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**ORIGINAL ARTICLE**
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# Sex differences in associations of comorbidities with incident cardiovascular disease: focus on absolute risk

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**Aim** To examine sex differences in associations of obesity, type-2 diabetes, hypertension, and atrial fibrillation (AF) with incident cardiovascular disease (CVD), focusing on absolute risk measures.

**Methods and results** We included a total of 7994 individuals (mean age 49.1 years; 51.2% women) without prior CVD from the PREVEND (Prevention of Renal and Vascular End-stage Disease) cohort with a median follow-up of 12.5 years. Using Poisson regression, we calculated the increase in absolute as well as relative CVD risk associated with a comorbidity using incidence rate differences ($IRD = IR_{comorbidity} - IR_{no\text{-}comorbidity}$) and incidence rate ratios ($IRR = IR_{comorbidity}/IR_{no\text{-}comorbidity}$), respectively. Sex differences were presented as women-to-men differences ($WMD = IRD_{women} - IRD_{men}$) and women-to-men ratios ($WMR = IRR_{women}/IRR_{men}$). Absolute CVD risk was lower in women than in men ($IR_{women}$: 6.73 vs. $IR_{men}$: 14.58 per 1000 person-years). While increase in absolute CVD risk associated with prevalent hypertension was lower in women than in men [WMD: −6.12, 95% confidence interval: (−9.84 to −2.40), $P = 0.001$], increase in absolute CVD risk associated with prevalent obesity [WMD: −4.25 (−9.11 to 0.61), $P = 0.087$], type-2 diabetes [WMD: −1.04 (−14.36 to 12.29), $P = 0.879$] and AF [WMD: 18.39 (−39.65 to 76.43), $P = 0.535$] did not significantly differ between the sexes. Using relative risk measures, prevalent hypertension [WMR: 1.49%, 95% confidence interval: (1.12–1.99), $P = 0.006$], type-2 diabetes [WMR: 1.73 (1.09–2.73), $P = 0.019$], and AF [WMR: 2.53 (1.12–5.70), $P = 0.025$] were all associated with higher CVD risk in women than in men.

**Conclusion** Increase in absolute risk of developing CVD is higher in hypertensive men than in hypertensive women, but no substantial sex-related differences were observed among individuals with obesity, type-2 diabetes and AF. On a relative risk scale, comorbidities, in general, confer a higher CVD risk in women than in men.

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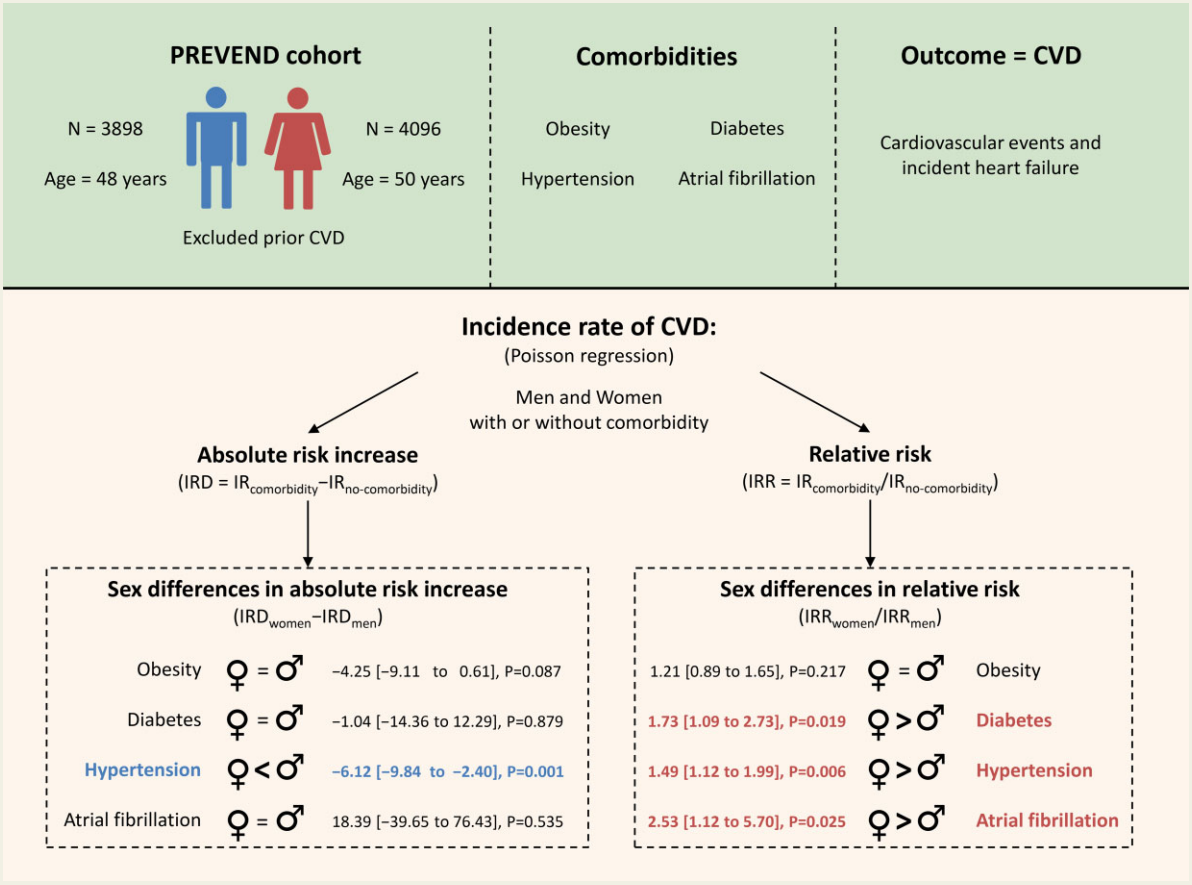
## Graphical Abstract




**Keywords** Incident cardiovascular disease • Comorbidities • Sex-related differences • Absolute risk • Relative risk

# Introduction

Cardiovascular disease (CVD) is the leading cause of death worldwide,[1] and the lifetime risk for CVD with an optimal risk factor profile is around 30–40% at an index age of 55 years.[2] This risk is even higher in individuals with comorbid conditions, such as obesity, diabetes mellitus, hypertension, and atrial fibrillation (AF).[2]

Data suggest that the risk of CVD associated with pre-existing comorbidities may differ among women and men. Specifically, diabetes and AF have been consistently shown to be more strongly associated with incident CVD in women than men.[3,4] On the other hand, obesity and hypertension appear to carry a similar risk of CVD in both sexes.[5,6] Interestingly, such conclusions are often exclusively based on sex-related differences in relative risk without the context of absolute risk.[7–9] Indeed, to effectively design sex-specific health interventions to reduce risk factor burden, it would be important to know the number needed to harm, which is an epidemiological measure derived from absolute risk increase.[10]

Recently, two large studies presented both relative and absolute risk estimates while examining sex-related differences in the association of multiple comorbidities with incident myocardial infarction and stroke. Nevertheless, major conclusions were again drawn based on sex-related differences in relative risk.[11,12] In the current study, we aimed to investigate sex-related differences in associations of obesity, type-2 diabetes, hypertension, and AF with incident CVD among community-dwelling adults, focusing on absolute risk measures.

# Methods

## Study population

The data from the PREVEND (Prevention of Renal and Vascular End-stage Disease) cohort study were used in this study, which has been described previously.[7,13] In short, between 1997 and 1998 residents of the city of Groningen aged 28–75 years old ($N = 85\,421$), were asked to complete a short questionnaire and to send in a morning urine sample. A total of 40 856 individuals responded. All participants with urinary albumin excretion (UAE) >10 mg/L ($N = 7786$) and randomly selected participants with UAE <10 mg/L ($N = 3395$) were

invited to an outpatient clinic. During the visit, anthropometrics were measured, general health was assessed using questionnaires, and blood and urine were sampled. Individuals unwilling to participate, with insulin-dependent diabetes or reported pregnancy were excluded resulting in the baseline PREVEND cohort of 8592 individuals (6000 with UAE >10 mg/L and 2592 with UAE <10 mg/L). From the baseline cohort, individuals with prior CVD ($N = 598$) were excluded, resulting in 7994 individuals for analyses (see Supplementary material online, *Figure S1*). The medical Ethics Committee of the University Medical Center Groningen approved the PREVEND study which was conducted following the principles of the Declaration of Helsinki. Written informed consent was obtained from all subjects.

## Measurements and study definitions

Blood pressure was calculated as mean from two seated measurements using an automatic Dinamap XL Model 9300 series device. Hypertension was defined as systolic blood pressure $\geq$ 140 mmHg, diastolic blood pressure $\geq$ 90 mmHg or the use of antihypertensive medication. Body mass index (BMI) was calculated as weight/height$^2$ (kg/m$^2$), and obesity was defined as BMI $\geq$ 30 kg/m$^2$. Type-2 diabetes was defined as a fasting glucose $\geq$ 7.0 mmol/L (126 mg/dL), a non-fasting glucose $\geq$ 11.1 mmol/L (200 mg/dL) or use of anti-diabetic medication. Smoking was defined as current use of nicotine or stopped smoking within the previous year. Diagnosis of AF was previously described in detail.[14] Briefly, AF was diagnosed if atrial flutter or AF was present on a 12-lead electrocardiogram. Suspected cases were identified by two investigators and verified by two cardiologists.

## Follow-up

The participants were followed from baseline visit (1997–1998) to death, last contact date or 31 December 2010, whichever date came first. During the study period, participants were invited for four scheduled follow-up visits with approximately 2–3 years between these visits, and parameters required to define obesity, type-2 diabetes and hypertension were assessed. AF was diagnosed either at a scheduled visit, outpatient visit or hospital admission.[14] The first occurrence of a particular comorbidity during the follow-up, was defined as an incident comorbidity. Participants that moved or did not attend the follow-up visit, were censored for this visit.

## Clinical outcomes ascertainment

Incident CVD included fatal and non-fatal CV (cardiovascular) events and heart failure (HF) events.[15] Data on incident CV events were retrieved from PRISMANT, the Dutch national registry of hospital discharge, and cause of death was obtained from Statistics Netherlands which were coded according to the 9th revision of the International Classification of Disease (ICD-9). CV events included acute myocardial infarction (ICD-9 code 410), acute and subacute ischaemic heart disease (411), haemorrhagic stroke (430, 431, and 432), ischaemic stroke (433 and 434), and specific vascular interventions consisting of coronary artery bypass grafting, percutaneous transluminal coronary angioplasty, bypass grafting of aorta, and peripheral vessels. Incident HF was assessed by patient files and subsequently adjudicated by independent HF experts.[16]

## Statistical analysis

Normally distributed continuous variables were presented as means $\pm$ standard deviations (SD) and categorical variables as counts with percentages. Baseline differences between men and women were tested by student *t*-test or chi-square, where appropriate.

When incidence of a specific comorbidity was calculated, we excluded individuals with that specific comorbidity at baseline. For example, when incidence of obesity was calculated, we excluded individuals with prevalent obesity. Similarly, when associations of incident comorbidities with incident CVD were assessed, individuals with that specific comorbidity at baseline were excluded. Cumulative incidences of comorbidities and CVD were modelled with death as a competing event and with age of comorbidity or CVD onset as timescale. Sex differences were tested by the method of Pepe and Mori.[17]

Using Poisson regression, we calculated crude sex-specific incidence rates (IR) per 1000 person-years of CVD according to comorbidity status, presented as IR either with ($IR_{comorbidity}$) or without ($IR_{no\text{-}comorbidity}$) comorbidity. Sex-specific increase in absolute risk was calculated as incidence rate differences ($IRD = IR_{comorbidity} - IR_{no\text{-}comorbidity}$) using bootstrapping with 1000 replications to normally distribute IRD. Sex differences in IRD were presented as women-to-men differences ($WMD = IRD_{women} - IRD_{men}$) and tested based on comparison of the mean. We examined sex-specific relative risk for CVD by calculating the incidence rate ratios ($IRR = IR_{comorbidity}/IR_{no\text{-}comorbidity}$). Sex differences in IRR were presented as women-to-men ratios ($WMR = IRR_{women}/IRR_{men}$) and tested by including sex*comorbidity interaction term in the Poisson regression.

Additionally, we tested for sex*comorbidity interaction in multivariable Cox-regression models after adjusting for age, sex, smoking, prevalent obesity, prevalent diabetes, prevalent hypertension, and prevalent AF.

All rates and ratios were reported with their corresponding 95% confidence intervals (95% CIs). Analyses were performed with Stata software (Version 14, StataCorp. College Station, TX, USA) and *P*-values <0.05 and *P*-interaction values <0.1 were considered statistically significant.

# Results

The current analyses included 7994 individuals, and 4096 (51.2%) were women. Women were slightly younger than men (48.3 $\pm$ 12.2 vs. 50.0 $\pm$ 12.6 years, $P < 0.001$). The prevalence as well as IR of diabetes, hypertension, and AF were lower in women than men. While the prevalence of obesity was higher in women, the IR of obesity was comparable in both sexes (*Table 1*, *Figure 1A*, Supplementary material online, *Table S1*).

**Table 1 PREVEND baseline characteristics**

| | Women $N = 4096$ | Men $N = 3898$ | *P*-value |
|---|---|---|---|
| Age (years) | 48.3 (12.2) | 50.0 (12.6) | <0.001 |
| Smoking (*N*) | 1541 (37.7) | 1487 (38.3) | 0.605 |
| Comorbidities, *N* (%) | | | |
| Obesity | 681 (16.8) | 547 (14.2) | <0.001 |
| Diabetes | 119 (2.9) | 148 (3.8) | 0.026 |
| Hypertension | 1104 (27.0) | 1433 (37.0) | <0.001 |
| Atrial Fibrillation | 16 (0.4) | 37 (0.9) | 0.002 |
| **Clinical measurements** | | | |
| BMI (kg/m$^2$) | 25.9 (4.7) | 26.2 (3.6) | <0.001 |
| Total cholesterol (mmol/L) | 5.6 (1.2) | 5.7 (1.1) | <0.001 |
| Glucose (mmol/L) | 4.7 (1.1) | 5.0 (1.2) | <0.001 |
| Systolic BP (mmHg) | 123.9 (20.5) | 133.4 (18.3) | <0.001 |
| Diastolic BP (mmHg) | 71.0 (9.0) | 78.9 (9.6) | <0.001 |

Data are presented as mean ($\pm$SD) or N (%). BMI, Body mass index; BP, Blood pressure.

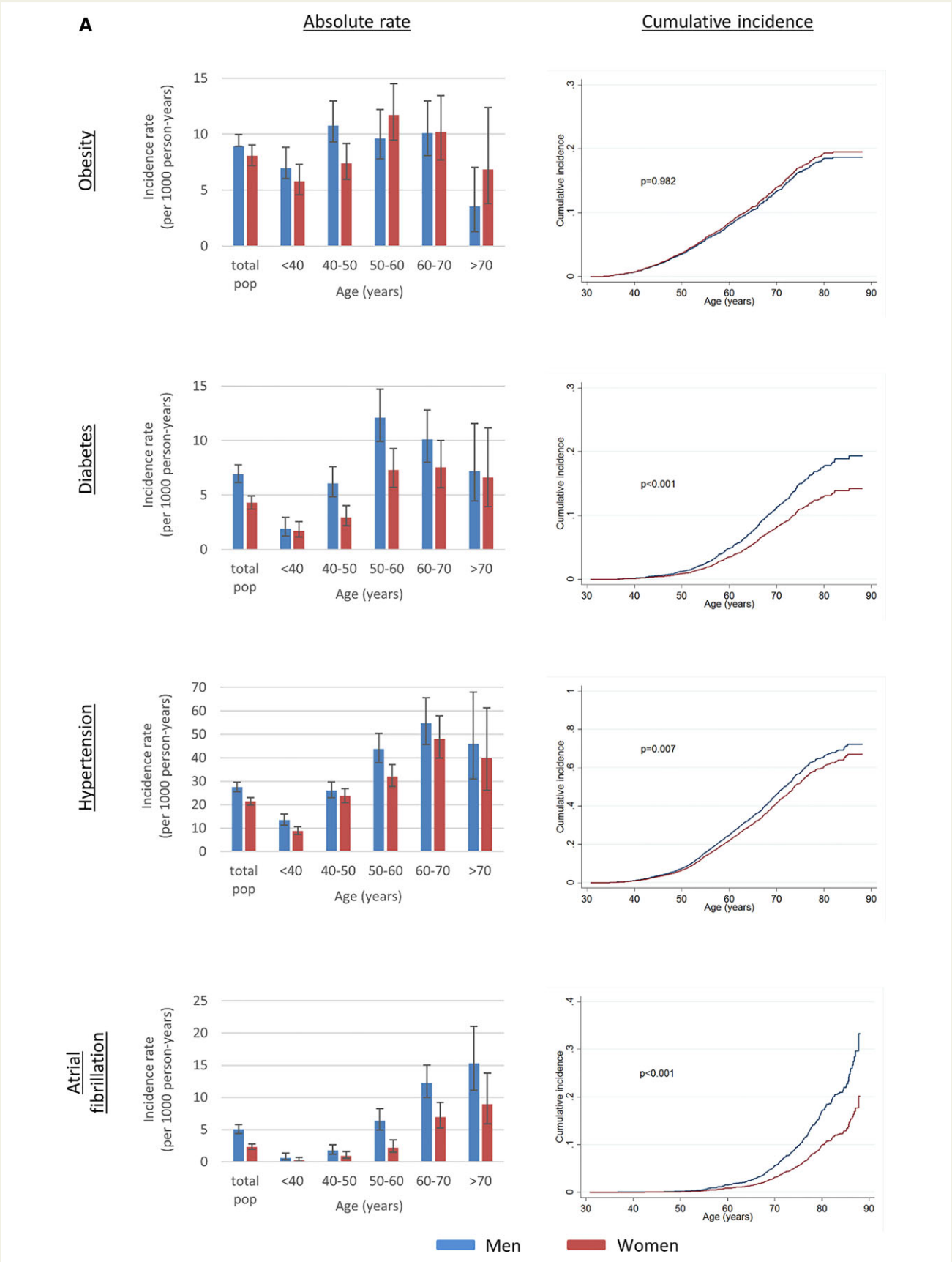



**Figure 1** Incidence of comorbidities and CVD. Incidence of obesity, diabetes, hypertension, and AF (*A*). Incidence of CVD (*B*). IR are reported per 1000 person-years follow-up with error bars representing the 95% confidence interval. Cumulative incidence was modelled with death as competing event and with age of comorbidity or CVD onset as timescale. Sex differences were tested by the method of Pepe and Mori.

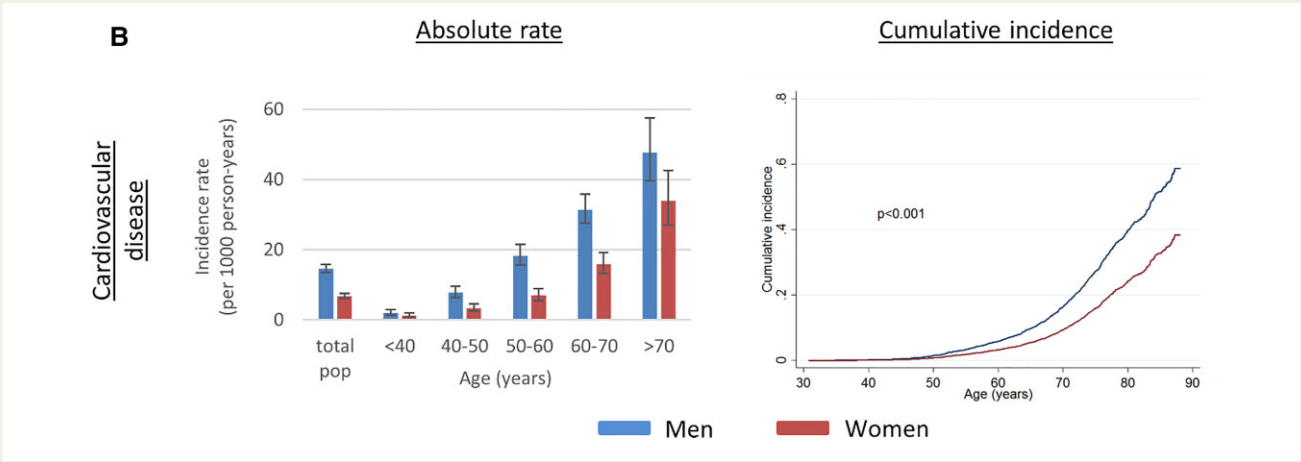



**Figure 1** Continued

## Incidence of CVD

During a follow-up time of 46 231 person-years in women and 41 564 person-years in men, a total of 311 and 607 incident CVD events occurred in women and men, respectively. This corresponded to an overall incidence rate of 6.73 (6.02–7.52) per 1000 person-years in women vs. 14.58 (13.46–15.79) per 1000 person-years in men (*Figure 1B*).

## Prevalent comorbidities and absolute CVD risk: women vs. men

IR of CVD among individuals with obesity and hypertension were significantly lower in women than in men ($P < 0.001$), but rates were comparable among individuals with diabetes ($P = 0.224$). Individuals with AF had the highest IR of CVD, with no significant difference between the sexes ($P = 0.711$). (*Table 2*, *Figure 2*, corresponding events follow-up time in Supplementary material online, *Table S2*).

## Prevalent comorbidities and increase in absolute CVD risk: women vs. men

Sex-specific impact of comorbidities on absolute CVD risk is presented in *Table 2*. When directly compared, the increase of absolute CVD risk in women with hypertension was significantly lower than in men with hypertension [WMD: −6.12 (−9.84 to −2.40), $P = 0.001$]. A similar trend was observed in individuals with obesity [WMD: −4.25 (−9.11 to 0.61), $P = 0.087$] (*Figure 3*), and a statistically significant difference was observed when we substituted obesity with central obesity ($P < 0.005$) (see Supplementary material online, *Figure S2*). Absolute CVD risk increase in individuals with diabetes [WMD: −1.04 (−14.36 to 12.29), $P = 0.879$] and AF [WMD: 18.39 (−39.65 to 76.43), $P = 0.535$] was not significantly different between sexes (*Figure 3*).

## Prevalent comorbidities and relative CVD risk: women vs. men

The relative risk of CVD associated with prevalent comorbidities was generally higher in women than in men (*Table 2*). Specifically, relative risk of CVD associated with prevalent diabetes [WMR: 1.73 (1.09–2.73), $P = 0.019$], hypertension [WMR: 1.49 (1.12–1.99), $P = 0.006$], and AF [WMR: 2.53 (1.12–5.70), $P = 0.025$] was higher in women than in men (*Figure 3*). Comparable results were obtained using multivariable Cox-regression models, although a significant interaction with sex, in the direction of women, was observed only for hypertension ($P_{int} = 0.056$) and AF ($P_{int} = 0.031$) (see Supplementary material online, *Table S3*). The relative risk of CVD associated with obesity was not significantly different between sexes, although effect sizes were numerically larger in women than in men [WMR: 1.21 (0.89–1.65), $P = 0.217$]. A reversal in trend was observed when obesity was substituted with central obesity defined according to waist-to-hip ratio [WMR: 0.75 (0.54–1.03), $P = 0.078$] (see Supplementary material online, *Figure S2*).

## Sensitivity analysis: postmenopausal women vs. men

As a first sensitivity analysis, we examined associations of prevalent comorbidities with incident CVD in postmenopausal women ($N = 2094$, age = 57.7 ± 8.9 years) vs. all men. We observed that the incidence rate of CVD increased from 6.73 (6.02–7.52) per 1000 person-years in all women to 11.37 (10.09–12.82) per 1000 person-years in postmenopausal women. While sex differences in the increase in absolute CVD risk associated with prevalent comorbidities were similar to analyses done on the total population, sex differences in relative CVD risk were absent in this sensitivity analysis (see Supplementary material online, *Figure S3*).

A second sensitivity analysis included postmenopausal women with age-matched men ($N = 2062$, age = 60.0 ± 8.0 years); the matching was performed by including men older than the mean age at menopause (47.7 ± 4.0 years). The incidence rate of CVD increased from 14.58 (13.46–15.79) per 1000 person-years in all men to 24.78 (22.74–27.01) in the older age-matched sample. Sex differences in increase in absolute CVD risk associated with prevalent comorbidities were again similar to analyses on the total population. However, sex differences in relative risk that were absent in the first sensitivity analysis re-emerged in the second analysis and were similar to sex differences observed in the total population (see Supplementary material online, *Figure S3*).

**Table 2 Associations of prevalent comorbidities with incident CVD in women and men**

| | $IR_{comorbidity}$ (95% CI) | $IR_{no\text{-}comorbidity}$ (95% CI) | IRD (95% CI) | IRR (95% CI) |
|---|---|---|---|---|
| Women | | | | |
| Obesity | 12.65 (10.35–15.47) | 5.59 (4.88–6.39) | 7.06 (4.43–9.70) | 2.26 (1.78–2.88) |
| Diabetes | 28.34 (20.35–39.47) | 6.11 (5.42–6.88) | 22.23 (13.27–31.20) | 4.64 (3.26–6.60) |
| Hypertension | 16.84 (14.67–19.34) | 3.19 (2.64–3.85) | 13.65 (11.20–16.10) | 5.28 (4.18–6.66) |
| Atrial fibrillation | 76.19 (39.64–146.44) | 6.55 (5.85–7.33) | 69.64 (21.29–118.00) | 11.63 (6.00–22.58) |
| Men | | | | |
| Obesity | 24.40 (20.62–28.89) | 13.09 (11.95–14.33) | 11.31 (7.23–15.40) | 1.86 (1.54–2.26) |
| Diabetes | 37.09 (28.03–49.07) | 13.82 (12.71–15.02) | 23.27 (13.41–33.13) | 2.68 (2.00–3.60) |
| Hypertension | 27.54 (24.95–30.41) | 7.77 (6.79–8.90) | 19.77 (16.98–22.56) | 3.54 (3.00–4.19) |
| Atrial fibrillation | 65.49 (41.26–103.95) | 14.24 (13.14–15.44) | 51.25 (19.15–83.36) | 4.60 (2.88–7.35) |

Data are presented as incidence rates (IR) of CVD per 1000 person-year follow-up. Increase in absolute risk is presented as incidence rate differences (IRD = $IR_{comorbidity} - IR_{no\text{-}comorbidity}$) and relative risk as incidence rate ratios (IRR = $IR_{comorbidity}/IR_{no\text{-}comorbidity}$). 95% CI = 95% confidence interval.

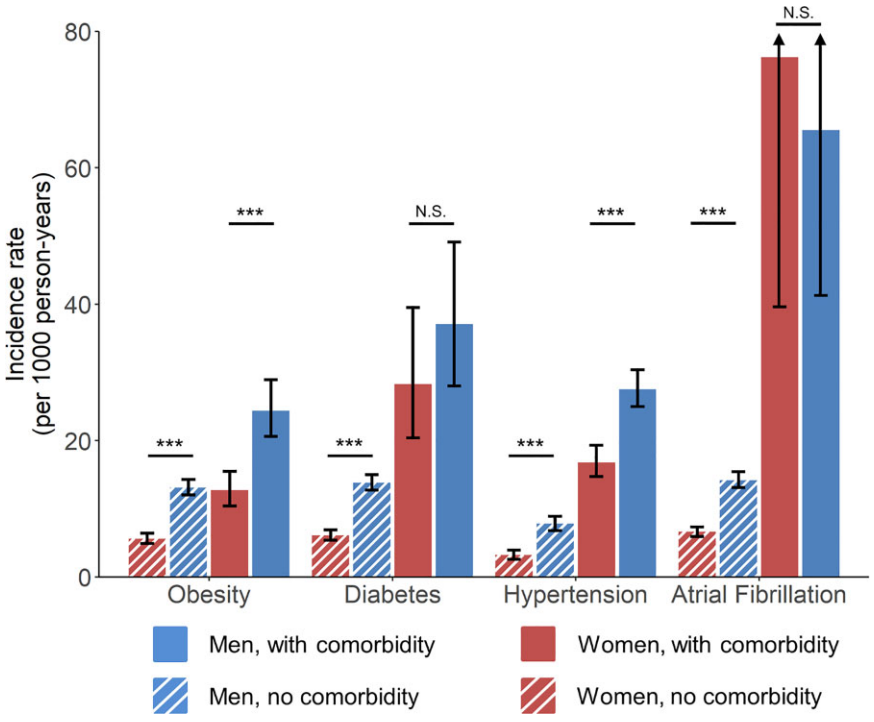



**Figure 2** Sex differences in IR of CVD associated with prevalent comorbidities. Data are stratified by sex and comorbidity status and presented as IR of CVD per 1000 person-years follow-up with error bars representing the 95% confidence interval. *** $P < 0.001$, N.S = not significant.

## Incident comorbidities and CVD risk: women vs. men

IR of CVD in individuals developing comorbidities were lower compared with individuals with prevalent comorbidities (see Supplementary material online, *Table S4*). On an absolute scale, no significant sex-related differences were observed in the increase of CVD risk associated with incident comorbidities (*Figure 4*). On a relative scale, incident hypertension and AF were associated with a greater risk in women than in men, whereas incident obesity and diabetes were associated with a similar risk in both sexes (*Figure 4*).

# Discussion

The key findings of our study are: (i) absolute risk increase of CVD associated with hypertension was lower in women than in men, whereas absolute risk increase of CVD associated with obesity, type-2 diabetes and AF did not substantially differ between sexes;

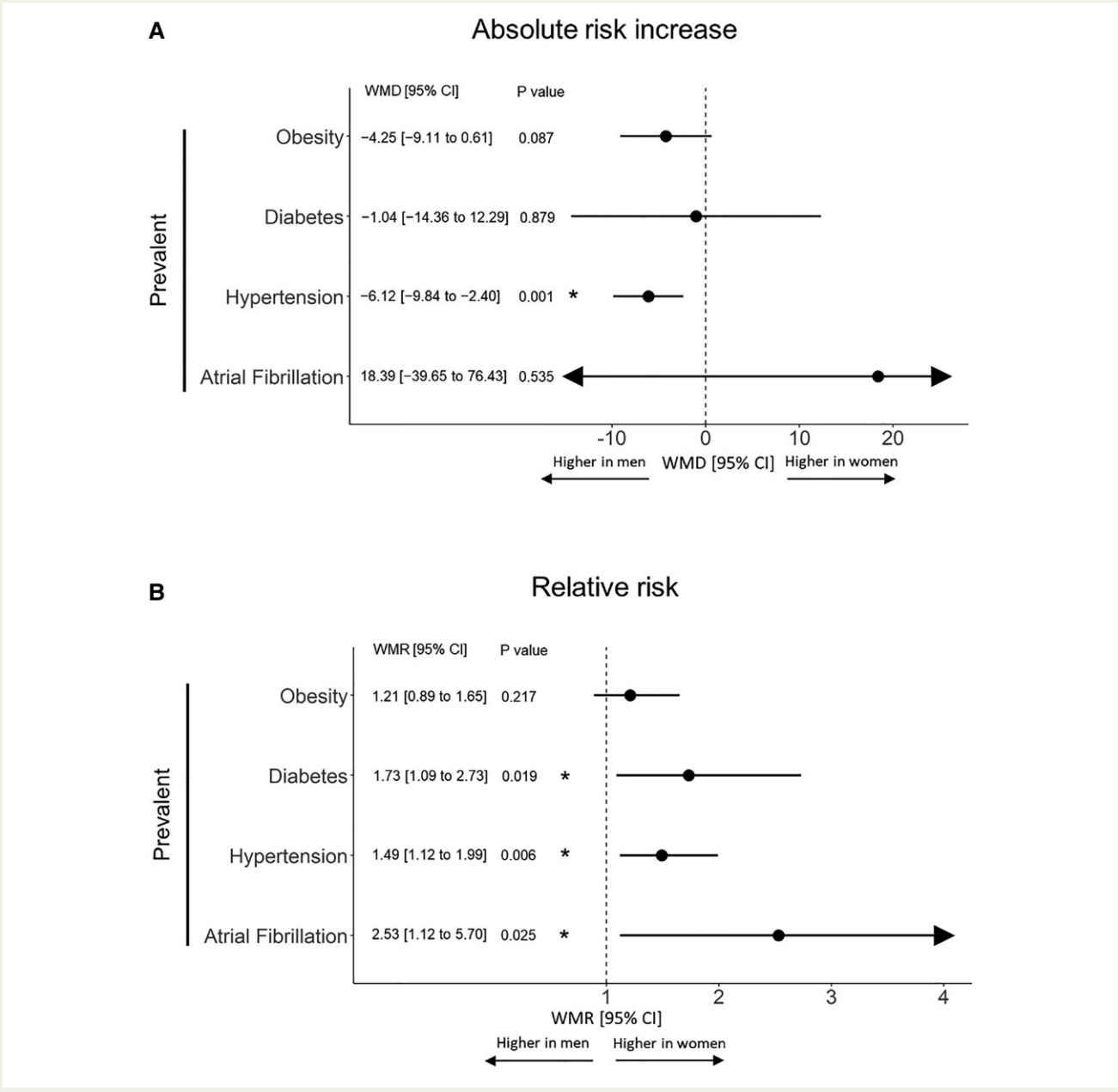



**Figure 3** Sex differences in CVD risk associated with prevalent comorbidities. Sex-related differences in absolute risk increase are presented by women-to-men differences (WMD = $IRR_{women} - IRR_{men}$). WMD <0 indicates higher absolute risk increase of CVD in men and WMD >0 indicates higher absolute risk increase in women. Sex-related differences in relative rates are presented by women-to-men ratios (WMR = $IRR_{women}/IRR_{men}$). WMR <1 indicates higher relative risk of CVD in men and WMR >1 indicates higher relative risk in women. 95% CI = 95% confidence interval, * $P < 0.05$.

and (ii) relative CVD risk associated with type-2 diabetes, hypertension and AF were all higher in women than in men.

In the present study we found that, on an absolute scale, the increase of CVD risk conferred by hypertension was greater in men than in women. In the UK biobank, increase in absolute myocardial infarction risk associated with stage 2 hypertension was also higher in men than in women, but increase in absolute stroke risk was similar among sexes.[11,12] This indicates that adequate blood pressure control on a population level would reduce the number of future CVD events, in particular myocardial infarction, to a greater extent in men than in women. Nevertheless, hypertension was the most prevalent comorbidity in both sexes, and individuals without hypertension carried the lowest absolute risk of CVD among all comorbidities evaluated. The excess CVD risk in both sexes could therefore be largely attributed to the burden of hypertension, which is also supported by the large population-attributable fraction of hypertension for incident CVD in other cohorts.[18]

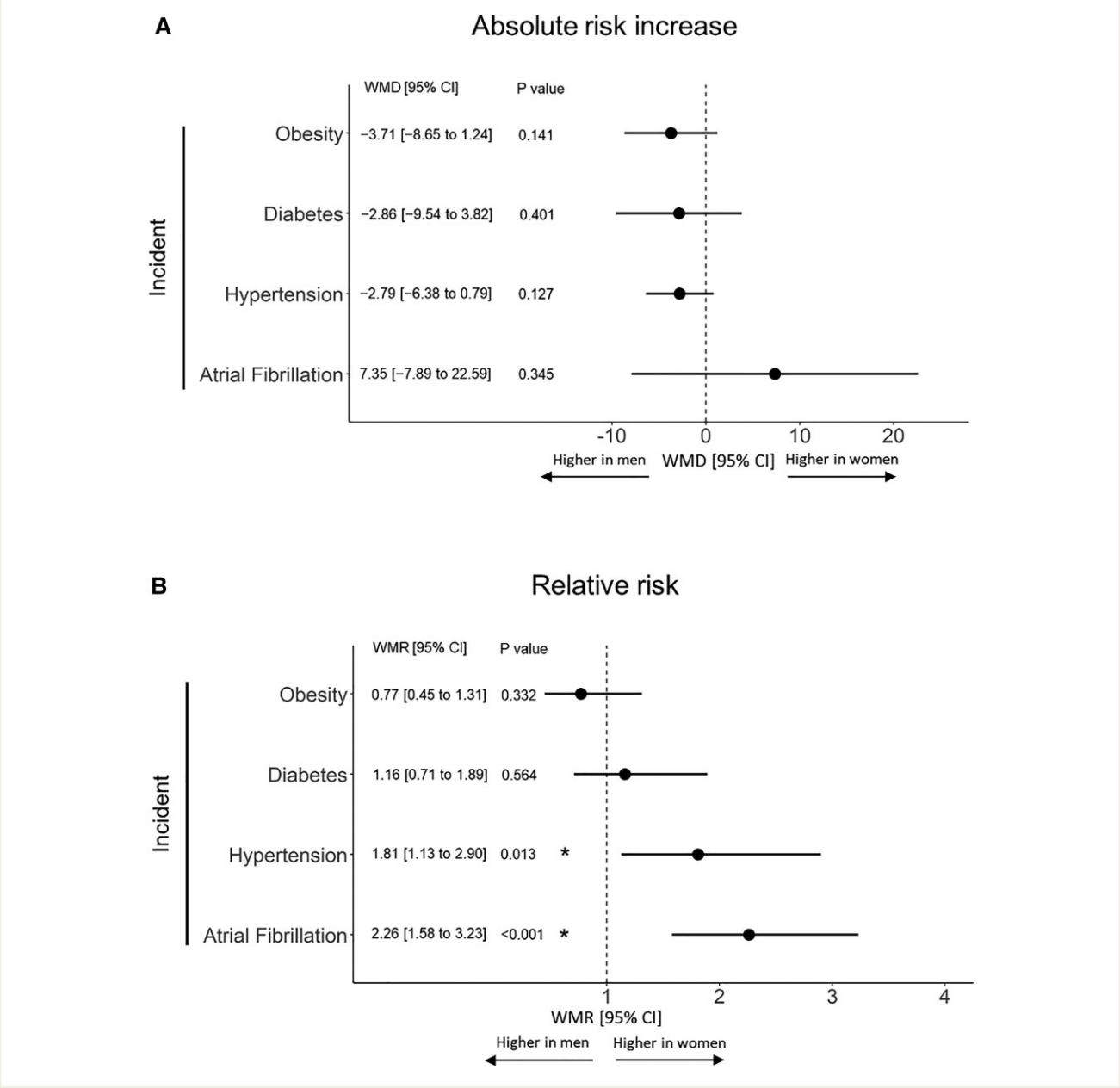



**Figure 4** Sex differences in CVD risk associated with incident comorbidities. Associations of incident comorbidities with CVD were performed on individuals without that specific comorbidity at baseline. Sex-related differences in absolute risk increase are presented by women-to-men differences (WMD = $IRR_{women} - IRR_{men}$). Sex-related differences in relative rates are presented by women-to-men ratios (WMR = $IRR_{women}/IRR_{men}$). 95% CI = 95% confidence interval, * $P < 0.05$.

The increase in absolute CVD risk associated with obesity also seemed to be higher in men than in women. Previous studies indicate that absolute risk increase conferred by obesity might be affected by which CV subtype is assessed; the increase in absolute myocardial infarction risk was greater in men than in women, but the increase in absolute stroke risk was similar in both sexes.[11,12] We additionally observed that the sex difference in absolute risk increase was more evident when 'obesity' was substituted by 'central obesity'. Surprisingly, we found that although the definition of central obesity[19] had little impact on sex differences in absolute CVD risk increase, it had a substantial impact on sex differences in relative risk. Central obesity, defined by waist circumference, was associated with a higher relative CVD risk in the direction of women; on the other hand, central obesity defined by waist-to-hip ratio, was associated with a higher relative CVD risk in the direction of men. However, a study on 58 cohorts observed that relative coronary heart disease risk associated with 1-SD increase of waist circumference or waist-to-hip ratio were both greater in women than in men.[20]

By contrast to hypertension and obesity, the increase in absolute CVD risk associated with AF was comparable in women and men.

We also found that although AF was the least prevalent comorbidity, it conferred the greatest increase of absolute risk in both sexes among all comorbidities examined. Previous studies also observed that AF associated with a high absolute risk increase of myocardial infarction or stroke, and especially the rates of stroke were substantially increased in both sexes in the presence of AF.[11,12] Taken together, these data suggest that improving AF management would substantially decrease CVD risk on an individual level in both sexes, but the numerical reduction of incident CVD on a population level might be minor due to the low prevalence of AF in the general population.

Increase in absolute CVD risk associated with type-2 diabetes was also similar among sexes, and based on our data adequate diabetes management appears to be equally important in both sexes to prevent CVD. This is in line with data from the UK biobank which showed that type-2 diabetes conferred a similar absolute risk increase of myocardial infarction or stroke in both sexes.[11,12] Two other large population-based cohort studies also presented absolute CVD risk in diabetic and non-diabetic individuals.[21,22] However, these studies mainly focused on sex differences in relative CVD risk without adequately quantifying sex differences in increase of absolute CVD risk. We calculated the increase in absolute risk from their data and report that excess risk with type-2 diabetes was greater in men than in women in the Danish resident registry [WMD: −1.95 (−2.60 to −1.30)] as well as in the French hospitalization cohort that pooled type-1 and type-2 diabetes together [WMD: −13.00 (−13.96 to −12.04)].[21,22] Taken together, these data indicate that reducing type-2 diabetes on a population level would prevent CVD events in both sexes, with a potential greater prevention in men than in women.

Although we focused on sex differences based on the increase of absolute risk, we would like to address that sex-related differences in associations of comorbidities with incident CVD are often reported based on relative risk differences; and suggestions to intensify preventive strategies in women vs. men are also frequently based on this measure.[7–9,22] If a similar approach would be followed for our study using only relative risk estimates to investigate sex differences in CVD, one would conclude that obesity was similarly associated with CVD in both sexes, but type-2 diabetes, hypertension, and AF were more strongly associated with CVD risk in women compared to men. Based on this line of reasoning, one would also advocate to reduce comorbidities predominantly in women. Although a relative risk measure would provide insight on the extent to which a comorbidity increases CVD risk, the negative effect on a population level is derived from absolute risk, i.e. number needed to harm to cause a future CVD event.

An additional remark on the use of relative risk is its potential dependence on baseline risk. In our study, the baseline risk of developing CVD was lower in women than in men, and associations of type-2 diabetes, hypertension and AF with incident CVD on a relative scale were stronger in women than in men. However, when the difference in baseline risk between men and women was reduced by excluding premenopausal women, sex differences in relative risk were no longer present. By further excluding younger men, the baseline risk of developing CVD was again lower in women than in men resulting in similar sex differences of relative risk previously observed in the whole cohort, i.e. stronger associations in women than in men. Taken together, sex differences in relative risk associated with comorbidities appear to originate from lower baseline risk in women compared to men.

Given the challenges of using relative risk estimates, we would like to emphasize that implications on sex-specific strategies to prevent CVD would be more solid when relative risk is interpreted in the context of absolute risk increase. Indeed, based on aggregate data it appears that reducing comorbidity burden and screening for risk factors should be actively pursued in both sexes in order to promote public health.[23] Nevertheless, considering the fact that women are often underdiagnosed and undertreated compared to men,[24] it would be important to ensure that women are also adequately screened and treated.

### Strengths and limitations

Strengths of this study are the detailed clinical assessment within a well-characterized cohort, the high specificity of CV events from hospital discharge codes, adjudication of AF and HF by experts and long follow-up time with repeated visits. Although incident CVD and AF were diagnosed either at a scheduled visit, outpatient visit, or hospital admission, a potential limitation of our study is that incident obesity, type-2 diabetes and hypertension were only recorded during scheduled patient visits to the clinic. We also acknowledge that the associations of CVD with incident comorbidities would be bidirectional, i.e. a comorbidity either developed before or after a CV event.[25] Furthermore, individuals included in PREVEND are primarily Caucasian limiting generalizability of our results to other ethnicities. Finally, individuals with slightly increased UAE are overrepresented in PREVEND and an effect cannot be excluded.

## Conclusion

An increase in absolute risk of developing CVD is higher in hypertensive men than in hypertensive women, but no substantial sex-related differences were observed among individuals with obesity, type-2 diabetes, and AF. On a relative risk scale, comorbidities, in general, confer a higher CVD risk in women.

## Lead author biography

Just Dronkers obtained his master degree in Biomedical Science from the University of Groningen. Recently, he joined the Cardiology department of the University Medical Centre in Groningen. His research will focus on the role of obesity and fatty tissue in heart failure development.

## Supplementary material

Supplementary material is available at *European Heart Journal Open* online.

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## Data availability

Please contact the authors for data requests.

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