# Sex differences in heart failure

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# Chapter 3

**Sex differences in new-onset heart failure.**

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## Abstract

### Background

Sex differences in patients with established heart failure have been well described, but much less is known in the development of heart failure.

### Methods

We studied sex-specific incidence and risk of new-onset heart failure in 8592 subjects (mean age 49.2 ± 12.7 years; 50.1 % women) of the Prevention of REnal and Vascular ENdstage Disease (PREVEND) study and distinguished reduced and preserved ejection fraction (HFrEF <40 % and HFpEF >50 %).

### Results

Of 374 cases with incident heart failure, 241 (64.4 %) occurred in men and 133 (35.6 %) in women (median follow-up 12.5 years; 96,550 person-years). Men developed heart failure earlier (7.0 vs. 8.6 years; $P < 0.001$). Incidence rates per 1,000 person-years in women compared to men were lower for HFrEF (1.2 vs. 3.0 %; $P < 0.001$), but higher for HFpEF (1.2 vs. 0.7 %; $P < 0.001$). Women developed HFpEF later in life than HFrEF (75.1 vs. 69.7 years; $P = 0.033$), while men showed no significant difference (72.2 vs. 69.5 years; $P = 0.116$). Multivariable competing risks analyses showed that women had lower risk for HFrEF (subhazard ratio = 0.47; 95 % CI 0.29–0.76, $P = 0.002$) but higher risk for HFpEF (subhazard ratio = 2.16; 95 % CI 1.21–3.83, $P = 0.009$) than men. Among all risk factors, only atrial fibrillation had a sex-specific predictive value and increased risk specifically for women (P-for interaction = 0.016).

### Conclusions

In a middle-aged population, men developed heart failure more frequently and at a younger age than women. However, women had higher risk for HFpEF, with atrial fibrillation being a specific female risk factor.

## Introduction

Sex differences in patients with established heart failure have been well described. Women with heart failure are typically older, have a higher body mass index and left ventricular ejection fraction, show a higher prevalence of hypertension and diabetes, but have lower mortality, independently of differences in clinical characteristics.[1,2] In patients with established heart failure, there are fundamental sex differences related to heart failure etiology and cardiac remodeling, which translate into differences in the prevalence of heart failure with preserved or reduced ejection fraction (HFrEF or HFpEF, respectively).[3] In most cross-sectional studies, HFrEF is more common in men while HFpEF more frequently affects women,[4] but the results are biased by sex differences in life expectancy. However, sex differences in the development of heart failure have been less well described. Clinical predictors of new-onset heart failure were studied in the Framingham Heart Study.[5] Male sex was an independent risk factor for the development for HFrEF, but this study was not specifically designed to evaluate sex differences in the onset of heart failure. The specific role of sex in the development of HFpEF is less clear and the knowledge about sex differences in risk factors for incident HFrEF and HFpEF in the general population is limited. The aim of this study was to analyze sex differences related to the new-onset of heart failure.

## Materials and methods

*Study design and population*

The Prevention of REnal and Vascular ENdstage Disease (PREVEND) cohort was used for the current study, the design and main results of which have been published previously.[6,7] Briefly, PREVEND is a prospective, observational cohort study including 8,592 subjects (baseline mean age 49.2 ± 12.7 years; range 28–75 years) from the general population, which primarily addresses the impact of albuminuria on future cardiovascular and renal disease (http://www.prevend.org). A total

of 85,421 residents of the city of Groningen, The Netherlands, were approached between 1997 and 1998 and asked to provide a first morning urine sample and complete a short questionnaire on demographics and cardiovascular disease history. In total, 40,856 subjects (47.8 %) responded; 30,890 subjects with urinary albumin excretion (UAE) ≥10 mg/L and 9,966 subjects with UAE <10 mg/L. Subjects with insulin-dependent diabetes mellitus, pregnancy and inability or unwillingness to participate were excluded. In total, 6,000 subjects with a morning UAE ≥10 mg/L and 2,592 randomly chosen subjects with a UAE <10 mg/L were eligible and completed the screening assessments. These 8,592 subjects comprise the study cohort, with available information on cardiovascular and renal risk factors, anthropometrics and blood and urine samples. The study was approved by the Ethics Committee and complies with the Declaration of Helsinki guidelines. Written informed consent was obtained from all patients.

*Follow-up and definitions*

Follow-up ranged from the baseline visit to occurrence of heart failure, up to December 31, 2010. Study participants were censored on the dates of either moving away to an unknown location or last study visit, whichever occurred first. Date and cause of death were retrieved from Statistics Netherlands, applying the 10th revision of the International Classification of Diseases (ICD-10) diagnostic codes. For the current analyses 23 patients with previous heart failure were excluded, leaving 8,569 subjects for the analysis of new-onset heart failure. The procedure of identification and adjudication of heart failure in PREVEND have previously been published.[8] In brief, clinical records of all subjects were analyzed retrospectively spanning over baseline and follow-up. They were screened for documented signs, symptoms, and objective evidence of heart failure applying the European Society of Cardiology diagnostic criteria for chronic heart failure.[9] An endpoint adjudication committee independently evaluated all suspicious 586 cases (case by case validation based on anonymized clinical charts, hospitalization-, and physician office records) and determined 374

subjects with 'definite new-onset heart failure'. For these subjects heart failure was further categorized based on left ventricular ejection fraction and diastolic dysfunction, as either HFrEF (LVEF <40 %) or HFpEF (LVEF >50 %), respectively, based on the clinically documented echocardiographic data at the time of diagnosis. Of the 374 subjects diagnosed with heart failure, those with LVEF of 41–49 % (n = 8) were excluded to ensure a clear distinction between both entities, as previously described. Atrial fibrillation was diagnosed if either atrial fibrillation or atrial flutter was present on a standard 12-lead electrocardiogram (ECG) obtained and stored digitally at the screening visit.[10] All ECGs were manually pre-evaluated by two independent investigators, and suspected cases identified by one or both investigators were independently manually verified and adjudicated by two cardiologists. Systolic blood pressure (SBP) was defined as the mean of the last two measurements of both baseline visits, measured using an automatic Dinamap XL Model 9300 series device. The glomerular filtration rate (eGFR) was estimated using the simplified modification of diet in renal disease formula.[11] Body mass index (BMI) was defined as body weight divided by height squared (kg/m2). History of myocardial infarction was defined as a self-reported condition, requiring hospitalization for at least 3 days. Type 2 diabetes was defined as fasting plasma glucose >7.0 mmol/L (126 mg/dL), nonfasting plasma glucose >11.1 mmol/L, or use of anti-diabetic drugs. Smoking was defined as current nicotine use or smoking cessation for <1 year. Total cholesterol to high-density lipoprotein cholesterol (TC/HDL-C) ratio was defined as ratio between those parameters. Left ventricular hypertrophy was defined based on the presence of high-amplitude R waves combined with indicators of repolarization abnormalities (Minnesota Codes[12] 3.1, 3.3 and 4.1–4.3 or 5.1–5.3) and left bundle branch block was defined as QRS duration >120 ms, on standard 12-lead ECGs. Alcohol consumption was defined as any self-reported alcohol intake. Antihypertensive therapy was defined based on self-reported use of drugs with Anatomical Therapeutic Chemical (ATC) Classification System codes C02, C03, C07, C08, C09. Urinary albumin excretion was defined as the average urinary albumin concentration measured in two consecutive 24-h urine collections.

Menstruation status and the history of hypertension and/or diabetes during pregnancy were retrieved from a standardized questionnaire at baseline.

*Statistical analyses*

By design, subjects with increased urinary albumin excretion (≥0.10 mg/L) are overrepresented in the PREVEND cohort, compared to a random sample from the general population. Statistical weighting was used to adjust for this overrepresentation, allowing estimates to be made for the general population.[13] Baseline PREVEND study sample data and inferential descriptive statistics for both sexes on the general population level are provided for the development of heart failure and mortality.[14] We analyzed the incidence rates and cumulative incidence of overall heart failure by sex and additionally assessed disparities between HFrEF and HFpEF. Differences in incidence rates and cumulative incidence were tested, using the method proposed by Pepe and Mori[15] for the latter. Competing risks regression analyses using the Fine and Grey method were performed to assess the sex-specific probability for either heart failure sub-entity in relation to pre-established explanatory variables, accounting for incident non-heart failure-related death and the respective other type of heart failure, whichever occurred first.[16] Age was used as the time scale for analyses.[17] We assessed the proportionality of hazard assumption for each covariate by plotting the scaled Schoenfeld residuals against log time. In sensitivity analyses, we allowed each covariate to have time-dependent effects by testing the influence of the respective interaction terms with log time on the sex difference between HFrEF and HFpEF, to rule out the influence of time-varying effects. The explanatory multivariate models consisted of the following pre-established risk factors for heart failure: sex, body mass index, systolic blood pressure, estimated glomerular filtration rate, atrial fibrillation, diabetes, history of myocardial infarction, smoking, total cholesterol to high-density lipoprotein cholesterol ratio, left ventricular hypertrophy, alcohol consumption, left bundle branch block, antihypertensive therapy, urinary albumin excretion, accounting for the effect of age by modeling on the age scale.

Covariates were tested for their interaction with sex in the multivariable models. Statistical analyses were performed using STATA (version 11.0, STATA Corp, College Station, TX, USA). Two-sided P values <0.05 were considered statistically significant.

## Results

*Epidemiological characteristics*

In total, of 374 subjects, who developed new-onset heart failure during median follow-up of 12.5 (12.2–12.9) years (96,550 person-years), 241 (64.4 %) were men and 133 (35.6 %) were women. Baseline differences in new-onset heart failure between women and men are presented in Table 1 and data stratified by HFrEF and HFpEF for both sexes are shown in Table 2; corresponding epidemiological heart failure characteristics are presented in Table 3.

**Table 1**

Baseline differences between women and men with and without general new-onset heart failure

| | Men | | Women | | HF |
|---|---|---|---|---|---|
| | No HF | New-onset HF | No HF | New-onset HF | ♂ vs. ♀ *P* value |
| *n* | 4,028 | 241 | 4,167 | 133 | |
| Clinical characteristics | | | | | |
| Age (years) | 49.6 ± 12.8 | 62.2 ± 9.5 | 47.6 ± 12.1 | 62.1 ± 9.8 | 0.964 |
| Caucasians | 95 | 97 | 96 | 98 | 0.297 |
| Body mass index (kg/m$^2$) | 26.2 ± 3.6 | 28.0 ± 3.9 | 25.8 ± 4.7 | 29.0 ± 5.6 | 0.022 |
| Systolic blood pressure (mmHg) | 133.1 ± 18.1 | 146.4 ± 21.0 | 123.7 ± 20.3 | 146.9 ± 25.9 | 0.818 |
| LBBB, QRS duration >120 ms | 8 | 21 | 2 | 8 | 0.002 |
| Left ventricular hypertrophy | 3 | 5 | 2 | 4 | 0.588 |
| Atrial fibrillation | 1 | 6 | 0.3 | 6 | 0.936 |
| Diabetes mellitus | 5 | 12 | 4 | 15 | 0.468 |
| Myocardial infarction | 6 | 31 | 4 | 16 | 0.002 |
| Renal impairment (KDOQI stage ≤3) | 4 | 10 | 7 | 18 | 0.026 |
| Hypercholesterolaemia | 27 | 44 | 25 | 53 | 0.076 |
| Smoking or quit <1 year | 38 | 38 | 38 | 38 | 0.931 |
| Alcohol consumption | 83 | 77 | 67 | 51 | <0.001 |
| Antihypertensive medication | 13 | 42 | 12 | 45 | 0.302 |

Data are presented as percentages (%) unless otherwise indicated HF heart failure, ♂ men, ♀ women, LBBB left bundle branch block, KDOQI Kidney Disease Outcomes Quality Initiative

**Table 2**

Baseline differences between women and men with and without new-onset HFrEF and HFpEF

| | Men | | | Women | | | HFrEF | HFpEF |
|---|---|---|---|---|---|---|---|---|
| | No HF | HFrEF | HFpEF | No HF | HFrEF | HFpEF | ♂ vs. ♀ P value | ♂ vs. ♀ *P* value |
| *n* | 4,032 | 177 | 60 | 4,171 | 64 | 65 | | |
| Clinical characteristics | | | | | | | | |
| Age (years) | 49.7 ± 12.8 | 62.2 ± 9.6 | 62.1 ± 9.5 | 47.6 ± 12.1 | 60.7 ± 11.2 | 63.4 ± 8.0 | 0.306 | 0.422 |
| Caucasians (%) | 95 | 97 | 95 | 96 | 98 | 100 | 0.579 | 0.068 |
| Body mass index (kg/m$^2$) | 26.2 ± 3.6 | 27.9 ± 3.7 | 27.8 ± 4.2 | 25.8 ± 4.7 | 28.1 ± 5.2 | 29.9 ± 5.9 | 0.790 | 0.028 |
| Systolic blood pressure (mmHg) | 133.1 ± 18.1 | 145.6 ± 21.2 | 147.9 ± 20.6 | 123.7 ± 20.3 | 145.6 ± 23.2 | 150.2 ± 28.4 | 0.635 | 0.618 |
| LBBB, QRS duration >120 ms (%) | 8 | 24 | 10 | 2 | 14 | 3 | 0.088 | 0.114 |
| Left ventricular hypertrophy (%) | 3 | 6 | 2 | 2 | 5 | 3 | 0.654 | 0.607 |
| Atrial fibrillation (%) | 1 | 7 | 5 | 0.3 | 6 | 6 | 0.884 | 0.779 |
| Diabetes mellitus (%) | 5 | 9 | 18 | 4 | 21 | 8 | 0.019 | 0.081 |
| Myocardial infarction (%) | 6 | 32 | 27 | 4 | 21 | 13 | 0.097 | 0.041 |
| Renal impairment (KDOQI stage ≤3) (%) | 4 | 9 | 12 | 7 | 22 | 14 | 0.007 | 0.742 |
| Hypercholesterolaemia (%) | 27 | 46 | 36 | 25 | 56 | 48 | 0.177 | 0.173 |
| Smoking or quit <1 year (%) | 38 | 43 | 27 | 38 | 46 | 31 | 0.639 | 0.613 |
| Alcohol consumption (%) | 83 | 75 | 81 | 67 | 48 | 55 | <0.001 | 0.002 |
| Antihypertensive medication (%) | 16 | 43 | 54 | 14 | 55 | 50 | 0.137 | 0.635 |

Data are presented as percentages (%) unless otherwise indicated.
*HF* heart failure, *HFrEF* heart failure with reduced ejection fraction, *HFpEF* heart failure with preserved ejection fraction, ♂ men, ♀ women, *LBBB* left bundle branch block, *KDOQI* Kidney Disease Outcomes Quality Initiative.

**Table 3**

Epidemiological characteristics of incident heart failure

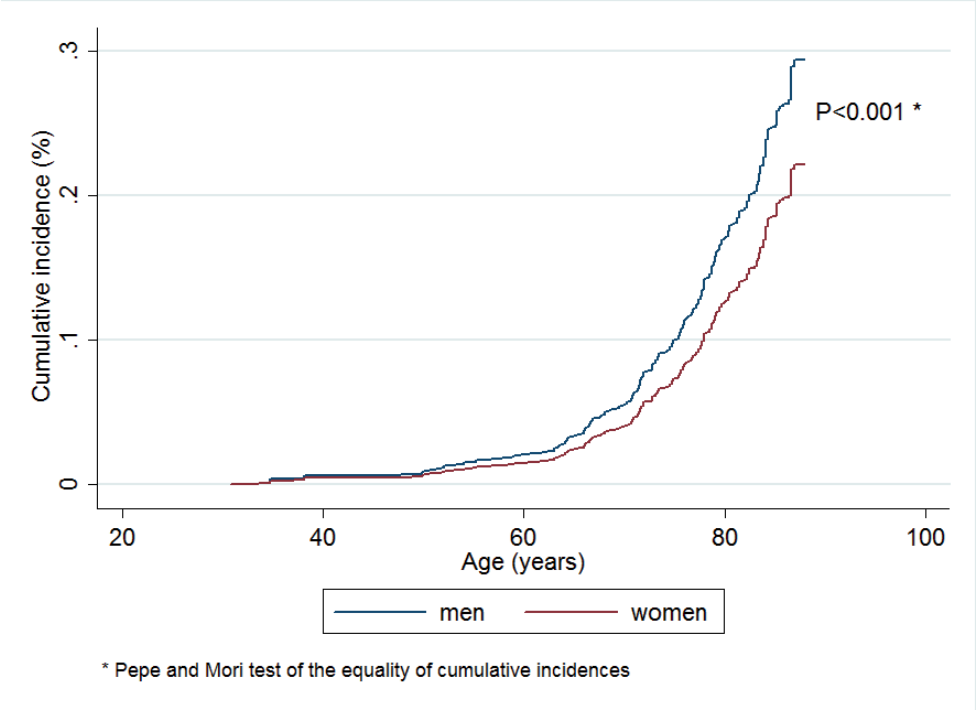
| Variable | Men | Women | *P* value |
|---|---|---|---|
| Events, *n* (%) | | | |
| Overall HF | 241 (5.6) | 133 (3.1) | <0.001 |
| HFrEF | 177 (4.1) | 64 (1.5) | <0.001 |
| HFpEF | 60 (1.4) | 65 (1.5) | 0.682 |
| Incidence rates per 1,000 person-years [95 % CI][a] | | | |
| Overall HF | 3.7 [3.1–4.5] | 2.4 [1.9–3.1] | <0.001 |
| HFrEF | 3.0 [2.4–3.7] | 1.2 [0.8–1.7] | <0.001 |
| HFpEF | 0.7 [0.5–1.1] | 1.2 [0.8–1.7] | <0.001 |
| Time to new-onset, years (IQR) | | | |
| Overall HF | 7.0 (3.6–10.5) | 8.6 (5.5–10.5) | <0.001 |
| HFrEF | 6.3 (3.3–10.1) | 7.4 (4.0–9.7) | <0.001 |
| HFpEF | 9.0 (4.5–11.1) | 9.2 (7.5–10.9) | 0.934 |
| Age at the time of diagnosis, years (IQR) | | | |
| Overall HF | 71.3 (64.9–76.3) | 72.7 (64.4–77.9) | <0.001 |
| HFrEF | 70.9 (64.4–76.0) | 69.6 (61.1–76.1) | <0.001 |
| HFpEF | 72.8 (66.0–77.4) | 74.4 (66.5–78.8) | 0.272 |

*HF* heart failure, *HFrEF* heart failure with reduced ejection fraction, *HFpEF* heart failure with preserved ejection fraction, *n* number, *CI* confidence interval, *IQR* interquartile range.
[a] Accounting for the urinary albumin excretion strata sampling weights

Overall, heart failure developed earlier in men compared to women, and men were younger at the time of diagnosis (Fig. 1).

**Figure 1**

Cumulative incidence of general new-onset heart failure in both sexes

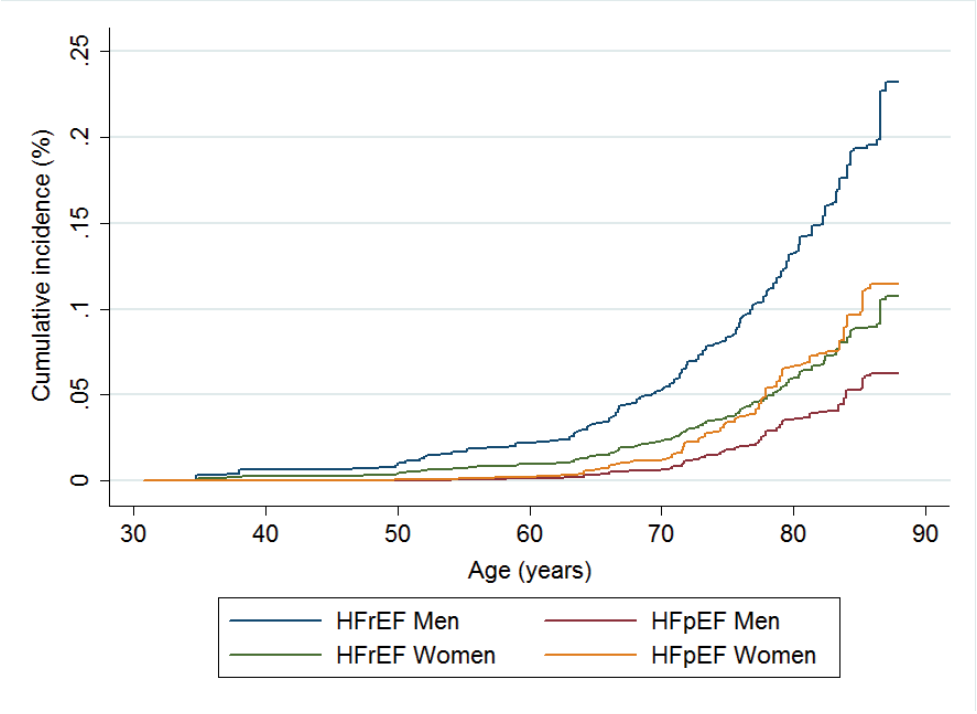



Analyses of HFrEF and HFpEF showed that among women, HFrEF and HFpEF occurred in similar proportions, while men more often showed HFrEF compared to HFpEF. The time to diagnosis of HFrEF was significantly longer in women compared to men, whereas no significant difference was detected for HFpEF. However, women developed HFpEF significantly later in life than HFrEF (P = 0.033), while no age difference was detectable for men (P = 0.116). In women, the inferred incidence

rates per 1,000 person-years were significantly lower for HFrEF (P < 0.001), but significantly higher for HFpEF (P < 0.001) compared to men, respectively. Likewise, women had a significantly lower cumulative incidence of HFrEF (P = 0.037) but no significant sex difference in the cumulative incidence of HFpEF was detectable (P = 0.318) (Fig. 2).

**Figure 2**

Cumulative incidence of HFrEF and HFpEF in both sexes.

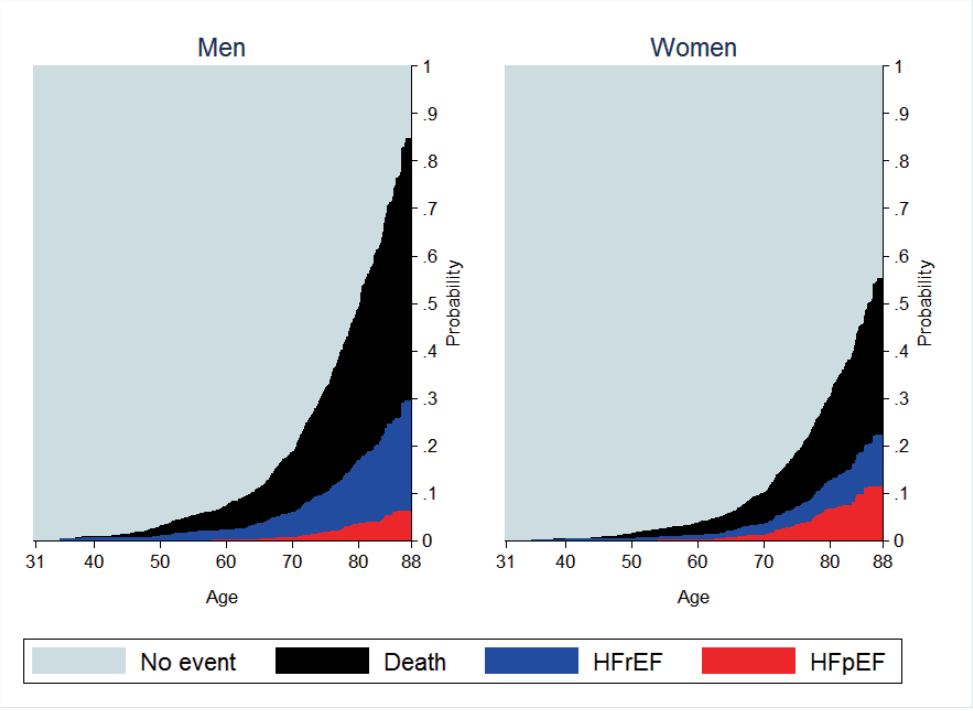



*HFPEF* heart failure with preserved ejection fraction, *HFREF* heart failure with reduced ejection fraction

The probabilities of both heart failure entities along with the competing risk of preceding death are shown in Fig. 3.

**Figure 3**

Stacked cumulative incidents of competing events by sex.

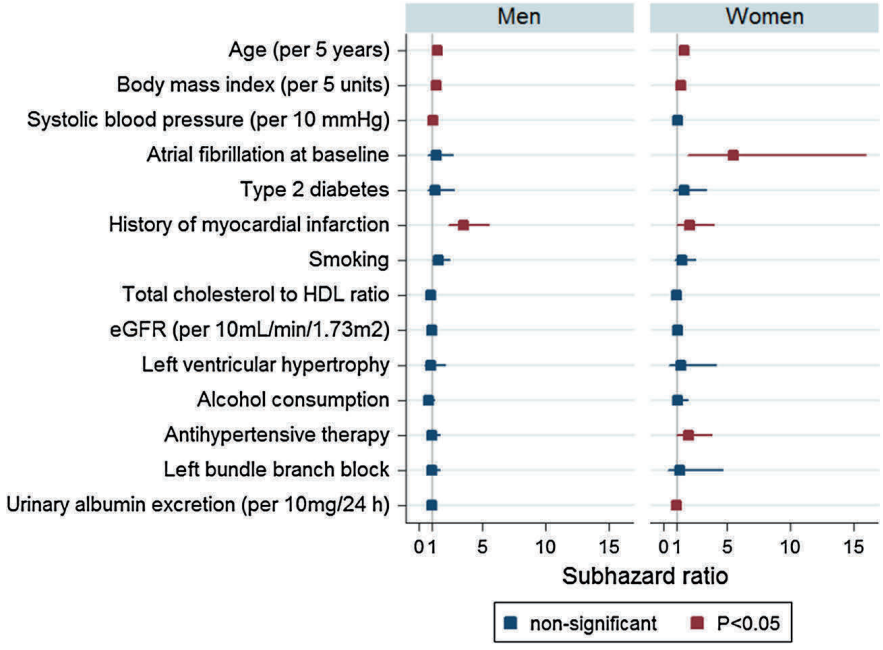



*HFPEF* heart failure with preserved ejection fraction, *HFREF* heart failure with reduced ejection fraction

Sex-specific associations of established risk factors with general new-onset heart failure and new-onset HFrEF and HFpEF  The explanatory multivariate risk factor-adjusted model revealed different independent associations of risk factors for new-onset heart failure in men and women (Fig. 4).

**Figure 4**

Multivariable association of individual predictors with overall heart failure by sex




In men, age, body mass index, systolic blood pressure and history of myocardial infarction were significant predictors of new-onset heart failure; in women, age, body mass index, atrial fibrillation, history of myocardial infarction, antihypertensive therapy and urinary albumin excretion were significantly related to new-onset heart failure, respectively.

Stratified multivariate analyses of both heart failure sub-entities revealed that female sex was less associated with new-onset HFrEF (subhazard ratio = 0.47; 95 % CI 0.29–0.76, P = 0.002), but independently related to new-onset HFpEF (subhazard ratio = 2.16; 95 % CI 1.21–3.83, P = 0.009) when accounting for the competing risks of developing the other type of heart failure and all-cause mortality. The explanatory model for HFrEF revealed that age, history of myocardial infarction,

history of smoking, systolic blood pressure and BMI were significantly related to the development of HFrEF, while age, urinary albumin excretion, atrial fibrillation, BMI, and left bundle branch block were significantly related to the development of HFpEF. Interaction analysis of these conventional risk factors revealed only atrial fibrillation as a risk marker for the development of HFpEF in women, but not in men (P-for interaction = 0.016), while the other risk factors did not show differential associations with sex for the development of HFrEF.

*Menopause- and pregnancy-related risk factors in women*

Postmenopausal status and hypertension during pregnancy had univariate association with overall incident heart failure, while parity, and diabetes during pregnancy were not significantly related to the development of heart failure in women (Table 4). After multivariate adjustment only postmenopausal status was significantly associated with the incidence of overall heart failure in women.

**Table 4**

Women-specific risk factors for the incidence of heart failure

| Women | HFrEF | HFpEF | Overall HF | Association with HF | |
|---|---|---|---|---|---|
| | | | | Univariate | Multivariate |
| Menstruation, *n* (%) | | | | <0.001 | <0.001 |
| Yes | 13 (20.6) | 7 (10.8) | 20 (15.2) | | |
| No, since a few months | 1 (1.6) | 2 (3.1) | 3 (2.3) | | |
| No, since 1–2 years | 2 (3.2) | 0 | 2 (1.5) | | |
| No, since 3–5 years | 2 (3.2) | 2 (3.1) | 4 (3.0) | | |
| No, since 6–10 years | 4 (6.4) | 10 (15.4) | 15 (11.4) | | |
| No, for longer than 10 years | 41 (65.1) | 44 (67.7) | 88 (66.7) | | |
| Hypertension during pregnancy, *n* (%) | 28 (44.4) | 36 (56.3) | 65 (50.0) | 0.002 | n.s. |
| Diabetes during pregnancy, *n* (%) | 1 (0.8) | 0 | 1 (0.8) | n.s. | n.s. |

*HF* heart failure, *HFrEF* heart failure with reduced ejection fraction, *HFpEF* heart failure with preserved ejection fraction, n number, *n.s.* non-significant test result

## Discussion

Our results show significant epidemiological differences in the development of heart failure between women and men. In addition to the finding that heart failure develops more often and earlier in men compared to women we were able to demonstrate that sex predisposes differently to HFrEF and HFpEF, independently of conventional cardiovascular risk factors. Women have a higher risk for the development of HFpEF but a lower risk for the development of HFrEF than men. These results point toward an underlying biologic sex difference as an important contributing factor in the pathogenesis of HFrEF and HFpEF. Notably, among all risk factors, only atrial fibrillation had a sex-specific predictive value and increased the risk in women but not in men.

*Development of heart failure in men and women*

Cardiovascular risk is usually more pronounced and has an earlier onset in men compared to women, which is commonly explained by secondary effects of a different dynamic of sex hormones.[18] This leads to higher rates of coronary artery disease, myocardial infarction, higher total incidence of heart failure and earlier and higher mortality in men.[19] However, ischemic heart disease manifests differently in women compared to men.[19] Additionally, women show characteristic cardiovascular risk factors, structural changes and comorbidities, most of which become clinically relevant with advanced age and do not necessarily coincide with impaired LVEF, but more often with diastolic dysfunction.[20–23]

*Sex differences in the risk for HFPEF vs. HFREF*

Various studies have indicated that among patients treated for heart failure a reduced EF is more common in men compared with women, who often have a preserved EF.[24] However, it remains unclear whether sex is involved in the pathogenesis of either disease entity as an independent factor, or whether HFrEF and HFpEF merely reflect a sex-related accumulation of comorbidities and

cardiovascular risk factors. Previous studies had limitations in their ability to assess independent effects of sex on the development of either HFrEF or HFpEF by design and the lack of relevant confounding variables.[25,26] Overall, these studies exhibit substantial heterogeneity of the applied HFrEF and HFpEF criteria, study size, socio-demographic characteristics and methodology. While these population-based data confirm an association between male sex, myocardial infarction and HFrEF, and between female sex, age and HFpEF, the effect of sex on the incidence of heart failure over time is much less clear.

Ho et al.[5] studied predictors of new-onset heart failure in 6,340 subjects (54 % women) in the Framingham Heart Study, focusing on differences between preserved versus reduced ejection fraction. HFrEF and HFpEF were diagnosed in 261 (56 %) and 196 (43 %) subjects, respectively, based on interim panel evaluation of the FHS criteria following initial HF hospitalization. They identified 14 independent predictors, including only male sex. Men had increased risk for incident HFrEF, with previous myocardial infarction being the strongest predictor. HFPEF occurred as frequently in men as in women, and the risk for HFpEF was not different in both sexes. When comparing our results with the Framingham Heart Study data, particular important cohort-specific and methodological differences should be considered. Subjects in the Framingham Heart Study were older, had shorter per-person follow-up and stem from different sub-cohorts spanning several decades. Importantly, valvular heart disease was the strongest predictor for HFpEF in the Framingham Heart Study. In PREVEND, subjects were about 10 years younger on average, had longer per-person follow-up, stem from a single contemporary cohort, but lack baseline information on valvular heart disease. These differences are important, because age and follow-up time strongly affect sex differences in the occurrence of heart failure events of both types; likewise, the difference in calendar periods implies altered underlying preventive measures, etiologic factors and management of relevant comorbidities, all affecting the risk for heart failure. Furthermore, we

accounted for the natural sex difference in mortality with increasing age by considering preceding all-cause mortality a competing risk for developing heart failure.

*Sex differences in cardiovascular risk factors*

Interaction analyses of individual covariates with sex in the fully adjusted multivariable models showed that atrial fibrillation had a different association with the incidence of HFpEF in both sexes; it predicted new-onset HFpEF in women, but not in men. A potential explanation for this sex difference could be that subjects with atrial fibrillation may have a higher underlying burden of diastolic dysfunction and adverse remodeling of the left atrium and ventricle.[27] In women with atrial fibrillation, sex-specific structural and functional characteristics may translate to a higher degree to clinically manifest HFpEF.[28] Women usually show a typical concentric remodeling pattern, compared to the more eccentric remodeling in men.[3] Additionally, aortic stiffness[29] and impairment of cardiovascular coupling[30] are typically more pronounced in women. In atrial fibrillation women normally present with higher heart rates than men,[31] what further limits diastolic filling time and may worsen symptoms in women. Women with atrial fibrillation have been shown to seek medical attention more often than men because of higher symptom intensity.[31]

However, this statistical interaction must be interpreted with caution, due to the chance of having found a spurious interaction. Considering the known pathophysiological differences between both sexes, the clinical relevance of these results currently remains unclear, but justifies further research on this subject.

*Strengths and limitations*

A particular strength of our study is the large, contemporary, community-based cohort with long and mostly complete per-person follow-up and a relatively low mean age. A variety of conventional risk factors were analyzed, allowing comparison with other studies. Additionally, we assessed the risk of

menopause and a history of diabetes and hypertension during previous pregnancies in women. All HFrEF and HFpEF diagnoses were independently adjudicated by an endpoint committee based on the currently recommended ESC criteria,[9] including available echocardiographic data at the time of diagnosis, what provides an up-to-date differentiation between both disease entities. Additionally, two independent cardiologists adjudicated baseline prevalence of atrial fibrillation. Methodological strengths of our study are the competing risk regression methodology, which accounts for the fact that cumulative incidences depend on the competing risks of dying from any cause and developing the respective other heart failure subtype. Limitations include a substantial predominance of Caucasians, which precludes generalizability to other ethnicities, and lack of data on baseline valvular heart disease. Our cohort is enriched for increased urinary albumin excretion and for this reason we corrected for study design using statistical weighting. However, compared with the Framingham Heart Study, urinary albumin excretion was not higher in PREVEND, and the incidence of all-cause mortality and new-onset heart failure is comparable to that in unselected general population studies.

## Conclusions

In a contemporary, middle-aged general population cohort, we showed that men develop heart failure more frequently and at a younger age than women, and that biological sex is independently and differentially associated with new-onset HFrEF and HFpEF. Men show a significantly higher rate and a higher risk of HFrEF, while women tend to have a higher adjusted rate and risk of developing HFpEF. Atrial fibrillation was risk factor for HFpEF in women but not in men.

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