index explained the largest proportion of AF risk.
- Sex interactions were seen for risk associations of body mass index 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 body mass index and total cholesterol need to be evaluated for their relevance in sex-specific prevention strategies.

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 as 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, eg, stroke risk is higher in women with AF.[9] Consistently reported risk factors for AF such as obesity, arterial hypertension, blood lipid profile, diabetes mellitus, 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, classic 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 before study inclusion. The cohorts were based on representative population samples with baseline examinations between 1982 and 2010. Individuals with self-reported and physician-diagnosed history of AF/atrial flutter and prior *International Classification of Diseases, 10th Revision* coding for AF/atrial flutter and AF/atrial flutter on the baseline ECG were defined as having prevalent AF and excluded from all analyses (N=687). Details on the enrollment and follow-up procedures of each study are provided in the online-only Data Supplement. 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 mellitus, antihypertensive 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 World Health Organization average volume drinking categories.[16] Because abstainers could not be separated from the average drinking category I, we merged these 2 categories. The diagnosis of AF was based on study ECG tracings, questionnaire information, and national hospital discharge registry data, including data on ambulatory visits to specialized hospitals. In addition, causes of death registry data were screened for incident AF as a comorbidity of individuals who died of other causes. Mortality data were derived from central death registries. The last follow-up was between 2010 and 2011 in the various cohorts.

### Biomarker Measurement

Biomarker measurements from stored blood samples were available for some of the cohorts (Table I in the

online-only Data Supplement). In N=37 902 individuals, CRP was determined by latex immunoassay CRP16 (Abbott, Architect c8000), with intra assay and interassay coefficients of variation of 0.93 and 0.83.[17] In N=29 038 participants, Nt-proBNP was measured on the ELECSYS 2010 platform using an electrochemiluminescence immunoassay (Roche Diagnostics). The analytic range is given as 5 to 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.

## Statistical Analysis

Continuous variables were presented as median (25th, 75th 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.[18] 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 mellitus, systolic blood pressure, and antihypertensive medication were used as time-fixed covariates, because they are available only 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.[19]

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 mellitus, daily smoking, and antihypertensive medication was fitted. Finally, 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 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$^2$, ≥30 kg/m$^2$), systolic blood pressure (<120 mm Hg, 120 to <140 mm Hg, 140 to <160 mm Hg, ≥160 mm Hg), and total cholesterol (cutoff 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 to 19.99 g alcohol daily, for men 0 to 39.99 g; category II: for women 20 to 39.99 g, for men 40 to 59.99 g; and 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 modeling protocols.

All statistical methods were implemented in R statistical software version 3.3.3.[20] A more detailed description of the statistical methods is provided in the online-only Data Supplement.

# RESULTS

Our study sample had an overall median age of 49.6 years; age range, 24.1 to 97.6 years at baseline; and 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 in men. Women smoked less, consumed lower amounts of alcohol, and had low-

**Table 1. Baseline Characteristics of the Sample by Sex**

| Variable | Women N=41 226 | Men N=38 567 | *P* Value |
|---|---|---|---|
| Age at examination, y | 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, mm Hg | 130 (118, 147) | 136 (125, 150) | <0.001 |
| Diabetes mellitus, n (%) | 1818 (4.4) | 2075 (5.4) | <0.001 |
| Daily smoking, n (%) | 8527 (20.8) | 10947 (28.6) | <0.001 |
| Antihypertensive medication, n (%) | 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, n (%)* | 37886 (94.7) | 32827 (88.1) | <0.001 |
| Average drinking category II, n (%)* | 1781 (4.5) | 2791 (7.5) | <0.001 |
| Average drinking category III, n (%)* | 342 (0.9) | 1663 (4.5) | <0.001 |
| History of stroke, n (%) | 445 (1.1) | 668 (1.7) | <0.001 |
| History of myocardial infarction, n (%) | 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 (25th, 75th percentile), binary variables as absolute and relative frequencies. The *P* value given is for the Mann-Whitney test or the $\chi^2$ test. N incident atrial fibrillation: all=4261 (5.3%), women=1796 (4.4%), men=2465 (6.4%). BMI indicates body mass index; and Nt-proBNP, N-terminal pro B-type natriuretic peptide.

*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; and category III, for women ≥40 g/day, for men ≥60 g/day.

er levels of diabetes mellitus 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 Table I in the online-only Data Supplement.

Over a median follow-up of 12.4 years (range, 0–29 years), fewer incident AF cases occurred in women, N=1796 (4.4%), than in men, N=2465 (6.4%; *P*<0.001) (for follow-up information by cohort see Table II in the online-only Data Supplement). Cumulative incidence curves with death as a competing risk are shown in Figure 1 and Figure I in the online-only Data Supplement (and by cohort in Figure II in the online-only Data Supplement). The curves differed by sex. After the age of 50 years, AF incidence in men increased steeply, whereas 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 years.

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

Multivariable-adjusted hazard ratios (HRs) for AF by sex and the respective interaction *P* values are shown in Table 2. All cardiovascular risk factors (with the exception of diabetes mellitus), 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 SD increase, 1.31; 95% confidence interval [CI], 1.25–1.38) in comparison with women (HR, 1.18; 95% CI, 1.12–1.23), with a relative risk ratio of 0.89 (95% CI, 0.84–0.96). Total cholesterol was inversely associated with incident AF with a stronger risk reduction in women (HR, 0.86; 95% CI, 0.81–0.90 versus 0.92; 95% CI, 0.88–0.97 in men), relative risk ratio 0.93 (95% CI, 0.87–0.99). The association persisted after accounting for cholesterol-lowering medication in an exploratory analysis (Table III in the online-only Data Supplement). Age-adjusted Cox regression models are provided in Table IV in the online-only Data Supplement. 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 than in women. The interaction did not reach statistical significance. Height revealed a stronger association with AF in women than in men (interaction *P* value of <0.001) (Table V in the online-only Data Supplement).

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, 5.4–12.0) in comparison with men (PAR, 3.8%; 95% CI, 0.2–7.3). 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, 4.2–8.2) in comparison with women (PAR, 3.0%; 95% CI, 1.5–4.5). 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 mellitus, 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.

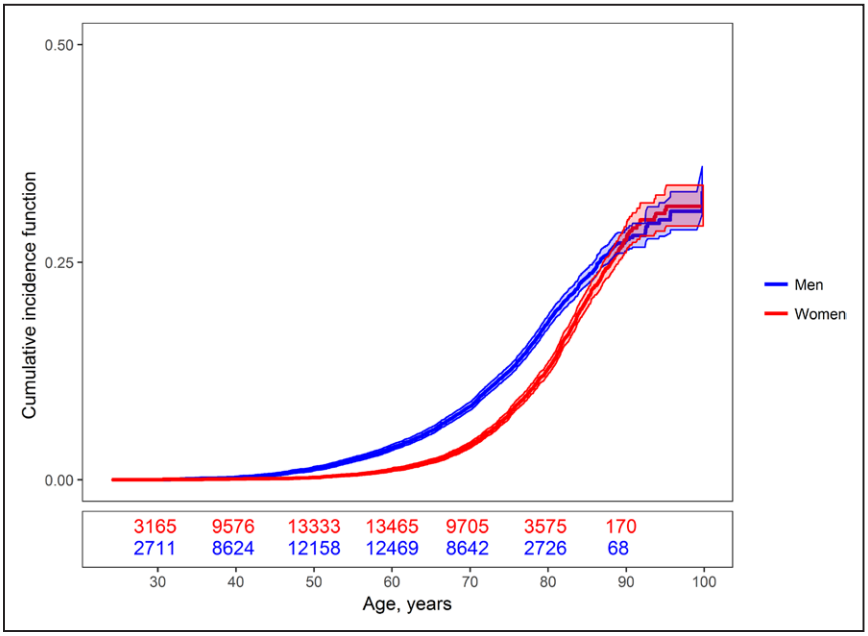


**Figure 1. Cumulative incidence curves and 95% confidence intervals for atrial fibrillation in women and men with death as a competing risk are shown.** The numbers of individuals at risk are provided under the figure. Testing for the equality of the cumulative incidence curves produces a *P* value of <0.001.

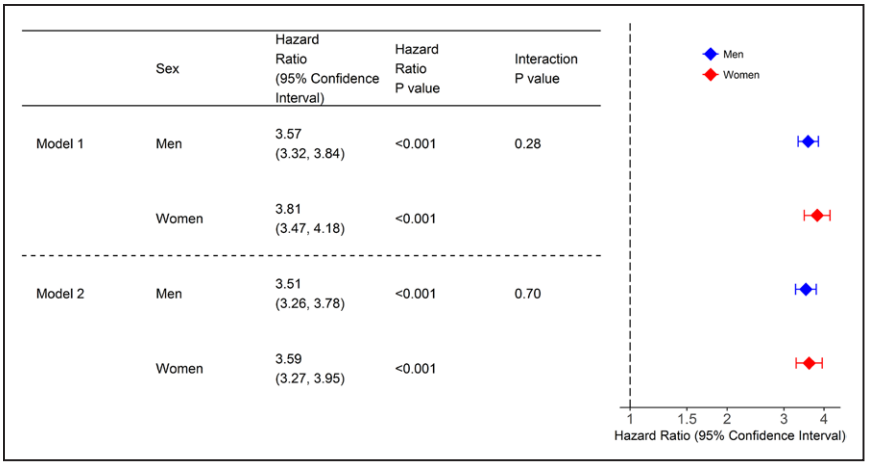


**Figure 2. Cox regression analyses for all-cause mortality with atrial fibrillation as time-dependent covariate, model 1.**
Model 2 is additionally adjusted for body mass index, systolic blood pressure, diabetes mellitus, daily smoking, antihypertensive medication, and total cholesterol. The *x* axis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

## 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 >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.[7,21,22] 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 years. Overall, one-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.[6,22–24] With a broader age range, our data estimate the risk to be even higher. The risk of mortality related to AF onset as described earlier[8,25] remains high. In both women and men, AF was associated with >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.[7,26,27] Prior studies have found sex differences in the association of obesity with long-term incidence of AF. Although no statistically significant interactions were reached in the Framingham Heart Study, the effect estimates showed a higher magnitude of association in men.[28] In the Danish Diet, Cancer, and Health Study, obese women had a 2-fold higher risk of AF than men (HR of 2.35 in multivariable-adjusted analyses).[29] An Australian study in >4000 individuals reported a possible sex interaction of BMI with incident AF.[30] 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.[31]

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.[32] This may be linked to a greater susceptibility to the arrhythmia through larger cardiac dimensions and higher excitability of the conduction system.[33,34] 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-up[35,36] and the close correlation of weight and weight fluctuations with AF patterns suggest a possible direct relationship with AF.[37] Evidence suggests that the effects of obesity on cardiac structural remodeling and function differ by sex,[38–40] which increases the predisposition to AF. Irrespective of the underlying mechanisms, BMI is a modifiable risk factor in AF.[37,41] Its PAR has significantly increased[5] and has been reported to account for up to 18% of risk for incident AF in women.[35] In our current sample, the attributable risk was similar, ≈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.[42] The counterintuitive inverse association of total cholesterol and other proatherogenic lipoproteins has been reported previously.[43,44] This observation has been explained by the membrane-stabilizing characteristics of cholesterol, although the exact pathophysiology remains unclear. It is important to note that this inverse association was observed in




*Circulation.* 2017;136:1588–1597. DOI: 10.1161/CIRCULATIONAHA.117.028981

**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 mellitus | 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 | |

The first 6 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 mellitus, and antihypertensive medication. Biomarker information was available in a subgroup only (Table I in the online-only Data Supplement).

Hazard ratios for continuous variables are for 1 SD increase: body mass index, 4.67 kg/m$^2$; 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. SDs were computed using all observations regardless of sex.

C-reactive protein, Nt-proBNP, and alcohol consumption were log-transformed. Because alcohol consumption can equal zero, 1 was added before applying the transformation. Nt-proBNP indicates N-terminal pro B-type natriuretic peptide.

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 nonsignificant 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.[45,46] 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 mellitus and smoking in relation to coronary heart disease and stroke, with a higher relative risk of developing disease in women.[47–49] In contrast to coronary heart disease and stroke, diabetes mellitus 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.[47,48] 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.[50,51] Our study indicates that previous myocardial infarction and stroke are associated with a similar risk of developing AF in women and men and are therefore comparable risk indicators in both sexes.

## Limitations and Strengths

Our data are restricted to epidemiological observations that cannot reveal potential mechanisms explaining the

**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 ≥30 kg/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 mellitus | 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 mellitus, 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 indicates population-attributable risk.

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.[52,53] In addition, biomarker information was available in only a subgroup of the study sample. The relating results are hypothesis generating and must thus 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. Although 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 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.

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## ACKNOWLEDGMENTS

We thank the participants and the staff of the cohorts for their continuing dedication and efforts.

## SOURCES OF FUNDING

The BiomarCaRE Project is funded by the European Union Seventh Framework Programme (FP7/2007–2013) under grant agreement no. HEALTH-F2-2011 to 278913. The activities of the MORGAM Data Center have been sustained by recent funding from European Union FP 7 project CHANCES (HEALTH-F3-2010–242244). A part of the biomarker determinations in the population cohorts was funded by the Medical Research Council London (G0601463, identification no. 80983: Biomarkers in the MORGAM Populations). The FINRISK surveys were mainly funded by budgetary funds of the National Institute for Health and Welfare, Finland (THL). Additional funding has been obtained from numerous nonprofit foundations. Dr Salomaa (principle investigator) has been supported by the Finnish Foundation for Cardiovascular Research and the Academy of Finland (grant no. 139635). The DanMONICA cohorts at the Research Center for Prevention and Health were established over a period of 10 years and have been funded by numerous sources that have been acknowledged, where appropriate, in the original articles. The Moli-sani was partially supported by research grants from Pfizer Foundation (Rome, Italy), the Italian Ministry of University and Research (MIUR, Rome, Italy)–Programma Triennale di Ricerca, Decreto n.1588 and Instrumentation Laboratory (Milan, Italy). The Northern Sweden MONICA project was supported by Norrbotten and Västerbotten County Councils. Dr Söderberg has been supported by the Swedish Heart–Lung Foundation (grant nos. 20140799, 20120631, 20100635), the County Council of Västerbotten (ALF, VLL-548791), and Umeå University. This project has received funding from the European Research Council under the European Union's Horizon 2020 research and innovation program (grant agreement no. 648131), German Ministry of Research and Education (BMBF 01ZX1408A), and German Research Foundation Emmy Noether Program (SCHN 1149/3-1) (to Dr Schnabel). Additional funding was provided to Dr Schnabel (81Z1710103) and Dr Zeller (81Z1710101) by the German Center for Cardiovascular Research (DZHK).

## DISCLOSURES

None.

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## FOOTNOTES

Received April 18, 2017; accepted August 10, 2017.

The online-only Data Supplement is available with this article at http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIRCULATIONAHA.117.028981/-/DC1.

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