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CLINICAL RESEARCH

Sex-Specific Epidemiology of Heart Failure Risk and Mortality in Europe

Results From the BiomarCaRE Consortium

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ABSTRACT

OBJECTIVES This study investigates differences between women and men in heart failure (HF) risk and mortality.

BACKGROUND Sex differences in HF epidemiology are insufficiently understood.

METHODS In 78,657 individuals (median 49.5 years of age; age range 24.1 to 98.7 years; 51.7% women) from community-based European studies (FINRISK, DanMONICA, Moli-sani, Northern Sweden) of the BiomarCaRE (Biomarker for Cardiovascular Risk Assessment in Europe) consortium, the association between incident HF and mortality, the relationship of cardiovascular risk factors, prevalent cardiovascular diseases, biomarkers (C-reactive protein [CRP]; N-terminal pro-B-type natriuretic peptide [NT-proBNP]) with incident HF, and their attributable risks were tested in women vs. men.

RESULTS Over a median follow-up of 12.7 years, fewer HF cases were observed in women (n = 2,399 [5.9%]) than in men (n = 2,771 [7.3%]). HF incidence increased markedly after 60 years of age, initially with a more rapid increase in men, whereas incidence in women exceeded that of men after 85 years of age. HF onset substantially increased mortality risk in both sexes. Multivariable-adjusted Cox models showed the following sex differences for the association with incident HF: systolic blood pressure hazard ratio (HR) according to SD in women of 1.09 (95% confidence interval [CI]: 1.05 to 1.14) versus HR of 1.19 (95% CI: 1.14 to 1.24) in men; heart rate HR of 0.98 (95% CI: 0.93 to 1.03) in women versus HR of 1.09 (95% CI: 1.04 to 1.13) in men; CRP HR of 1.10 (95% CI: 1.00 to 1.20) in women versus HR of 1.32 (95% CI: 1.24 to 1.41) in men; and NT-proBNP HR of 1.54 (95% CI: 1.37 to 1.74) in women versus HR of 1.89 (95% CI: 1.75 to 2.05) in men. Population-attributable risk of all risk factors combined was 59.0% in women and 62.9% in men.

CONCLUSIONS Women had a lower risk for HF than men. Sex differences were seen for systolic blood pressure, heart rate, CRP, and NT-proBNP, with a lower HF risk in women. (J Am Coll Cardiol HF 2019;7:204–13)

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Heart failure (HF) is a growing epidemic worldwide, associated with significant morbidity, mortality, and health care costs in both sexes (1). To improve HF prevention, the epidemiology and risk factors of HF need to be understood, and differences between sexes require consideration.

Women and men differ in disease distribution, risk factors, and outcome of HF. The sex-specific incidence of HF varies according to study population characteristics (2,3). HF hospitalizations are more frequent in men than in women (4). Women are hospitalized in more advanced states of HF than men (5). There are a number of established risk factors that significantly contribute to the population burden of HF; among them, the distribution of arterial hypertension, obesity, blood lipids, diabetes, smoking, alcohol consumption, and prevalent cardiovascular diseases have been shown to differ by sex (6–8). In addition, circulating biomarker concentrations related to the disease typically differ by sex (e.g., high-sensitivity C-reactive protein [CRP] and N-terminal pro-B-type natriuretic peptide [NT-proBNP]) (9,10). The relevance of these known sex differences in circulating biomarkers for the association with incident HF remains unknown.

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HF prognosis is poor in both sexes (11). Despite advances in therapy and management, the present number of deaths attributed to HF was approximately as high in 2013 as it was in 1995 (12). Evidence suggests that death rates for HF are higher for men than for women (12).

In the BiomarCaRE (Biomarker for Cardiovascular Risk Assessment in Europe) consortium, we systematically examined the sex-specific epidemiology of HF incidence, the role of classic cardiovascular risk factors and circulating biomarkers and their population-attributable risks (PARs). The risk of mortality after new onset HF according to sex was determined.

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

BMI = body mass index

CRP = C-reactive protein

HF = heart failure

NT-proBNP = N-terminal pro-B-type natriuretic peptide

PAR = population-attributable risk

RRR = relative risk ratio

METHODS

STUDY SAMPLE. Our prospective cohort study used a subcohort of the BiomarCaRE consortium, which harmonizes risk factors, biomarker measurements, and endpoints from European community-based cohorts (13). Data for HF status at baseline and follow-up were available in 78,657 individuals from 4 cohorts: DanMONICA, FINRISK, Moli-sani, and Northern Sweden (baseline examinations between 1982 and 2010). Participants with self-reported and/or physician-diagnosed history of HF and/or prior International Classification of Diseases-10th Revision (ICD-10) codes for HF at baseline were excluded from analyses (n = 1,582). Details for enrollment and follow-up procedures for each study separately are provided in the Online Methods. Local ethics committees approved all participating studies.

RISK FACTORS AND FOLLOW-UP. Risk factor information was collected at baseline visits. Variables, including body mass index (BMI), systolic blood pressure, and total cholesterol, were measured locally by routine methods according to the World Health Organization MONICA (Multinational MONItoring of trends and determinants in CArdiovascular disease) protocol. Information on smoking was obtained from patient self-reports and collected locally in the study

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centers. Diabetes, antihypertensive medication, history of stroke, and myocardial infarction were centrally harmonized in the MORGAM (MONICA Risk, Genetics, Archiving and Monograph) project (14). Average alcohol consumption was assessed in grams per day and classified according to World Health Organization average volume drinking categories. As "abstainers" could not be separated from "average drinking category I," we merged these 2 categories.

HF diagnosis was based on questionnaire information and national hospital discharge registry data, including data on ambulatory visits to specialized hospitals. In addition, cause of death registry data were screened for incident HF as a comorbidity of individuals who died from other causes. Mortality data were derived from central death registries. The survey period from baseline examination to follow-up was between 1982 and 2010 for all cohorts. The last follow-up was performed between 2010 and 2011 in the different cohorts (detailed information by study cohort is provided in the Online Methods).

BIOMARKER MEASUREMENT. Biomarker measurements from stored blood samples were available for most of the cohorts (Online Table 1). CRP was determined by latex immunoassay (Architect c8000, Abbott Labs, Rockville, Maryland), with intra-assay and interassay coefficients of variation of 0.93 and 0.83, respectively (15), and available in 37,644 individuals. NT-proBNP concentrations were measured by the Elecsys 2010 immunoassay analyzer (Roche Diagnostics, Mannheim, Germany) using an electrochemiluminescence immunoassay (Eclia, Roche Diagnostics). Information on NT-proBNP was available in 30,443 individuals. The given analytical range is 5 to 35,000 ng/l. Intra-assay and interassay coefficients of variation were 2.58 and 1.38, respectively.

STATISTICAL ANALYSIS. Missing data were handled by available case analyses (e.g., for each computation, only those without missing values on the variables involved in that particular analyses were used). Continuous variables are presented as median (25th, 75th percentile) and binary variables as absolute and relative frequencies. Prevalent HF cases were excluded from all analyses (n = 1,582) (Online Table 9). Survival analyses used the "time-to-HF diagnosis." The Aalen-Johansen estimator was used in computing cumulative incidence curves for HF and death before HF as competing risks. Cumulative incidence curves were also computed for HF and myocardial infarction as competing risks. To examine the association between incident HF and all-cause mortality, a sex- and cohort-stratified Cox regression for all-cause mortality with HF, atrial fibrillation (AF), and cardiovascular disease during follow-up as time-dependent covariates was computed. A second model that also included BMI, systolic blood pressure, antihypertensive medication, total cholesterol, diabetes, and daily smoking was computed; these variables were used as time-fixed covariates as they were available only at baseline. For all these covariates and HF, AF, and cardiovascular disease, 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.

Sex- and cohort-stratified Cox regressions were performed to examine the associations of HF risk factors with incident HF in women and men. Cubic splines were used to explore the linearity of the association of continuous variables with time-to-HF. First, for each risk factor, a Cox model was computed. Then, a model including simultaneously BMI, systolic blood pressure, antihypertensive medication, total cholesterol, diabetes, and daily smoking (and estimated glomerular filtration rate [eGFR] in a refining analysis) was fitted. Each of the variables: heart rate, alcohol consumption, history of myocardial infarction, history of stroke, CRP, and NT-proBNP were added in turn to this last model, which we called the base model. For all covariates, a sex interaction was included in each model. Whenever a model included systolic blood pressure, antihypertensive medication was also part of the model. In a refining analysis, for each covariate in the base model, an interaction with age categories was included to obtain sex- and age-specific hazard ratio(s) (HR) for each covariate of interest. To the base model we further added NT-proBNP and AF during follow-up together with sex interaction terms. In the data used for this last model, there were 84 individuals with HF and AF diagnosed at the same time during follow-up. For these observations, the onset of AF was treated as occurring shortly before HF. Relative risk ratios for the women-to-men ratio of HR and PARs for incident HF were calculated. The proportional hazard assumption was examined graphically and by using formal tests, using the methods described by Grambsch et al. (16). No major deviations from this assumption were observed.

For the PAR calculations, categorization of the continuous variables BMI (<25 kg/m^2, 25 to <30 kg/m^2, and ≥30 kg/m^2), systolic blood pressure (<120 mm Hg, 120 to <140 mm Hg, 140 to <160 mm Hg, and ≥160 mm Hg), and total cholesterol (cutoff value of 200 mg/dl = 5.17 mmol/l) were performed. The p values were not corrected for multiple testing and are provided for descriptive purposes (17).

R version 3.4.1 software (R Foundation for Statistical Computing, Vienna, Austria) was used to perform all statistical analyses. A more detailed description of the statistical methods is provided in Online Methods.

RESULTS

BASELINE CHARACTERISTICS. At baseline, our study sample were 49.4 median years of age with a range of 24.1 to 98.7 years of age. A total of 40,656 participants (51.7%) were women. Median age for women was similar to that for men (49.0 vs. 49.9 years, respectively). Baseline characteristics of the study sample by sex are shown in **Table 1**. Overall, women had a more preferable cardiovascular risk factor profile than men, with a lower BMI, lower systolic blood pressure, lower total cholesterol, and a lower prevalence of diabetes, cigarette abuse, and daily alcohol consumption. Heart rate was higher in women than in men. Women were less likely to have a history of prevalent cardiovascular disease (including stroke and myocardial infarction) than men. CRP concentration did not differ by sex. NT-proBNP levels were higher in women than in men.

Study characteristics by cohort are shown in Online Table 1a. Missing value information of baseline characteristics according to cohort (Online Table 1b) and sex (Online Table 1c), and regarding missingness of NT-proBNP (Online Table 1d) and CRP (Online Table 1e), are also shown in the Online Methods version of this paper.

HF INCIDENCE AND MORTALITY BY SEX. Over a median follow-up of 12.7 years (range 0 to 29 years), less incident HF cases were observed in women (2,399 [5.9%] events) than in men (2,771 [7.3%] events; for follow-up information by cohort please see Online Table 2). Cumulative incidence curves for HF and death before HF as a competing risk are shown in **Figure 1** (cumulative incidence curves for HF by cohort are shown in Online Figures 1a and 1b for HF and myocardial infarction). HF incidence was low in both sexes before the age of 60 years. After 60 years, HF incidence increased markedly, initially with a more rapid increase in men. More men died before they could develop HF (**Figure 1**, solid lines). At 85 years of age, cumulative incidence curves crossed with those of women, who then exceeded men in HF incidence (**Figure 1**, dashed lines). Lifetime risk was approximately 38% in both sexes at 90 years of age (Online Table 3).

In both age-adjusted and risk factor-adjusted models, incident HF resulted in a more than 5-fold increase in the risk of death in both sexes, while men were even at higher risk than women (**Figure 2**).

TABLE 1 Baseline Characteristics of the Study Sample by Sex

	Women (n = 40,656)	Men (n = 38,001)
Age at examination, yrs	49.0 (39.4, 58.9)	49.9 (39.8, 59.9)
Body mass index, kg/m^2	25.6 (22.8, 29.4)	26.7 (24.3, 29.4)
Systolic blood pressure, mm Hg	130 (118, 146)	136 (125, 150)
Antihypertensive medication, %	6,474 (16.7)	5,989 (16.5)
Total cholesterol, mmol/l	5.6 (4.89, 6.4)	5.61 (4.9, 6.4)
Diabetes, %	1,682 (4.1)	1,955 (5.2)
Daily smoking, %	8,460 (21)	10,752 (28.6)
Average daily alcohol consumption, g	1 (0, 6)	9 (1, 23)
Average drinking category I, %	37,332 (94.6)	32,294 (87.9)
Average drinking category II, %	1,777 (4.5)	2,789 (7.6)
Average drinking category III, %	342 (0.9)	1,655 (4.5)
Heart rate, beats/min	69 (63, 76)	66 (60, 74)
History of myocardial infarction, %	393 (1)	1,313 (3.5)
History of stroke, %	404 (1)	610 (1.6)
C-reactive protein, mg/l	1.4 (0.6, 3.2)	1.4 (0.7, 2.9)
NT-proBNP, ng/ml	58 (33, 99)	32 (15, 69)
eGFR, ml/min per 1.73 m^2	93.1 (79.3, 105.8)	93.6 (80.6, 105.6)

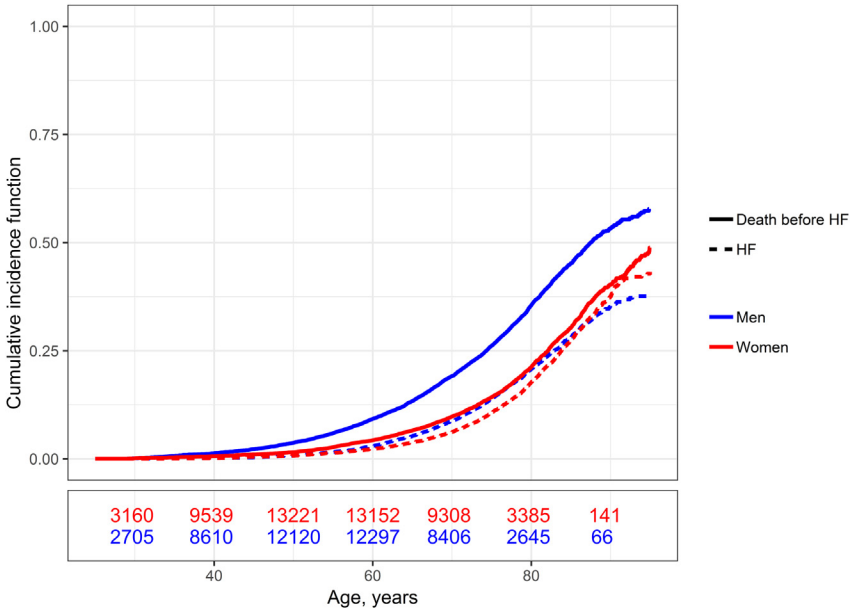
Continuous variables are presented as median (25th, 75th percentile) and binary variables as absolute and relative frequencies. N incident HF: all = 5,170 (6.6%); women = 2,399 (5.9%); men = 2,771 (7.3%). Average drinking categories are based on pure alcohol intake. Category I for women = 0 to 19.99 g/day; 0 to 39.99 g/day for men. Category II for women = 20 to 39.99 g/day; 40 to 59.99 g/day for men. Category III for women ≥40 g/day; ≥60 g/day for men. C-reactive protein was available in a subgroup of 37,644 individuals; NT-proBNP in 30,443 individuals. eGFR was only available in 37,602 individuals.

eGFR = estimated glomerular filtration rate; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

SEX INTERACTIONS IN HF RISK FACTORS. Multivariable-adjusted HRs for HF by sex and the respective interaction p values are shown in **Table 2**. Except for total cholesterol in men, where no association with HF could be shown, all classic cardiovascular risk factors, a history of myocardial infarction and stroke, and the biomarkers CRP and NT-proBNP were associated with new onset HF in women and men. We observed significant sex interactions in the association of systolic blood pressure, heart rate, CRP, and NT-proBNP with incident HF with a lower magnitude of association in women than in men (**Table 2**).

Results for multivariable-adjusted Cox regression models after exclusion of individuals with prevalent cardiovascular disease are shown in Online Table 4. Results did not change markedly. Age-adjusted Cox regression models are shown in Online Table 5. Examination of the results by survey decade revealed no relevant differences in the associations between cardiovascular risk factors and incident HF (Online Table 6a). An age interaction was seen for the association of systolic blood pressure and incident HF in individuals between 45 and 54 years of age with a higher risk in men (Online Table 6b). After we included eGFR in the base model, the sex

FIGURE 1 Cumulative Incidence Curves for Incident HF and Death Without HF



Cumulative incidence curves are shown for HF and death without HF in women and men. Incident HF and death were treated as competing risks. The numbers of individuals at risk are provided below the x-axis. Only curves until 95 years of age are shown. HF = heart failure.

interactions of systolic blood pressure and heart rate with incident HF were no longer statistically significant (Online Table 7). There was no interaction according to NT-proBNP level in the association of BMI and incident HF (Online Table 8). Combining NT-proBNP and AF during follow-up in 1 equation, we did not see a statistically significant sex interaction (interaction p value = 0.53; analysis not shown).

POPULATION-ATTRIBUTABLE RISKS BY RISK FACTORS AND SEX. PARs for 5-year HF incidence resulting from the classic risk factors are presented in **Figure 3**. PARs, additionally including heart rate, are shown in Online Figure 2. The overall PAR of all risk factors combined (BMI, systolic blood pressure, total cholesterol, daily smoking, diabetes, history of myocardial infarction, and stroke) was 59.0% for women and 62.9% for men. Highest PARs were seen for obesity and systolic blood pressure in both sexes with highest attributable risk for obese women and hypertensive men.

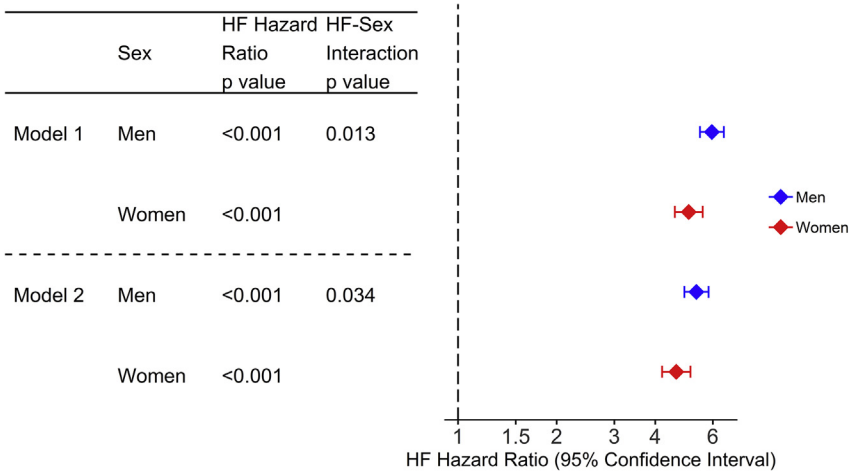
The main results are summarized in **Figure 4**.

DISCUSSION

Across 4 European community cohorts, women had a lower risk for incident HF than men in middle-aged to older individuals, whereas women exceeded men in HF risk in the oldest age groups. Lifetime risk was up to 38% when individuals reached 90 years of age. Incident HF resulted in a more than 5-fold increased risk of mortality in both sexes, while men were even at higher risk than women. Among clinical variables, increased systolic blood pressure, heart rate, CRP, and NT-proBNP carried a lower risk of HF in women than in men. PARs from classic risk factors were largely comparable in both sexes with highest attributable risk for obese women and hypertensive men.

HF is an age-dependent disease, showing a clear sex-specific incidence. Consistent with prior reports (18,19), overall HF incidence was lower in women than in men. Although men developed HF earlier than women in middle-aged to older age groups, women revealed a higher HF incidence in the oldest group. Death was a stronger competing risk in men. Our data confirm similar trends observed in U.S. cohorts (20). HF-related mortality is still high despite public health strategies to reduce risk factor levels (11). Although there is evidence of lower mortality rates in women at a 3-year follow-up (10), we found no differences in mortality risk by sexes during our long follow-up. Because women develop HF later than men, the initial survival benefit for women seems to be

FIGURE 2 Cox Regression Analyses for All-Cause Mortality



Cox regression analyses are shown for all-cause mortality with heart failure, atrial fibrillation, and cardiovascular disease during follow-up as time-dependent covariates, model 1 (age-adjusted). Model 2 is additionally adjusted for body mass index, systolic blood pressure, diabetes, daily smoking, antihypertensive medication, and total cholesterol. The x-axis is shown on a log scale. Continuous variables were modeled using quadratic terms, with the exception of age which was used as the time scale. Available men n = 36,247; available women n = 38,880. HF = heart failure.

diminished in the long-term. In our study, incident HF was associated with a more than 5-fold increased mortality risk in both sexes and calls for improved therapies and management.

Elevated BMI and obesity are among the most relevant HF risk factors (21). These factors are also related to other risk factors such as arterial hypertension or cardiovascular diseases, which themselves carry a high risk for new onset HF. In line with other studies (22,23), we could confirm a strong relationship between BMI and incident HF with no significant sex interaction. Of all the risk factors examined, obesity showed the highest 5-year PARs for new onset HF, with obese women being at highest risk. BMI is a modifiable risk factor, and HF prevention strategies should focus on weight loss with a BMI target of <25 kg/m^2. At the population level, weight control in women may have higher prognostic relevance due to the PAR of more than 30% compared to 22% in men.

Arterial hypertension plays a major role in the development of HF and carries a high risk for related cardiovascular events (24). The Framingham Heart Study showed a doubling of HF risk in individuals with blood pressure >160/90 mm Hg compared to those with blood pressure <140/90 mm Hg (3). Evidence from the Framingham cohort and the Cardiovascular Health Study showed that the association of systolic blood pressure with incident HF was stronger in women than in men (6,25). In contrast, we found a higher HF risk in men with elevated blood pressure accounting for antihypertensive medication. Interestingly, the association between blood pressure and incident HF may be even stronger in middle-aged men. It is known that men have a higher risk of hypertension-related cardiac diseases such as myocardial infarction and AF (26). Because HF often develops as a consequence of these diseases, the observed higher HF risk in men may be related to elevated blood pressure. However, as antihypertensive therapy leads to a significant reduction in cardiovascular events and deaths (27), all individuals at risk should receive targeted blood pressure control to prevent HF and its sequelae.

Elevated resting heart rate is a known predictor of cardiovascular risk (28). Increased heart rate independently predicts HF (29), HF hospitalizations and cardiovascular mortality (30). Our female study population had a higher median heart rate at baseline, as seen in prior data (31), but increased heart rate was more hazardous for men with no significant association in women. These results are consistent with prior studies that showed a steeper risk gradient for all-cause mortality in men (32). In most studies, the association between heart rate and cardiovascular outcomes was stronger in men or even confined to men (33,34). Using a large community-based study sample, increased heart rate was associated with

TABLE 2 Multivariable-Adjusted Hazard Ratios for Incident Heart Failure by Sex and Interaction p Values for Heart Failure Risk Factors in the Overall Sample

	Interaction p Value	Sex	Hazard Ratio (95% CI)	p Value	Women:Men Relative Risk Ratio (95% CI)	n Available
Body mass index, kg/m^2	0.79	Women	1.43 (1.38–1.48)	<0.001	0.99 (0.94–1.05)	38,197
		Men	1.44 (1.38–1.50)	<0.001		35,606
Systolic blood pressure, mm Hg	**0.004**	Women	1.09 (1.05–1.14)	<0.001	0.92 (0.86–0.97)	38,197
		Men	1.19 (1.14–1.24)	<0.001		35,606
Antihypertensive medication	0.89	Women	1.49 (1.34–1.64)	<0.001	1.01 (0.88–1.16)	38,197
		Men	1.47 (1.33–1.61)	<0.001		35,606
Total cholesterol, mmol/l	0.22	Women	0.95 (0.91–0.99)	0.027	0.96 (0.91–1.02)	38,197
		Men	0.99 (0.95–1.03)	0.60		35,606
Diabetes	0.23	Women	1.87 (1.63–2.15)	<0.001	0.89 (0.74–1.07)	38,197
		Men	2.09 (1.85–2.36)	<0.001		35,606
Daily smoking	0.70	Women	1.98 (1.77–2.23)	<0.001	1.03 (0.89–1.19)	38,197
		Men	1.93 (1.77–2.10)	<0.001		35,606
Alcohol consumption	0.11	Women	0.95 (0.89–1.02)	0.13	0.94 (0.87–1.01)	37,168
		Men	1.01 (0.97–1.06)	0.52		34,607
Heart rate	**<0.001**	Women	0.98 (0.93–1.03)	0.36	0.90 (0.84–0.96)	29,430
		Men	1.09 (1.04–1.13)	<0.001		26,974
History of myocardial infarction	0.08	Women	1.86 (1.50–2.31)	<0.001	0.80 (0.63–1.03)	38,159
		Men	2.32 (2.05–2.63)	<0.001		35,554
History of stroke	0.73	Women	1.39 (1.07–1.81)	0.013	0.94 (0.67–1.32)	38,168
		Men	1.48 (1.20–1.83)	<0.001		35,582
C-reactive protein, mg/l	**0.002**	Women	1.10 (1.00–1.20)	0.043	0.83 (0.75–0.93)	18,935
		Men	1.31 (1.23–1.41)	<0.001		17,568
NT-proBNP, ng/ml	**0.006**	Women	1.54 (1.37–1.74)	<0.001	0.83 (0.73–0.95)	15,465
		Men	1.89 (1.75–2.05)	<0.001		14,098

The first 6 variables (body mass index, systolic blood pressure, antihypertensive medication, total cholesterol, diabetes, and daily smoking) represent our base model; the other variables were separately added on top of the base model. All models included the first 6 variables. Biomarker information was available in a subgroup only (Online Table 1a). Hazard ratios for continuous variables are for 1 SD increase: body mass index = 4.65 kg/m^2; systolic blood pressure = 21 mm Hg; total cholesterol = 1.17 mmol/l; heart rate = 12 beats/min; log(C-reactive protein, mg/l) = 1.1, log(NT-proBNP ng/ml) = 0.98; transformed alcohol consumption = 1.36. Interaction p values in **bold** indicate significance. 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.

CI = confidence interval; NT-proBNP = N-terminal pro B-type natriuretic peptide.

incident HF in initially healthy men. Different mechanisms that may explain the sex-specific association between heart rate with cardiovascular disease have been proposed including increased heart rate as a sign of sympathetic overactivity in men and its adverse effects on the development of metabolic syndrome and insulin resistance (31).

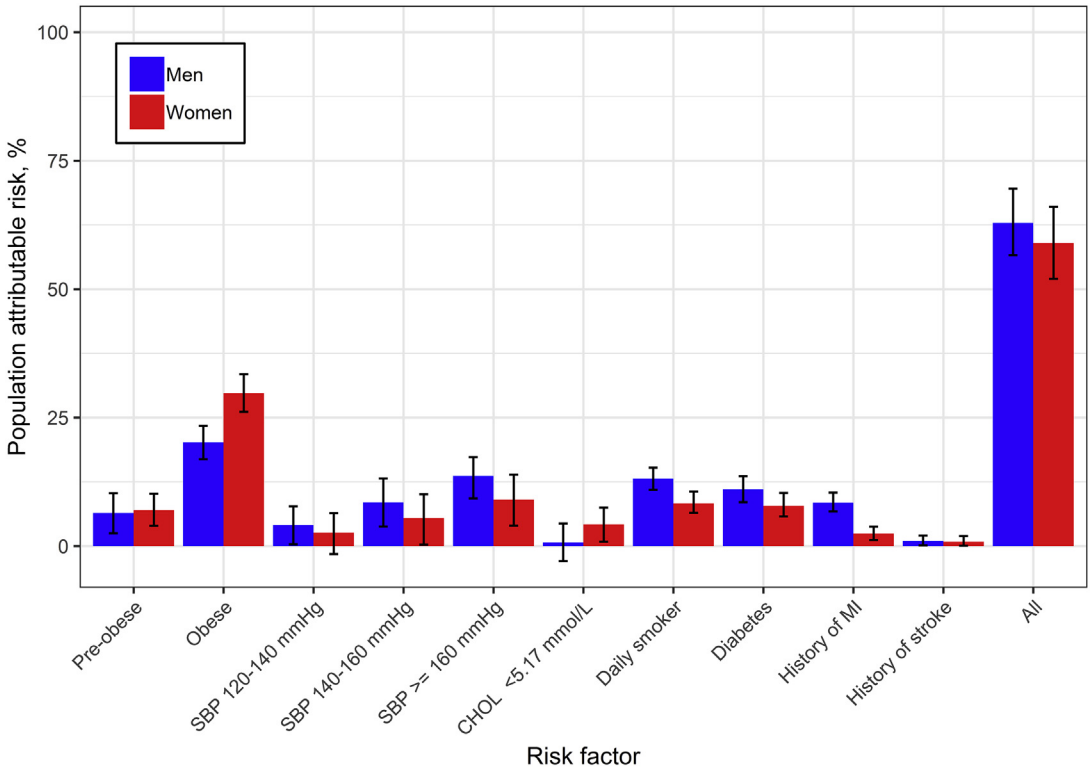
Use of biomarkers has increased our understanding of the pathophysiology of HF. Increased levels of inflammatory biomarkers have consistently been related to increased HF risk (35) and mortality (36). In the MESA (Multi-Ethnic Study of Atherosclerosis) study, high CRP levels were related to progressive deterioration of myocardial function regardless of age and sex (37). The role of inflammation for the development of coronary artery disease, which often precedes HF, is well known (38). Most of the common cardiovascular risk factors that were more prevalent in men in the current study are related to increased inflammatory activity mirrored by elevated CRP levels (39). We and others (40) found a strong association of CRP and HF risk in men that may be an expression of a higher proinflammatory state in men than in women.

Prior studies demonstrated that NT-proBNP provides an incremental prognostic value for incident HF beyond the classic risk factors (10). NT-proBNP levels in our cohort were higher in women than in men. Female sex has been described as a strong predictor of elevated natriuretic peptides (9). In relation to incident HF, NT-proBNP was a stronger predictor of risk in men than in women. Elevated NT-proBNP levels have shown a stronger association with incident HF with reduced ejection fraction (41), which is more common in men (42). This fact may explain the stronger association observed in men in our study population.

STUDY LIMITATIONS. Due to the epidemiologic nature of our data, pathophysiological mechanisms of the observed sex interactions cannot be fully explained.

Besides ICD-based HF ascertainment in all cohorts, HF diagnosis was additionally accepted through self-reporting in FINRISK and Moli-sani. We cannot

FIGURE 3 Population-Attributable Risks for 5-Year Incidence of Heart Failure



The n events/n total used in the computation of the models were 2,496/34,547 (men) and 2,158/37,112 (women). Confidence intervals were computed using the bootstrap method (with 500 iterations). Regression models used in the estimation of the PARs include all the risk factors shown above and antihypertensive medication. CHOL = total cholesterol; MI = myocardial infarction; SBP = systolic blood pressure.

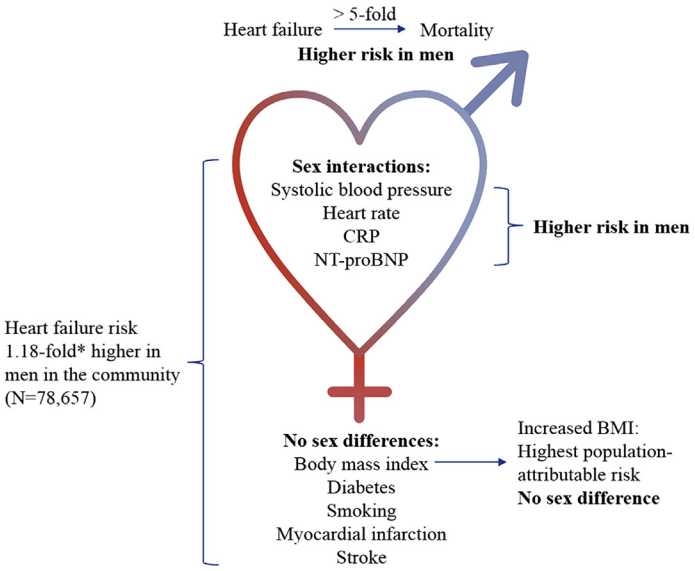
provide information for HF subtypes (HF with preserved and reduced ejection fraction), as this depth of phenotypic classification was not collected consistently in the BiomarCaRE cohorts. Because HF with preserved ejection fraction often remains undetected, particularly in the outpatient sector (43), we assume a predominance of HF with reduced ejection fraction, which may have led to an underdiagnosis of HF in women. Overall, the specificity of HF data in the cohorts has been shown to be good with limitations in sensitivity (44), with a possible bias towards more severe HF cases. Because prevalent HF cases were removed before computing incidences, the incidences may be slightly underestimated. We are unable to relate prevalent AF to HF risk, as this variable is not reliable enough to be used in the current analyses. Additionally, information about prevalent chronic obstructive pulmonary disease was not available as a harmonized variable.

Information about biomarkers and heart rate was available only in a subcohort of the study sample. However, the number of individuals with biomarker measurements was still large enough to provide reliable estimates. As usual in community-based studies, residual confounding cannot be excluded and is very likely.

The cohorts were formed by the respondents of surveys based on random population samples. Possible selective survey nonparticipation, particularly if different for women and men, might have biased the results.

Some of the baseline data are several decades old, which permitted us to examine long-term incidence of the lifetime disease HF up to oldest age groups. Risk factor information was available at baseline only. However, we could demonstrate that classic risk factor associations by sex are strong and similar across cohorts, whether in older samples or cohorts with more recent enrollment or whether from northern or southern Europe. Because we present data from northern and southern Europe, our study includes mainly Caucasian participants. That limits, at least in

FIGURE 4 Heart Failure Incidence, Risk Factors, and Mortality in the Community



*The relative incidence is derived from the weighted integrated ratio of the cumulative incidence curves in men compared to those in women between 35 and 95 years of age. BMI = body mass index; CRP = C-reactive protein; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

part, the generalizability (45) of our findings to other racial or ethnic groups.

Strengths of the study are the large size of the community-based cohorts using harmonized risk factors and endpoints with sufficient power to examine sex interactions.

CONCLUSIONS

Our data provide evidence showing that part of the sex differences in HF incidence may be explained by sex-specific distribution and association of classic risk factors. Importantly, a large proportion of HF risk can be attributed to classic cardiovascular risk factors, with overweight and obesity highlighted as key factors on HF incidence in both sexes. Our population-based data indicate that weight control should be equally recommended to overweight and obese women and men. We found significant sex differences in the association of systolic blood pressure, heart rate, and the biomarkers CRP and NT-proBNP, with a higher risk of HF in men than in women. Whether sex-specific blood pressure and heart rate targets or biomarker-guided therapy regimens can reduce HF incidence and mortality needs further investigation. The pathophysiology accounting for our observations requires further biological investigation. Considering the epidemic dimension of HF in aging populations, understanding sex differences in HF risk is crucial for developing long-term preventive measures to reduce mortality, public health burden, and health care costs related to HF in both, women and men.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In European community cohorts, overall HF risk was lower in women than in men, whereas women's risk exceeded that of men in the oldest age groups. Incident HF posed a more than 5-fold increased risk of mortality in both sexes. Sex interactions were seen for systolic blood pressure, heart rate, C-reactive protein, and N-terminal pro-B-type natriuretic peptide, with a lower risk for HF in women. Among the classic risk factors, obesity explained the largest proportion of attributable risk in both sexes.

TRANSLATIONAL OUTLOOK: HF occurs frequently and has a high mortality risk. At the community level, modification of risk factors such as weight seems to be crucial for women and men, although smoking cessation and strict blood pressure control may be even more important for men than for women. Sex differences observed among classic risk factors and biomarkers must be evaluated for their pathophysiological mechanisms and sex-specific prevention strategies.

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KEY WORDS biomarkers, cohort, epidemiology, heart failure, mortality, sex

APPENDIX For an expanded Methods section as well as supplemental tables and figures, please see the online version of this paper.