Sex differences in the association of risk factors for heart failure incidence and mortality

AUTHORS

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ABSTRACT

BACKGROUND – There are known risk factors associated with the development of heart failure (HF), but it is not fully understood whether these differ by sex.

OBJECTIVES - To investigate sex differences in risk factors for HF incidence and mortality.

METHODS – 468 941 participants (55.9% women, age range 37 to 73 years) were included. Established CVD risk factors (hypertension, hypercholesterolemia, diabetes type 1 and 2, adiposity, smoking, physical activity and poor diet) and novel risk factors (grip strength, fitness, TV-viewing and sleep duration) were the exposures of interest. HF incidence and mortality were the outcomes.

RESULTS – Over a mean follow-up of 9.0 years, 1812 participants developed HF and 763 died due to HF. Women with type 1 diabetes (T1DM), type 2 diabetes (T2DM), hypertension, hypercholesterolemia, low levels of physical activity and fitness, low strength, high levels of TV-viewing, sleep duration <7 h/day, smokers, those who were underweight and who were obese, had high body surface area, and those who drink >14 units of alcohol, were at higher risk of HF incidence. However, in women T2DM, hypercholesterolemia, >3 h/day of TV and sleep <7 h/day, low level of physical activity and high level of TV viewing were more strongly associated with HF incidence compared with men.

CONCLUSION – Several modifiable risk factors (in particular diabetes) appear more strongly associated with HF in women compared with men. The relevance of these findings to HF characteristics and future outcomes, needs to be established.

Keywords – heart failure, lifestyle, obesity, physical activity, diet

What is already known about this subject?

It is already known that traditional risk factors including hypertension, smoking, obesity, as well as emerging risk factors including grip strength, cardiorespiratory fitness and physical activity levels are associated with heart failure incidence. It is also known that there are differences between the sexes in established heart failure. However, whether traditional or emerging risk factors differ by sex has not been investigated.

What does this study add?

We have demonstrated that several risk factors, including diabetes (T1DM & T2DM), high cholesterol, high TV viewing, low physical activity and those sleeping less than 7 hours per night, were associated with a higher hazard ratio for HF incidence and mortality in women compared to men.

How might this impact on clinical practice?

The early identification of women at risk of HF could be mediated by focusing on emerging modifiable risk factors including physical activity, sleep duration and TV-viewing alongside traditional risk factors including T1DM & T2DM, hypertension, hypercholesterolemia, smoking and alcohol consumption. These emerging risk factors could be a useful clinical measurement used in conjunction with traditional methods to more specifically risk stratify patients in the clinical setting.

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death worldwide. Over the last three decades there has been a decline in most CVDs, due to improvements in treatment. However, simultaneously, there has been an increase in the prevalence of heart failure (HF) in the UK and across Europe [1,2]. Within the UK, HF affects approximately 900 000 people and has a poor prognosis, with a 17% mortality rate within the first year of diagnosis [3]. Although there has been progress in the management of HF, the social and economic burden to both patients and the health service remains high, accounting for ~2% of total NHS expenditure [4]. In Europe, as well as the UK, HF accounts for 1-2% of all hospital admissions, with the trend increasing over recent years [5]. With an aging population the prevalence of HF is projected to increase, [1,6] thus prevention at a population level is key to improving outcomes.

To help direct specific interventions for HF, a clear understanding of modifiable risk factors is important. It has been shown, for example, that hypertension, smoking, obesity, grip strength, cardiorespiratory fitness, physical activity levels, alcohol intake and diet quality are associated with heart failure incidence [7–9]. However, whether these risk factors differ by sex has not been investigated. This is despite the fact that differences between the sexes in established heart failure have been previously reported [10]. Women who are older, have a higher BMI and have hypertension or diabetes are more likely to develop HF compared with men. Women are also more likely to develop HF with a preserved Ejection Fraction (HFpEF), with men being more likely to have a reduced ejection fraction (HFrEF) [11], and thus poorer outcomes.

What is less well known however, is the effect that modifiable risk factors have on the risk of developing heart failure between the sexes. Previous work using data from the PREVEND study, a Dutch study investigating the effects of albuminuria on cardiovascular and renal disease, demonstrated that HF did occur earlier in men, that women were more likely to develop HFpEF later in life, and that atrial fibrillation, anti-hypertensive therapy and urinary-albumin excretion were the only sex specific risk factors associated with an increased risk of HF in women [11]. However, the study only looked at three modifiable risk factors – BMI, smoking habits and alcohol consumption, in a cohort of ~8500 participants.

The aim of this study, therefore, is to investigate potential sex differences in the association of modifiable and traditional risk factors with heart failure incidence and mortality using data from the UK Biobank, a large population-based cohort study.

METHODS

Ethical Approval

The UK Biobank study was approved by the North West Multi-Centre Research Ethics Committee (REC reference: 11/NW/03820) and all participants provided written informed consent to participate in the UK Biobank study. The study protocol is available online (**http://www.ukbiobank.ac.uk/**).

Study design

Between April 1st 2007 and December 31st 2010, UK Biobank recruited 502 536 participants (5.5% response rate), aged between 40-69 years from the general population [12]. We included a total of 468 941 participants in this current study, excluding those with self-reported or hospital admission diagnosis of cardiovascular disease (CVD)

(heart failure (HF), atrial fibrillations (AF), ischemic heart disease including myocardial infarction (MI) or stroke) at baseline (n=33 595). Participants attended one of 22 assessment centres across England, Wales and Scotland [13,14] where they completed a touch-screen questionnaire, and had physical measurements taken and provided biological samples. In this prospective, population-based study HF incidence and mortality (HF fatal and non-fatal) events, in females and males were the measured outcomes. Analyses were adjusted for sociodemographic factors (age, ethnicity, deprivation index, month of assessment), lifestyle factors (dietary intake of major food groups, physical activity, sleeping, TV viewing and smoking) and obesity-related traits (height, weight, body mass index (BMI)).

Procedures

Date of death was obtained from death certificates held by the National Health Service (NHS) Information Centre (England and Wales) and the NHS Central Register Scotland (Scotland). Date and reason of hospital admissions were identified via record linkage to Health Episode Statistics (HES) (England and Wales) and to the Scottish Morbidity Records (SMR01) (Scotland). Detailed information regarding the linkage procedure can be found at **http://www.ic.nhs.uk/services/medical-research-information-service**. At the time of analysis, mortality data were available up to 31 January 2016. Mortality analysis was therefore censored at these dates or date of death if this occurred earlier. Hospital admission data were available until 31 March 2015, resulting in disease specific analyses being censored at this date, or the date of hospital admission or death if these occurred earlier. Incident heart failure was defined as a hospital admission or death with ICD10 code I50.0, I50.2, I50.9 [15].

Details of the procedures used to obtain all medical, socio-economic and anthropometric measurements can be found in the UK Biobank online protocol (**http://www.ukbiobank.ac.uk**).

Statistical analysis

Sex-specific associations of predictors on HF incidence and mortality were studied using Cox-proportional hazard models for both females and males independently. Hazard ratios (HR) were used to determine the effect sizes. Women-to-men HR ratios were then estimated using Cox models with *sex: risk factor* interaction terms. This term represents the statistical interaction between sex and the predictor and can be interpreted as the ratio of HR between female and male. Continuous predictors were categorised by quartiles to avoid assuming linear associations. Predictors with sex differences due to physiology (aerobic fitness, grip strength, and body surface area) were categorised within each sex; other predictors (socio-economic status, physical activity, and blood/pulse pressure) were categorised using the overall sample. Dietary intake and TV viewing were categorised using overall tertiles instead of quartiles because of tied values.

A comprehensive list of covariates was fitted into the models: age, ethnicity, deprivation index, height, medication for CVD, and prevalent comorbidity (any cancers, depression, anxiety, schizophrenia, substance and alcohol problems, chronic obstructive pulmonary disease, chronic live disease, inflammatory bowel disease, and chronic fatigue syndrome) at recruitment. These factors were regarded as potential confounders based on the causal assumptions presented in a directed acyclic graph (Supplementary Figure 1). A sensitivity analysis was conducted to exclude any participants with HF events in the first two years of follow-up (Supplementary Table 2). Complete case analysis was used in handling missing data. All analyses were conducted in R version 3.5.1 with the package *survival*.

RESULTS

Of the 502 536 participants recruited to UK Biobank, 468 941 (96%) participants were included in the current study, after excluding participants with CVD at baseline (n=33 595). The mean follow-up period was 9.0 years [range 7.4–11.9] for HF mortality and 8.2 [range 6.5–13.0] years for incidence. During the follow-up 1812 participants had a HF event, in which 763 were fatal. Among the 262 325 women, 651 had HF events where 221 were fatal. The incidence rate for women and men were 3.53 and 8.00 per 10,000 person-years. The hazard for HF incidence and mortality in women was 0.45 ([95% CI: 0.41–0.49], p<0.0001) and 0.33 ([0.28; 0.38], p<0.0001) compared to men.

The characteristics of participants by sex are presented in Table 1. Compared to men, women had lower levels of physical activity, fitness and grip strength. A higher proportion of healthy lifestyle factors were observed in women, including non-smokers, lower intake of red and processed meat and higher intake of fruit and vegetables. However, a higher proportion of women reported consuming more than >14 units of alcohol per week.

Table 1. Cohort characteristics

	Female (n=262 325)		Male (n=206 600)	
	Data available[d]	n (%) / mean (SD)	Data available[d]	n (%) / mean (SD)
Mean (SD) age (years)	262 325	56.1 (7.99)	206 600	56.2 (8.21)
Ethnicity	261 100		205 225	
White		247 041 (94.6)		193 898 (94.5)
Mixed		1 800 (0.7)		1 035 (0.5)
South Asian		4 372 (1.7)		4 666 (2.3)
Black		4 417 (1.7)		3 245 (1.6)
Chinese		997 (0.4)		559 (0.3)
Other		2 493 (1.0)		1 822 (0.9)
Mean (SD) height (m)	260 994	1.63 (0.06)	205 294	1.76 (0.07)
Any medications for CVD	259 895	54 011 (20.8)	204 627	55 417 (27.1)
Any prevalent comorbidities	260 979	51 034 (19.6)	205 688	28 727 (14.0)
Deprivation	262 011		206 331	
Lowest		65 182 (24.9)		51 922 (25.2)
Middle/Low		65 922 (25.2)		51 152 (24.8)
Middle/High		66 449 (25.4)		50 675 (24.6)
Highest		64 458 (24.6)		52 582 (25.5)
Mean (SD) physical activity (MET.mins/week)	193 496	2549.7 (2358.3)	167 905	2799.5 (2657.5)
Mean (SD) aerobic fitness (METs)	35 258	8.46 (2.2)	29 106	10.7 (2.4)
Mean (SD) grip strength	261 169	23.4 (6.2)	205 539	39.6 (8.8)
Mean (SD) systolic blood pressure (mmHg)	246 589	135.16 (19.2)	194 393	141.1 (17.3)
Mean (SD) diastolic blood pressure (mmHg)	238 350	80.7 (9.9)	188 461	84.4 (9.8)
Mean (SD) pulse pressure (mmHg)	238 349	54.4 (14.1)	188 461	56.6 (12.5)
BMI categories[a]	260 995		205 294	
Underweight		2023 (0.8)		510 (0.2)

Normal		103 204 (39.5)		53 041 (25.8)
Overweight		95 749 (36.7)		102 008 (49.7)
Obese		60 019 (23.0)		49 735 (24.2)
Central obesity[b]	261 261	78 991 (30.2)	205 559	142 851 (69.5)
Waist-height ratio > 0.5	260 932	143 642 (55.0)	205 256	161 014 (78.4)
Mean (SD) body surface area (m^2)	260 994	1.79 (0.18)	205 294	2.04 (0.19)
Mean (SD) hours of watching television a day	258 211	2.75 (1.5)	202 006	2.76 (1.5)
Sleep duration	259 963		205 174	
Short sleeper (< 7 h/day)		62 373 (24.0)		51 466 (25.1)
Normal (7-9 h/day)		192 939 (74.2)		150 514 (73.4)
Long sleeper (> 9 h/day)		4651 (1.8)		3194 (1.6)
Smoking	260 906		205345	
Never		156 584 (60.0)		103 661 (50.5)
Former		81 265 (31.1)		76 013 (37.0)
Current		23 057 (8.8)		25 671 (12.5)
Weekly alcohol intake <14 units	236 273	174 837 (74.0)	191 079	78276 (41.0)
Mean (SD) frequency of processed meat intake a week	261 273	1.58 (1.00)	205 583	2.20 (1.06)
Mean (SD) frequency of oily fish intake a week	260 558	1.66 (0.92)	204 608	1.59 (0.94)
Mean (SD) portion of red meat intake	262 325	1.97 (1.3)	206 600	2.26 (1.5)
Mean (SD) portion of fruit and vegetable intake	262 325	4.38 (2.3)	206 600	3.76 (2.4)
Prevalent conditions at recruitment[c]				
Type 1 diabetes	262 223	543 (0.2)	206 448	822 (0.4)
Type 2 diabetes	262 223	7548 (2.9)	206 448	11 020 (5.3)
Hypertension	262 325	58 034 (22.1)	206 600	57 058 (27.6)
High cholesterol	259 895	27 321 (10.5)	204 627	34 642 (16.9)

[a] Underweight: BMI < 18.5; Normal: 18.5–<25; Overweight: 25–<30; Obese: ≥30

[b] Central obesity: waist-hip ratio >85 cm for female and >90 cm for male

[c] Prevalent conditions at recruitments were self-reported clinician diagnosis

[d] Participants with data available out of 273,391 females and 229,129 males recruited in UK Biobank.

Obesity-related risk factors and HF risk

The HR for the association of HF (incidence) with adiposity are presented in Figures 1 and Figure 2 for men and women, respectively. Results for HF mortality are presented in supplementary Table S1. BMI, central obesity, waist-to-height ratio, body fat % and body surface area (BSA) were associated with a higher risk of HF incidence in both women and men, after adjustment for age, sex, ethnicity, height, medication for CVD and prevalent morbidities at recruitment (Figures 1 and 2). A higher risk for HF incidence and mortality was observed for underweight, obese, central obese and in those with high waist-to-height ratio in both men and women. When the risk of obesity for HF incidence and mortality by sex was compared, there were no evidence of any significant difference between men and women (Table 2).

Existing conditions at recruitment

Type 1 (T1DM) and type 2 diabetes (T2DM), hypertension, and hypercholesterolemia were associated with HF incidence (Figures 1 and 2) and mortality regardless of sex (Supplementary Table S1). However, the association of T2DM and hypercholesterolemia were stronger in female than in male, the ratios of HR ranged from 32% to 92% (Table 2).

Table 2. Women-to-men HR ratio on HF incidence and mortality

	Incident heart failure		Heart failure mortality	
	W:M HR Ratio (95% CI)	P	W:M HR Ratio (95% CI)	P
Prevalent conditions[a]				
Type 1 diabetes	1.68 (0.77, 3.68)	0.19	1.98 (0.62, 6.31)	0.25
Type 2 diabetes	1.73 (1.34, 2.24)	< 0.0001	1.92 (1.25, 2.94)	0.003
Hypertension	1.18 (0.97, 1.44)	0.09	1.21 (0.88, 1.66)	0.24
High cholesterol	1.32 (1.06, 1.63)	0.01	1.46 (1.03, 2.07)	0.03
Deprivation				
Low	0.90 (0.68, 1.19)	0.45	0.70 (0.44, 1.10)	0.12
Lower-middle	0.80 (0.60, 1.08)	0.14	0.69 (0.43, 1.12)	0.14
Upper-middle	0.79 (0.57, 1.08)	0.13	0.65 (0.39, 1.10)	0.11
High	1 (Reference)		1 (Reference)	
Total PA MET.min/week				
≤802	1.43 (1.02, 2.00)	0.04	2.49 (1.41, 4.41)	0.002
>802 to 1737	1.21 (0.84, 1.74)	0.30	1.48 (0.78, 2.81)	0.23
>1737 to 3386	1.22 (0.84, 1.77)	0.30	1.64 (0.87, 3.11)	0.13
>3386	1 (Reference)	-	1 (Reference)	-
Aerobic fitness (MET)				
Lowest	0.59 (0.17, 1.96)	0.39	1.65 (0.17, 15.85)	0.66
Middle/Low	0.89 (0.24, 3.24)	0.86	2.37 (0.22, 26.06)	0.48
Middle/High	0.68 (0.13, 3.46)	0.64	0.00 (0.00, Inf)	1.00
Highest	1 (Reference)	-	-	-
Grip strength (Kg)				
Lowest	0.92 (0.66, 1.29)	0.65	0.99 (0.56, 1.78)	0.98
Middle/Low	1.25 (0.87, 1.79)	0.23	1.39 (0.76, 2.55)	0.29
Middle/High	1.08 (0.74, 1.59)	0.68	0.95 (0.49, 1.83)	0.87
Highest	1 (Reference)	-	1 (Reference)	-
Systolic blood pressure (mmHg)				
≤125	1 (Reference)	-	1 (Reference)	-
>125 to 138	1.34 (0.94, 1.93)	0.11	0.92 (0.52, 1.63)	0.77
>138 to 152	1.31 (0.94, 1.83)	0.11	0.97 (0.57, 1.64)	0.91
>152	1.28 (0.92, 1.76)	0.14	1.03 (0.62, 1.71)	0.92
Diastolic blood pressure (mmHg)				
≤75	1 (Reference)	-	1 (Reference)	-
>75 to 82	1.05 (0.78, 1.43)	0.74	0.87 (0.54, 1.40)	0.56
>82 to 89	1.27 (0.95, 1.69)	0.11	0.81 (0.51, 1.29)	0.37
>89	1.31 (0.98, 1.75)	0.07	1.07 (0.66, 1.72)	0.79
Pulse pressure (beats/min)				
≤47	1 (Reference)	-	1 (Reference)	-
>47 to 55	1.20 (0.83, 1.72)	0.34	1.03 (0.58, 1.83)	0.93

>55 to 66	1.18 (0.84, 1.65)	0.33	0.93 (0.54, 1.59)	0.79
>66	1.16 (0.86, 1.57)	0.33	1.03 (0.63, 1.67)	0.92
BMI categories [b]				
Underweight	0.62 (0.23, 1.66)	0.34	0.68 (0.17, 2.62)	0.57
Normal	1 (Reference)	-	1 (Reference)	-
Overweight	0.95 (0.72, 1.26)	0.71	0.82 (0.53, 1.27)	0.37
Obese	1.17 (0.90, 1.53)	0.23	1.28 (0.85, 1.92)	0.24
Body surface area categories				
Lowest	1 (Reference)	-	1 (Reference)	-
Middle/Low	0.91 (0.66, 1.25)	0.55	0.71 (0.43, 1.16)	0.17
Middle/High	0.94 (0.69, 1.28)	0.69	0.67 (0.41, 1.08)	0.1
Highest	1.00 (0.76, 1.31)	0.99	0.85 (0.56, 1.30)	0.46
Central obesity [c]	0.91 (0.72, 1.16)	0.46	0.89 (0.62, 1.30)	0.56
Waist-height ratio > 0.5	0.91 (0.69, 1.20)	0.51	0.90 (0.59, 1.38)	0.63
TV viewing				
≤ 1 h/day	1 (Reference)	-	1 (Reference)	-
> 1 to 3 h/day	1.48 (1.11, 1.97)	0.007	1.38 (0.84, 2.25)	0.2
> 3 h/day	1.59 (1.25, 2.02)	0.0001	2.09 (1.41, 3.09)	0.0003
Sleep duration				
Short sleeper (< 7 h/day)	1.13 (0.91, 1.41)	0.27	1.02 (0.72, 1.46)	0.89
Normal (7-9 h/day)	1 (Reference)	-	1 (Reference)	-
Long sleeper (> 9 h/day)	0.84 (0.53, 1.35)	0.48	0.81 (0.36, 1.85)	0.62
Smoking				
Never	1 (Reference)	-	1 (Reference)	-
Former	0.95 (0.76, 1.19)	0.68	1.18 (0.82, 1.70)	0.36
Current	0.91 (0.69, 1.21)	0.53	0.94 (0.61, 1.44)	0.76
Weekly alcohol intake <14 units	0.98 (0.77, 1.25)	0.87	1.01 (0.68, 1.49)	0.97
Processed meat intake				
Never or less than once a week	1 (Reference)	-	1 (Reference)	-
Once a week	0.88 (0.69, 1.14)	0.34	0.88 (0.59, 1.33)	0.56
More than once a week	0.82 (0.64, 1.06)	0.13	0.75 (0.50, 1.13)	0.16
Oily fish intake				
Never or less than once a week	0.96 (0.73, 1.25)	0.75	0.95 (0.62, 1.48)	0.84
Once a week	0.92 (0.70, 1.20)	0.53	0.99 (0.63, 1.54)	0.96
More than once a week	1 (Reference)	-	1 (Reference)	-
Red meat intake				
≤ 1.5 portions/week	1 (Reference)	-	1 (Reference)	-
> 1.5 to 2 portions/week	1.06 (0.79, 1.40)	0.71	0.97 (0.60, 1.57)	0.89
> 2 portions/week	0.92 (0.74, 1.15)	0.47	0.91 (0.64, 1.29)	0.61
Fruit and vegetable intake				
≤ 3 portions/week	0.90 (0.71, 1.14)	0.4	0.95 (0.65, 1.39)	0.78
> 3 to 4.7 portions/week	0.93 (0.72, 1.20)	0.57	1.00 (0.66, 1.51)	1
> 4.7 portions/week	1 (Reference)	-	1 (Reference)	-

Data presented are HR with 95% CI. Analyses adjusted for age, ethnicity, deprivation index, month of assessment, height, medication for CVD (except for prevalent conditions at recruitment), prevalent comorbidity at recruitment.

[a] Prevalent condition at recruitments were self-reported clinician diagnosis

[b] Underweight: BMI < 18.5; Normal: 18.5–<25; Overweight: 25–<30; Obese: ≥30

[c] Central obesity: waist-hip ratio >85 cm for female and 90 cm for male

Lifestyle factors and HF risk

For physical activity, fitness and grip strength, HF incidence and mortality were higher for those individuals in the lowest quartile (the most inactive, unfit and the lowest strength) compared to the reference category (the highest quartile) for women and men (Figures 1 and 2), respectively, as expected. However, the association between physical activity and HF mortality in men, was not significant (Supplementary Table 1).

Higher levels of TV-viewing had a more deleterious association with risk in women compared to men (Table 2). The risk associated with being a smoker was higher for HF mortality than HF incidence, for women and men, respectively. For sleep duration, being a short sleeper (<7 h/day) and long sleeper (>9 h/day) were associated with a higher risk of HF incidence compared to a normal sleeper (7-9 h/day). The association between HF outcomes and alcohol consumption showed that men and women who reported a weekly intake ≤14 units of alcohol had a lower risk of HF incidence and mortality, with similar risk between women and men. There was evidence of excess risk of HF incidence and mortality in women compared to men for those reporting high levels of TV-viewing (>3 h/day) and low levels of physical activity (Table 2). A two-year landmark analysis has shown consistent results as the main analysis.

DISCUSSION

The current study has demonstrated that a wide range of physical and lifestyle factors are associated with HF incidence and mortality, and generally these associations do not differ by sex, except for some modifiable life-style factors which carry higher risk in woman compared with men. This means that screening for HF risk and intervention in those at high risk can be uniform between men and women, although vigilance may be warranted in women who have diabetes, high cholesterol, low physical activity and high sedentary behaviours, as these were stronger risk factors in women. Several studies have demonstrated the association of physical and lifestyle factors with HF incidence and mortality, and the current findings are in broad agreement with these [7]. Meyer et al conducted a sub-analysis of the participants in the PREVEND study, looking at incidence and epidemiology of new onset HF in ~8500 middle-aged adults [11]. Similar to our analysis, they concluded that obesity, hypertension, previous MI, atrial fibrillation, diabetes mellitus, and hypercholesterolemia were significantly associated with new onset HF in both genders. Their analysis differed thereafter, as they looked at HF with and without preserved ejection fraction as the outcomes. They analysed biomarkers as novel risk factors, in contrast to the novel physical risk factors we analysed. They concluded, as has previously been published, that women were more likely to develop HF with HFpEF, which may be due to differing underlying pathophysiology from those with HFrEF; which we are unable to comment on in this current study.

When looking at associations with dietary intake it has been shown that a higher diet score based on intake of fruits, vegetables, whole grains, fish, nuts/seeds, red and processed meats, sugar-sweetened beverages, trans fat, sodium and the polyunsaturated to saturated fat ratio, was associated with lower HF incidence [9]. The same authors also investigated associations of Dietary Approaches to Stop Hypertension (DASH), Alternative Healthy Eating Index (AHEI) and American Heart Association (AHA) 2020 dietary goals diet scores with HF incidence with similar findings. Furthermore, Pandey and colleagues have demonstrated a linear, dose-response negative association between physical activity levels and HF incidence [16]. Similarly, it has been previously shown that

cardiorespiratory fitness and grip strength have an inverse relationship with HF incidence [8,17]. Sedentary behaviours, such as time spent watching TV, have previously been found to be associated with CVD mortality, independently of physical activity levels [18–20] and Young et al have extended these findings to show that high sedentary time was associated with increased risk of HR incidence in males only [21]. The current paper agrees with these, and extends them, to also look at HF mortality and importantly to investigate whether the associations are consistent between men and women. A recent study investigating risk of myocardial infarction found higher HR for systolic blood pressure, hypertension, and smoking status/intensity in women compared to men, [22] highlighting sex differences in associations with other CVDs. Furthermore, previous work has indicated that women with a higher BMI and who have hypertension or diabetes are more likely to develop HF than men [10]. We have shown that for the majority of factors there was little difference in the HR for either HF incidence or mortality between men and women. We did, however, find that in women with diabetes, high cholesterol, high TV viewing, and low physical activity were associated with a higher hazard ratio for HF incidence and mortality compared to men. This may indicate that increasing physical activity, and improving sleep and reducing sedentary behaviours may offer more benefit in women compared to men to lower their HF risks. Further work is clearly needed to confirm these associations. It is also notable that others have shown sex differences in the associations of T2DM with CVD in general [23] with emerging evidence for T1DM [24], lending external validity to our findings. With respect to cholesterol, we have previously shown that statins lower HF risk in a meta-analysis of randomised trials [25] and it may be women, who receive less statins generally, are exposed to greater HF risk as a result of this. However, this remains speculative and requires formal examination.

UK Biobank aimed to be representative of the general population in terms of age, sex, ethnicity and socioeconomic status but is unrepresentative in terms of lifestyle, with participants less likely to be obese and have lower disease frequency – indicative of a "healthy volunteer" selection bias [26]. Therefore, caution should be heeded in generalizing summary statistics to the general population. Our study benefited from a very large number of participants, recruited from the general population, across the whole of the UK, which allowed us to investigate sex differences in the current analyses. Reverse causality is possible in any observational study; and whilst our results were similar after a landmark analysis of events occurring from 2 years after recruitment, we cannot exclude the potential of reverse causality in the current study. We also acknowledge we do not have information on different types of HF, including HFpEF or HFrEF, which would have been informative. It should be noted that there are multiple tests conducted in this study, and the number of false positives may be disproportionally inflated. On the other hand, given the relatively small number of events, some of analysis may be underpowered and resulting in the lack of statistical significance.

In conclusion the current study has demonstrated that a broad range of physical and lifestyle factors are associated with HF incidence and mortality. We have extended previous work by demonstrating that whilst the risk was broadly similar between men and women, diabetes, high cholesterol, physical activity, TV viewing and sleep show significant differences in HF risk between the sexes. The early identification of women at risk of HF could be mediated by focusing on these modifiable lifestyle risk factors in particular. They may be useful measurements used in conjunction with traditional methods to more specifically risk stratify patients in the clinical setting. The relevance of these findings to differentiate HF characteristics by sex and future outcomes, needs further established.

Acknowledgments

We are grateful to UK Biobank participants. This research has been conducted using the UK Biobank resource under application number 7155.

Footnotes

Contributors Study conception: AS, FH, SG and CCM. Study design, analysis and drafting: AS, FH, SG and CCM. All authors contributed to interpretation of data and critical revision of the content of the work.

Competing interests: None to declare.

Patient consent: Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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Figure legends

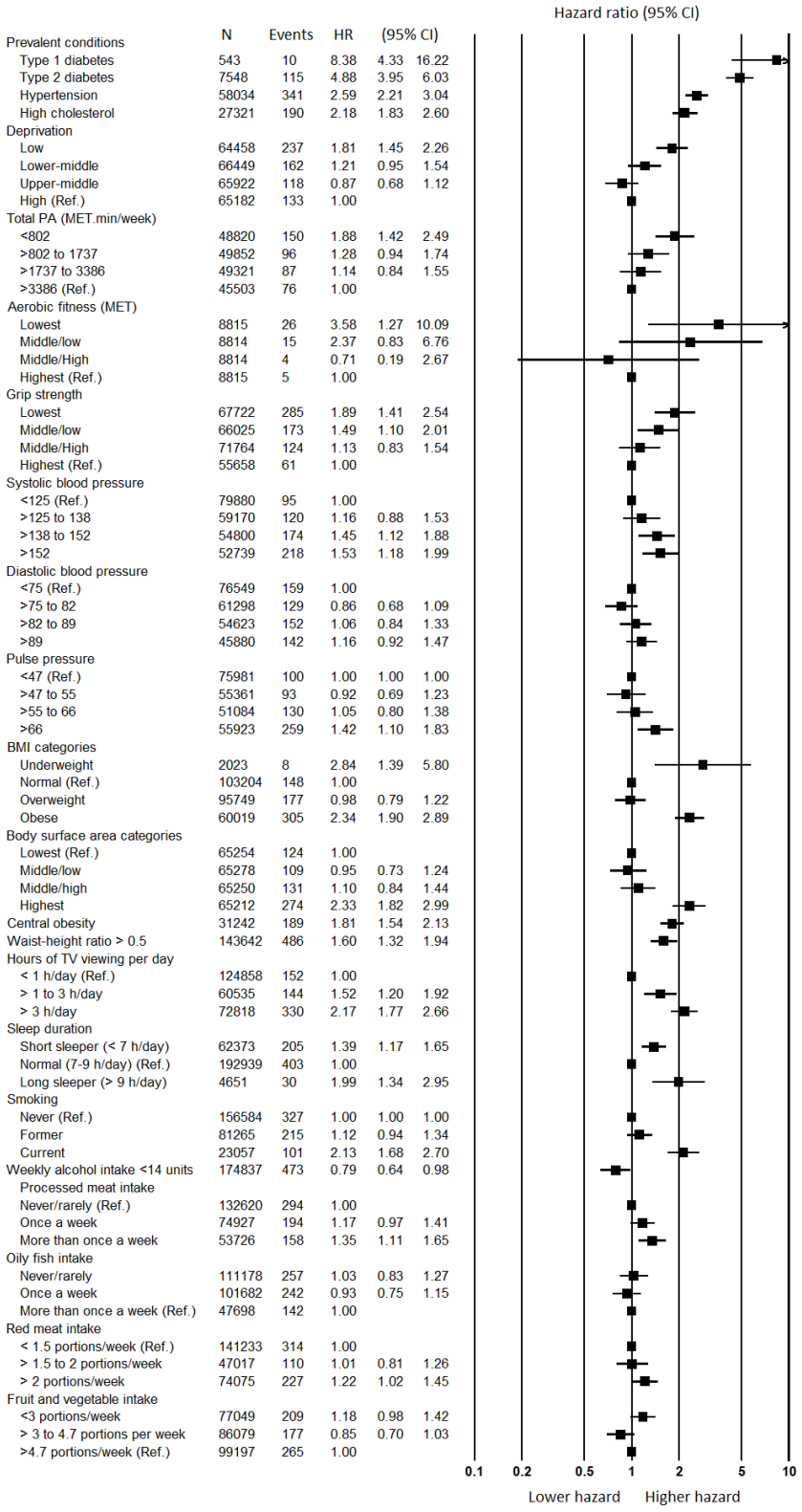

Figure 1. Risk factors for heart failure incidence in women

Data presented as hazard ratio and their 95% CI. Adjusted for age, ethnicity, deprivation index, month of assessment, height, medication for CVD (except for prevalent conditions at recruitment), prevalent comorbidity score at recruitment.

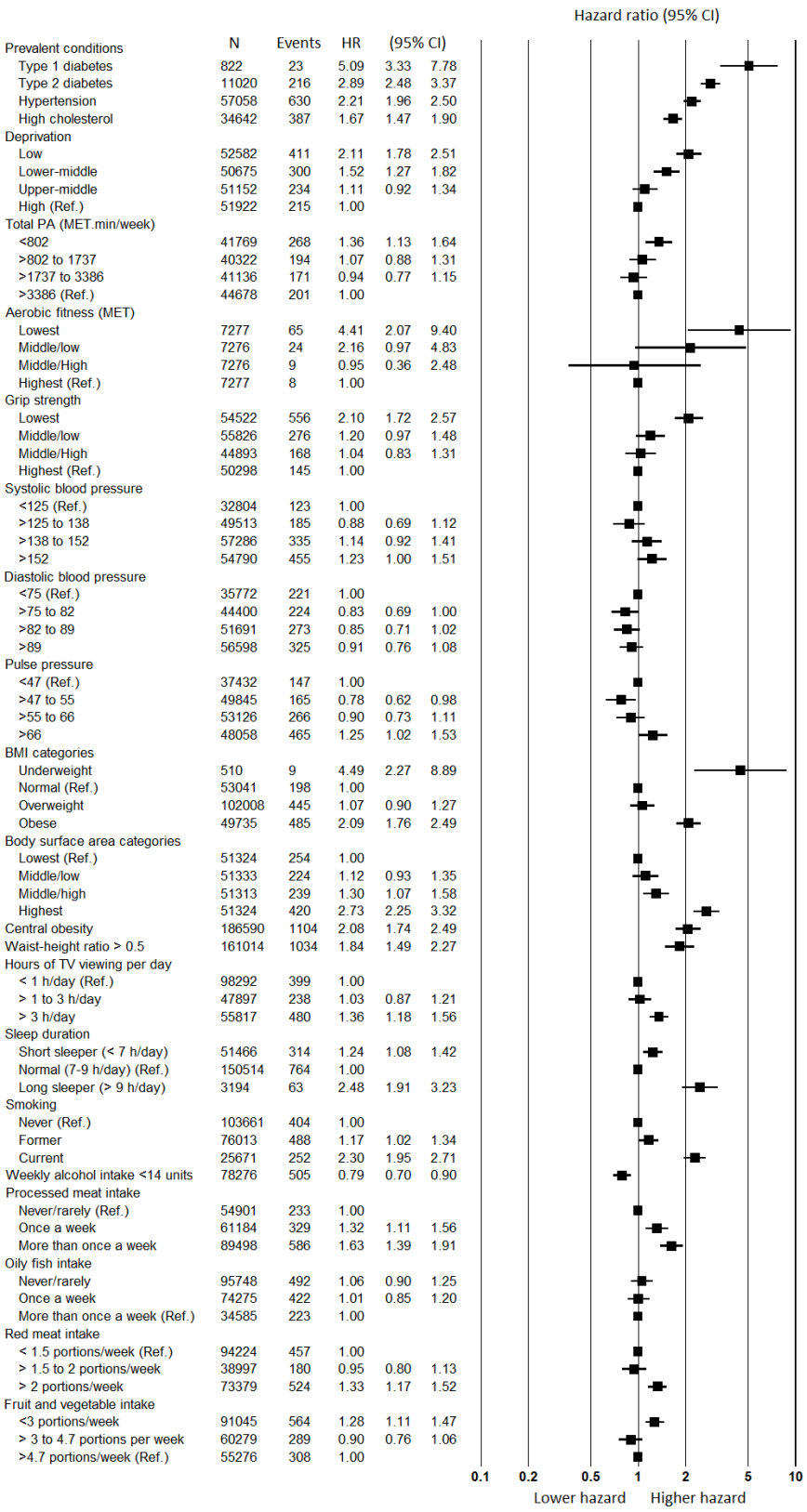

Figure 2. Risk factors for heart failure incidence in men

Data presented as hazard ratio and their 95% CI. Adjusted for age, ethnicity, deprivation index, month of assessment, height, medication for CVD (except for prevalent conditions at recruitment), prevalent comorbidity score at recruitment. *Fitness has insufficient number of events to perform the analyses for mortality in women.

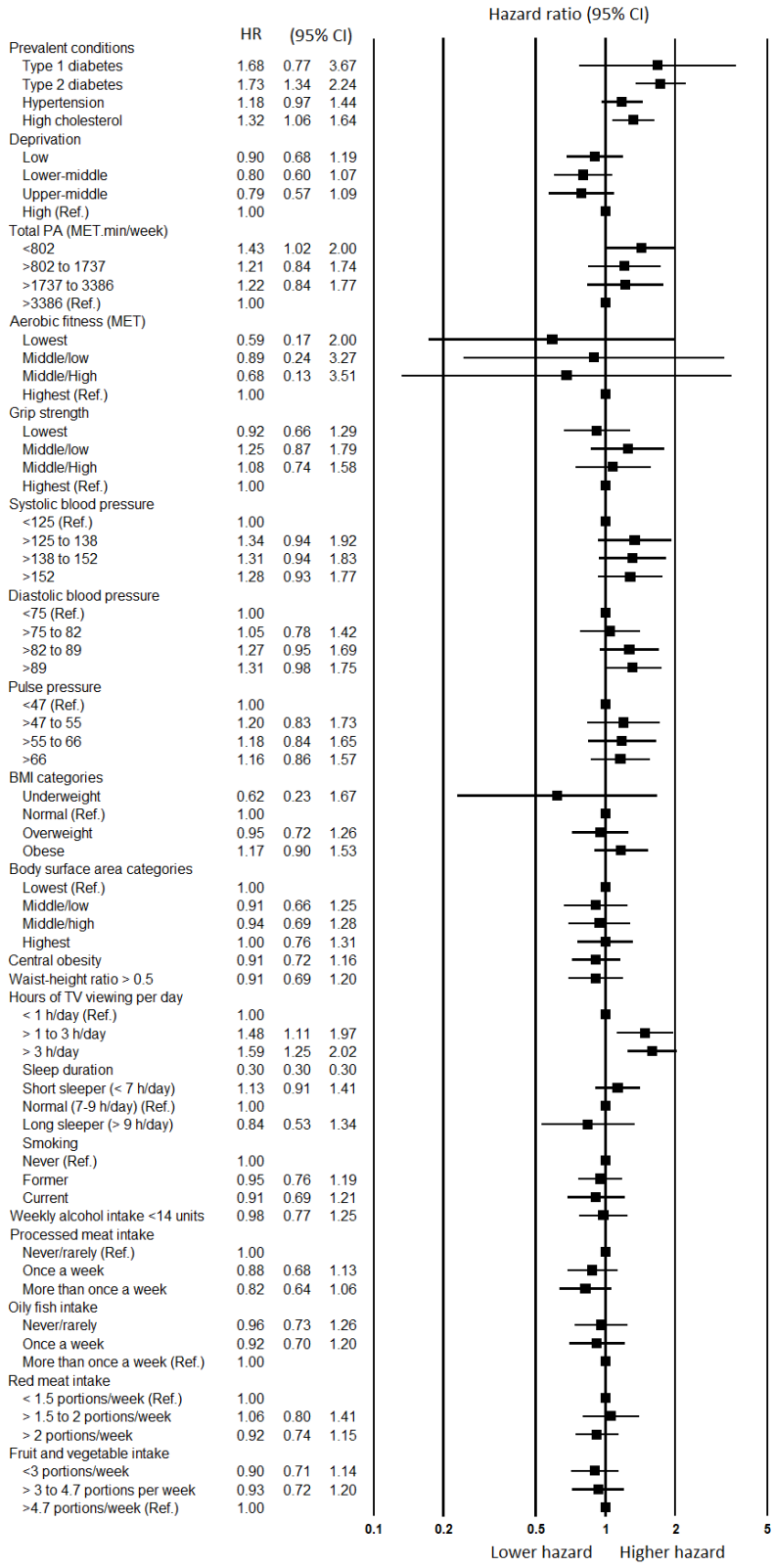

Figure 3. Women-to-men HR ratio on heart failure incidence.

Data presented as ratio of the hazard ratio of women-to-men, and their 95% CI. Adjusted for age, ethnicity, deprivation index, month of assessment, height, medication for CVD (except for prevalent conditions at recruitment), prevalent comorbidity score at recruitment. I hazard ratio above 1 suggest a higher risk in women compare to men, whereas a hazard ratio below 1 suggest a higher risk in men compare to women.