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Modifiable risk factors predict incident atrial fibrillation and heart failure

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ABSTRACT

Objective Heart failure (HF) frequently complicates atrial fibrillation (AF) and significantly increases mortality risk. Limited data exist on the modifiable risk factors associated with development of HF in AF patients.

Methods We examined two large, prospective, population-based cohorts without prior AF or HF at baseline: Malmö Preventive Project (MPP, n=32 625) and Malmö Diet and Cancer Study (MDCS, n=27 695). Using Lunn-McNeil competing risks, multivariable Cox models were constructed to determine hazard ratios (HR) and 95% confidence intervals (CI) of risk factors for incident HF with AF, and AF alone.

Results Mean follow-up in MPP and MDCS was 27.6±8.4 and 17.7±5.3 years. In MPP, body mass index (HR 1.11, 95% CI 1.09 to 1.13 vs HR 1.05, 95% CI 1.04 to 1.06 per kg/m^2), systolic blood pressure (HR 1.20, 95% CI 1.24 to 1.26 vs HR 1.08, 95% CI 1.06 to 1.10 per 10 mm Hg) and current cigarette smoking (HR 1.73, 95% CI 1.54 to 1.95 vs HR 1.23, 95% CI 1.15 to 1.32) had stronger associations with incident AF with HF compared with AF alone (all p for difference <0.0001). Similar results were observed in MDCS (all p for difference <0.009). These three risk factors and diabetes accounted for 51.8% and 54.1% of the population attributable risk (PAR) for AF with HF in MPP and MDCS, respectively, compared with 20.1% and 27.0% for AF alone.

Conclusions Obesity, hypertension and active smoking preferentially associated with AF with HF, compared with AF alone, and accounted for >50% of the PAR. Randomised trials are needed to assess whether risk factor modification can reduce the incidence of AF with HF and reduce mortality.

Key questions

What is already known about this subject?

► Heart failure (HF) is a common complication in patients with atrial fibrillation (AF), and when both conditions occur together, there is a significant increase in the risk of mortality. Limited data exist on the modifiable risk factors associated with the development of HF in patients with AF.

What does this study add?

► Hypertension, obesity and current smoking were more strongly associated with the development of AF and HF compared with AF alone. The three risk factors and diabetes accounted for >50% of the population attributable risk of AF and HF. The present study is the largest to date examining the modifiable risk factors associated with the development of the combination of AF and HF.

How might this impact on clinical practice?

► Clinical trials are needed to assess whether risk factor modification can reduce the risk of HF in patients with AF, and subsequently reduce mortality.

INTRODUCTION

Heart failure (HF) represents one of the cardiovascular epidemics of the 21st century and is a global public health problem.[1] The prevalence of HF is increasing and the condition is associated with increased morbidity, mortality and high costs of care.[2 3] Despite significant improvements in the care of HF patients in the last two decades, their outcomes remain poor with mortality rates of 50% at 5 years, rivalling many cancers.[2] Given the significant and persistent poor outcomes associated with HF, increased efforts at identifying and increasing our understanding of modifiable risk factors predisposing to HF require emphasis, as such knowledge may lead to development of novel preventive and management strategies.

Atrial fibrillation (AF) represents the most common arrhythmia, is highly prevalent in patients with HF and is also a major cause of morbidity and mortality.[4–7] AF and HF are intimately related in terms of pathophysiology; both conditions predispose to each other, and have many shared risk factors.[6] When AF and HF occur together, the risk of mortality increases two to three fold, irrespective of their temporal occurrence.[5 6 8] Furthermore, therapies known to improve adverse outcomes in HF patients do not appear to carry over to patients with both HF and AF.[9] Given the strong link between HF and AF, and the poor outcomes associated with the development of both conditions, focus on preventing the occurrence of the combination of both AF and HF may thus present an important strategy to improve clinical outcomes.

In order to identify the modifiable risk factors predisposing to both AF and HF and their prognostic significance, we analysed data from the Malmö Preventive Project (MPP)[10] and Malmö Diet and Cancer Study (MDCS),[11] two large population-based, longitudinal prospective cohort studies. We hypothesised that a considerable proportion of the risk of developing both AF and HF can be explained by modifiable risk factors, and that these factors may represent important preventative targets.

METHODS

Study populations

The MPP and MDCS cohorts have been previously described.[10 11] MPP is composed of 33 346 individuals (67% men, mean age 45.7 years) from the city of Malmö, Sweden, who participated in a screening programme to identify individuals at high risk for cardiovascular events. Recruitment was through invitation of full prespecified age-cohorts and attendance rate was >70%. Men were screened during 1974 to 1982 and women between 1982 and 1992.[10] For the purposes of this analysis, we excluded subjects with prevalent AF (n=44), HF (n=8) or missing data for systolic blood pressure (SBP, n=36), height (n=4), weight (n=2) or smoking status (n=627). Final study population consisted of 22 382 men and 10 243 women. MDCS consists of 28 098 individuals from Malmö (39% men, mean age 58.2 years) who participated in baseline examination during 1991 to 1996. Men born between 1923 and 1945 and women born between 1923 and 1950 were invited to participate.[11] The attendance rate was around ~40%. For this analysis, we excluded subjects with prevalent AF (n=268), prevalent HF (n=52) or missing data for SBP (n=42), height (n=28), weight (n=1) or smoking status (n=12). Final study population consisted of 10 832 men and 16 863 women.

Data collection

Height and weight were measured standing in light indoor clothes using a fixed stadiometer and a balance beam scale. Body mass index (BMI) was calculated as kg/m^2. Blood pressure was measured twice after 10 min of supine rest. Blood samples were drawn after overnight rest and analysed using standard laboratory procedures at the Department of Clinical Chemistry at Malmö University Hospital. Current smoking was defined as self-reported smoking at the time of screening. Sedentary lifestyle was defined as a positive answer to the question 'Are you mostly sedentary in your spare time?' in MPP and as the lowest sex-specific quartile of a previously described modification of the Minnesota Leisure Time Physical Activity Questionnaire in the MDCS.[12] In MPP, alcohol use was defined as risk use in subjects with two or more positive answers to a modification of the Michigan Alcohol Screening test (Mm-Mast),[13] and in MDCS, alcohol use was defined in terms of g/day consumption derived from a self-reported dietary questionnaire. Low socioeconomic index was defined as Statistics Sweden group 11 to 36 in the MPP and as 9 years of schooling or less in the MDCS.

Endpoint retrieval and national registries

The endpoints of this analysis were incident AF and HF, diagnosed in a hospital setting and retrieved from the Swedish Registers for inpatients and outpatients, administered by the Swedish National Board of Health and Welfare. All Swedish residents are included in these registers and therefore there was no missing data at the time of registry linkage. The inpatient register has been in use in the south of Sweden during the entire follow-up and became nation-wide in 1987. The outpatient register became operational in 2000. Incident AF was defined as diagnosis codes 427.92 (InternationalClassification of Diseases (ICD)-8), 427D (ICD-9) and I48 (ICD-10). The AF diagnosis has recently been validated and found to be of high quality (95% accurate).[14] AF and atrial flutter have not been distinguished due to similarities of these diagnoses. HF was defined as a primary diagnosis with codes 428 (ICD-9) or I.11 (ICD-9). The HF register diagnosis has also been validated and is >95% accurate.[15] Patients who had AF without HF were defined as those individuals with incident AF during follow-up who did not experience an HF diagnosis. Patients who had AF with HF were defined as individuals with incident AF during follow-up and whose AF diagnosis was either preceded or followed by an HF diagnosis.

Statistical analyses

Analyses were performed using Stata for Macintosh (V.15.1. Stata Corporation, College Station, Texas). In order to evaluate mortality across categories of AF and HF, we calculated incidence rates for mortality across four groups: AF without prevalent HF, AF with prevalent HF, HF without prevalent AF and HF with prevalent AF. Sex-adjusted and age-adjusted incidence rates were calculated from the time of first diagnosis of AF or HF, whichever occurred first, using 10-year age strata with weights derived from the total number of corresponding AF or HF cases. HRs were calculated using a competing risks approach in stratified Cox regression described by Lunn and McNeil[16] as previously described, which allow for separate estimations of the relative hazard between covariates and each outcome (AF without HF vs AF with HF) under a proportional hazards assumption.[17] Briefly, the method involves duplication of the data set so that each subject occurs in two strata. The failures were separated by strata, with AF without HF occurring only in one strata and AF with HF only in the other, and the covariates duplicated resulting in separate but identical variables in each stratum that are assigned the value of 0 in the other stratum. A stratified Cox regression analysis was performed, by failure stratum, which produces cause specific HRs for each failure. After this, for each covariate, another stratified Cox regression was performed, with a single covariate included as an unduplicated variable.

This forces the model to give the same effect estimate for the unduplicated variable in both strata. This model was then compared with the model where effect sizes were allowed to be different over strata using the likelihood ratio test. P values for difference in effect sizes are thus derived from the likelihood ratio test. The same multivariable model, including age, sex, height, BMI, systolic blood pressure, current smoking, prevalent coronary events and prevalent diabetes, was used in both cohorts. These variables were prespecified, with the intention to include the most important modifiable risk factors for AF available in both cohorts.[11] Continuous variables were assessed for normality and non-normal variables (alcohol use in the MDCS) were log transformed before inclusion in the model, after adding the small constant 1. Patients were censored at the first diagnosis of AF for the outcome of AF without HF, at the first diagnosis of either AF or HF for the outcome of AF with HF, and all other subjects were censored at death, emigration from Sweden or end of follow-up (31 December 2013 in the MPP and 31 December 2014 in the MDCS). To assess the competing risk of death on results, we conducted a competing risks regression as described by Fine and Gray, with each endpoint modelled separately. In order to assess whether the risk factor profile for the combination of AF and HF differed by whether AF or HF occurred first, we also conducted a sensitivity analysis excluding cases of AF with HF when the HF diagnosis occurred before the AF event. Finally, as there was some missing data for alcohol use and sedentary lifestyle, these covariates were therefore also examined in sensitivity analyses.

Population attributable risks (PAR) for modifiable risk factors were calculated using failure-specific endpoints, with the Stata plug-in punafcc, and under the assumption of a causal relationship.[18] The model included age, sex, height, current smoking, systolic blood pressure >140 mm Hg, BMI >25 kg/m^2, prevalent diabetes and known prevalent coronary events. For the PAR calculations, the modifiable predictors of interest were dichotomised to be either present or absent. The PAR's derived from this model represent a comparison between the observed data and hypothetical scenarios without either smoking, systolic blood pressure >140 mm Hg, BMI >25 kg/m^2, prevalent diabetes or known prevalent coronary events, with all other factors remaining equal.

RESULTS

Baseline characteristics are reported in table 1. Briefly, the MPP cohort had a younger mean age at baseline screening and a greater proportion of male participants than MDCS. Mean follow-up (SD) was 27.6 (8.4) years in MPP and 17.7 (5.3) years in MDCS. There were 3277 incident cases of AF without HF (cumulative incidence 10.0%) in MPP and 3167 cases (cumulative incidence 11.4%) in MDCS. There were 1153 cases of AF with HF in MPP (cumulative incidence 3.5%) and 890 cases (cumulative incidence 3.2%) in MDCS. Among those with AF and HF, the diagnosis of AF preceded HF diagnosis in 622 cases (53.9%) in MPP and 537 cases in MDCS (60.3%), and was concurrent in 213 cases (18.5%) in MPP and 146 cases in MDCS (16.4%). Age and gender adjusted incidence rates for mortality are depicted in table 2. AF subjects with prevalent HF had a higher adjusted incidence rate for mortality compared with patients with AF or HF alone.

Results from the multivariable stratified Cox regression model with p values for difference in effect estimates between the AF with HF and AF without HF groups are reported in table 3. In both cohorts elevated BMI, elevated systolic blood pressure and current smoking independently predicted both AF without HF, and AF with HF. However, the effect estimates for these variables were significantly and substantially higher for AF with HF, compared with AF alone. BMI >25 kg/m^2, systolic blood pressure >140 mm Hg and current cigarette smoking were associated with a greater risk of developing AF with HF in both MPP (HR 1.80, 95% CI 1.59 to 2.03; HR 1.71, 95% CI 1.51 to 1.95; HR 1.73, 95% CI 1.54 to 1.95, respectively) and MDCS cohorts (HR 1.63, 95% CI 1.41 to 1.89; HR 1.48, 95% CI 1.27 to 1.73; HR 1.67, 95% CI 1.43 to 1.94, respectively). Prevalent diabetes was associated with an increased risk of AF with HF in MDCS (HR 1.78, 95% CI 1.43 to 2.22), a finding that was borderline significant in MPP (HR 1.29, 95% CI 0.99 to 1.66). Prevalent coronary events were associated with a greater risk of AF with HF in MDCS, but was similarly associated with AF without HF in MPP. In sensitivity analysis, we observed similar results when study participants who developed HF prior to AF were excluded from the analysis (online supplementary table 1).

A competing risks analysis was performed in order to assess the effect of death as a competing risk (table 4) and similar results were observed. We additionally tested whether the inclusion of alcohol use, sedentary lifestyle and low socioeconomic index influenced the results, by including these variables in the Lunn-McNeil model (online supplementary table 2), and found that inclusion of these variables did not influence the results substantially.

The population attributable risk of AF with HF due to obesity, systolic hypertension and current cigarette smoking can be seen in table 5. The combination of BMI ≥25 kg/m^2, systolic blood pressure ≥140 mm Hg and active cigarette smoking accounted for 51.3% (95% CI 47.4 to 54.9) and 52.9 (95% CI 46.3 to 58.7) of the population attributable risk of AF with HF in the MPP and MDCS cohorts, respectively. Similar results were obtained when results were stratified by sex (table 5).

DISCUSSION

In this prospective analysis of the modifiable risk factors associated with development of the combination of AF and HF, in two large, population-based, longitudinal cohorts free of AF and HF at baseline, we have identified several

Table 1 Baseline characteristics by incident event status

	MPP			MDCS		
	Full population (n=32 625)	AF without HF (n=3277)	AF with HF* (n=1153)	Full population (n=27 695)	AF without HF (n=3167)	AF with HF* (n=890)
Age, years	45.5 (7.4)	47.4 (6.3)	48.6 (5.9)	58.1 (7.6)	61.5 (7.1)	63.6 (6.3)
Follow-up time, years	29.8 (23.5–33.8)	26.2 (20.7–30.6)	23.4 (17.0–28.4)	19.8 (18.0–21.4)	19.9 (18.0–21.6)	14.8 (10.1–18.2)
Time to AF diagnosis, years	25.8 (20.2–30.2)	26.2 (20.7–30.6)	24.5 (18.7–29.3)	14.1 (9.7–14.5)	14.3 (10.0–17.8)	12.8 (8.4–16.6)
Age at AF diagnosis, years	73.4 (66.8–78.5)	73.5 (66.8–78.6)	73.2 (66.8–78.3)	75.8 (69.9–81.2)	75.5 (69.5–81.1)	76.4 (71.0–81.3)
Survival after AF, years	4.2 (1.4–8.6)	4.2 (1.3–8.6)	4.6 (1.5–8.6)	4.2 (1.6–8.1)	4.1 (1.5–8.1)	4.6 (1.7–8.3)
Female sex, %	31.4	28.0	23.2	60.9	50.5	44.2
Height, cm	173 (9)	175 (9)	174 (8)	169 (9)	170 (9)	171 (9)
BMI, kg/m^2	24.6 (3.6)	25.1 (3.8)	26.3 (4.2)	25.7 (4.0)	26.6 (4.1)	27.5 (4.4)
BMI >25 kg/m^2, %	39.5	46.0	58.4	52.7	61.6	69.3
SBP, mm Hg	126 (16)	129 (16)	133 (17)	141 (20)	147 (20)	152 (20)
SBP >140 mm Hg, %	12.5	15.5	24.8	43.0	55.5	66.6
FBG, mmol/L†	4.9 (0.7)	4.9 (0.7)	4.9 (0.8)	4.9 (0.7)	5.0 (0.8)	5.1 (0.9)
Current smoking status, %	45.4	42.4	49.0	28.3	22.8	27.5
Sedentary lifestyle, %	55.2	52.2	53.7	25.0	24.3	27.6
Alcohol risk use, %	27.0	26.8	29.6			
Alcohol, g/day†				7.2 (13.7)	7.6 (14.2)	7.5 (14.2)
Prevalent diabetes	3.4	2.8	5.6	4.3	4.5	10.2
Prevalent coronary event	0.4	0.5	1.2	1.9	2.8	8.0

Values are mean (SD) or median (IQR), unless stated otherwise. Follow-up time in MPP and MDCS was 27.6 (8.4) and 17.7 (5.3) years, respectively.
*Includes subjects with HF before AF.
†Presented as median and IQR.
.AF, atrial fibrillation; BMI, body mass index; FBG, fasting blood glucose; HF, heart failure; MDCS, Malmö Diet and Cancer Study; MPP, Malmö Preventive Project; SBP, systolic blood pressure.

important findings. First, among patients who developed both AF and HF, AF appeared to more frequently precede the occurrence of HF. Second, elevated BMI, systolic blood pressure ≥140 mm Hg and active smoking were stronger predictors of AF with HF, than AF alone; a finding which persisted after sensitivity analysis. Third, these modifiable

Table 2 Incidence rates (95% CI) for mortality, per 1000 person-years

	HF without prevalent AF*	HF with prevalent AF†	AF without prevalent HF‡	AF with prevalent HF§
MPP				
Unadjusted	160 (150–170)	188 (170–207)	68 (65–71)	202 (176–231)
Adjusted¶	209 (192–226)	200 (178–221)	95 (90–100)	214 (183–246)
MDCS				
Unadjusted	164 (150–178)	204 (183–228)	70 (67–74)	235 (199–278)
Adjusted¶	220 (197–242)	230(200-260)	91 (85–96)	423 (56–790)

*Based on 1324 individuals and 942 deaths in the MPP and 814 individuals and 541 deaths in the MDCS.
†Based on 622 individuals, and 384 deaths in the MPP and 537 individuals and 318 deaths in the MDCS.
‡Based on 3899 individuals and 1668 deaths in the MPP and 3704 individuals and 1449 deaths in the MDCS.
§Based on 318 individuals and 202 deaths in the MPP and 207 individuals and 135 deaths in the MDCS.
¶Adjusted for sex and age at the time of diagnosis of AF and HF respectively, in 10-year age bands.
AF, atrial fibrillation; HF, heart failure; MDCS, Malmö Diet and Cancer Study; MPP, Malmö Preventive Project.

Table 3 HRs for incident AF with or without heart failure

	MPP cohort*							MDCS cohort†						
	AF without HF			AF with HF				AF without HF			AF with HF			
	HR	95% CI	P value	HR	95% CI	P value	P for difference	HR	95% CI	P value	HR	95% CI	P value	P for difference
Age, years	1.09	1.09 to 1.10	<0.0001	1.12	1.11 to 1.13	<0.0001	0.0005	1.09	1.09 to 1.10	<0.0001	1.13	1.12 to 1.14	<0.0001	<0.0001
Female sex	1.46	1.30 to 1.63	<0.0001	0.67	0.55 to 0.81	<0.0001	<0.0001	1.02	0.92 to 1.13	0.71	0.86	0.73 to 1.08	0.23	0.22
Height, per cm	1.02	1.01 to 1.03	<0.0001	1.04	1.04 to 1.06	<0.0001	0.0001	1.04	1.03 to 1.05	<0.0001	1.04	1.03 to 1.04	<0.0001	0.71
BMI, per kg/m^2	1.05	1.04 to 1.06	<0.0001	1.11	1.09 to 1.13	<0.0001	<0.0001	1.05	1.04 to 1.06	<0.0001	1.10	1.08 to 1.12	<0.0001	<0.0001
SBP, per 10 mm Hg	1.08	1.06 to 1.10	<0.0001	1.20	1.16 to 1.24	<0.0001	<0.0001	1.07	1.05 to 1.09	<0.0001	1.13	1.09 to 1.16	<0.0001	0.009
Current smoking	1.23	1.15 to 1.32	<0.0001	1.73	1.54 to 1.95	<0.0001	<0.0001	1.09	1.00 to 1.18	0.05	1.67	1.43 to 1.94	<0.0001	<0.0001
Prevalent coronary event	2.87	1.75 to 4.69	<0.0001	5.29	3.11 to 8.99	<0.0001	0.10	1.47	1.19 to 1.81	<0.0001	3.23	2.51 to 4.14	<0.0001	<0.0001
Prevalent diabetes	0.90	0.73 to 1.12	0.35	1.29	0.99 to 1.66	0.06	0.04	0.95	0.80 to 1.12	0.53	1.78	1.43 to 2.22	<0.0001	<0.0001

*Includes 32 624 subjects, 3277 AF events without heart failure and 1153 AF events with heart failure (AF before HF n=622, concurrent (same day) n=213, HF before AF n=318).
†Includes 27 694 subjects, 3167 AF events without heart failure and 890 AF events with heart failure (AF before HF n=513, concurrent (same day) n=146, HF before AF n=197).
AF, atrial fibrillation; BMI, body mass index; HF, heart failure; MDCS, Malmö Diet and Cancer Study; MPP, Malmö Preventive Project; SBP, systolic blood pressure.

Table 4 Competing risks models for incident AF with and without heart failure

	MPP cohort*						MDCS cohort†					
	AF without HF			AF with HF			AF without HF			AF with HF		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
Age, years	1.08	1.08 to 1.09	<0.0001	1.11	1.10 to 1.12	<0.0001	1.08	1.08 to 1.09	<0.0001	1.12	1.11 to 1.13	<0.0001
Female, sex	0.86	0.77 to 0.96	0.009	0.42	0.35 to 0.52	<0.0001	0.99	0.89 to 1.10	0.83	0.86	0.70 to 1.06	0.16
Height, per cm	1.04	1.04 to 1.05	<0.0001	1.02	1.01 to 1.03	<0.0001	1.04	1.03 to 1.04	<0.0001	1.04	1.03 to 1.05	<0.0001
BMI, per kg/m^2	1.05	1.03 to 1.06	<0.0001	1.11	1.09 to 1.12	<0.0001	1.05	1.04 to 1.06	<0.0001	1.10	1.08 to 1.11	<0.0001
SBP, per 10 mm Hg	1.08	1.06 to 1.11	<0.0001	1.20	1.16 to 1.24	<0.0001	1.06	1.04 to 1.08	<0.0001	1.12	1.08 to 1.16	<0.0001
Current smoking	1.21	1.13 to 1.30	<0.0001	1.71	1.52 to 1.93	<0.0001	1.07	0.98 to 1.16	0.13	1.67	1.44 to 1.94	<0.0001
Prevalent coronary event	2.87	1.71 to 4.83	<0.0001	5.09	2.93 to 8.88	<0.0001	1.40	1.12 to 1.74	<0.0001	3.20	2.48 to 4.15	<0.0001
Prevalent diabetes	0.86	0.70 to 1.06	0.16	1.28	0.98 to 1.66	0.07	0.95	0.80 to 1.12	0.53	1.82	1.43 to 2.27	<0.0001

*Includes 32 624 subjects, 3277 AF events without heart failure and 1153 AF events with heart failure (AF before HF n=622, concurrent (same day) n=213, HF before AF n=318).
†Includes 27 694 subjects, 3167 AF events without heart failure and 890 AF events with heart failure (AF before HF n=513, concurrent (same day) n=146, HF before AF n=197.
AF, atrial fibrillation; BMI, body mass index; HF, heart failure; MDCS, Malmö Diet and Cancer Study; MPP, Malmö Preventive Project; SBP, systolic blood pressure.

risk factors accounted for over 50% of the PAR for incident AF with HF. Similar PAR's were observed between men and women when we stratified our results by sex. Our findings suggest that risk factor modification may have significant implications in the reduction of both AF and HF.

In the present study, we report the largest analysis to date examining the modifiable risk factors associated with developing the combination of AF and HF. Studies of incident HF among patients with AF have focussed primarily on risk prediction and have thus examined the combination of both modifiable and non-modifiable risk factors.[19–21] Only one prior study has exclusively evaluated the modifiable risk factors associated with subsequent HF development in AF patients.[22] In a subcohort of 1495 female healthcare professionals with AF within the Women's Health Study, Chatterjee *et al* found that systolic blood pressure >120 mm Hg, BMI>30 kg/m^2, current tobacco smoking and diabetes were independent predictors of the development of HF after AF. In the present analysis, which examined a population-based cohort and included >5 fold the number of AF cases than the Women's Health Study, we hypothesised that it did not matter whether AF or HF occurred first, but that the occurrence of both conditions would be associated with worse outcomes. In this context, we similarly found that elevated blood pressure, elevated BMI and active cigarette smoking were preferentially associated with the subsequent development of the combination of AF and HF. Diabetes was a significant risk factor for AF with HF in the MDCS cohort, but borderline significant in the MPP cohort; a finding likely attributed to the low prevalence of diabetes in MPP at baseline. Our findings remained significant when we excluded the subset of patients who developed HF prior to AF. These baseline risk factors in a population initially free of both AF and HF could predict the subsequent development of the combination of AF with HF many years later speak to their importance and robustness. Overall, our results are in agreement with data reported from the Women's Health Study and extend these findings to their male counterparts.[22]

Obesity appeared to account for the largest proportion of the PAR for incident AF with HF. This is consistent with literature supporting an important role for obesity in the development of both AF and HF, individually. In the Women's Health Study, short-term elevations in BMI in the obesity range accounted for 18.3% of incident AF.[23] In addition, in the Framingham Heart Study, the population attributable risk for HF due to obesity was estimated to be 10.9% for men and 13.9% for women.[24] In the present study, a BMI >25 kg/m^2 accounted for 11.1% to 14.4% of the PAR of incident AF alone, and a staggering 27% of the risk of developing AF with HF. In light of the ongoing obesity epidemic worldwide, reducing obesity may thus have the greatest impact in reducing the combination of AF and HF, and randomised trials are needed to test this hypothesis. Systolic blood pressure >140 mm Hg also contributed to a large proportion of the PAR in this analysis, accounting for 17.0% to 27.5% of incident AF with HF, and consistent with results observed in the Women's Health Study.[22] A recent analysis of the SPRINT trial found that

Table 5 Estimated population attributable fractions (95% CI), for modifiable risk factors by heart failure status

	Atrial fibrillation without heart failure		Atrial fibrillation with heart failure	
	MPP	MDCS	MPP	MDCS
Full cohort				
BMI ≥25	10.4 (7.8–12.9)	13.6 (10.0–17.2)	26.9 (22.9–30.6)	26.3 (19.7–32.4)
Current smoking	6.7 (4.2–9.2)	1.2 (-0.7–3.0)	19.3 (15.8–22.8)	10.3 (7.7–12.9)
SBP ≥140	4.6 (2.9–6.3)	14.6 (10.6–18.6)	16.7 (14.1–19.2)	26.9 (19.1–34.0)
Prevalent diabetes at baseline	-0.09 (-0.6–0.5)	-0.1 (-0.9–0.7)	2.0 (1.1–2.9)	5.3 (4.2–6.3)
Total modifiable PAF	20.1 (16.6–23.6)	27.0 (22.2–31.4)	51.8 (48.0–55.3)	54.1 (47.7–59.8)
Men				
BMI ≥25	9.2 (6.0–12.3)	11.9 (5.8–17.6)	27.5 (22.8–31.8)	24.7 (14.4–33.8)
Current smoking	7.0 (3.7–10.1)	0.1 (-2.7–2.8)	19.7 (15.3–23.8)	14.1 (10.7–17.4)
SBP ≥140	4.7 (2.7–6.6)	15.3 (9.5–20.7)	16.2 (13.1–19.1)	31.8 (21.7–40.7)
Prevalent diabetes at baseline	-0.02 (-0.8–0.5)	-0.2 (-1.4–1.0)	2.5 (1.6–3.4)	4.7 (3.0–6.4)
Total modifiable PAF	19.3 (14.9–23.5)	25.2 (17.7–32.0)	52.1 (47.6–56.3)	57.8 (49.2–64.9)
Women				
BMI>25	12.5 (8.2–16.7)	14.3 (9.9–18.5)	26.4 (19.1–33.0)	27.1 (18.5–34.8)
Current smoking	6.4 (2.5–10.1)	2.1 (-0.3–4.6)	18.1 (12.3–23.5)	5.0 (0.6–9.2)
SBP ≥140	4.5 (1.0–7.8)	13.2 (7.5–18.6)	18.5 (13.3–23.3)	19.2 (6.0–30.5)
Prevalent diabetes at baseline	-0.02 (-1.3–1.2)	0.0 (-1.0–0.9)	0.3 (-2.4–2.8)	6.0 (4.7–7.3)
Total modifiable PAF	21.8 (15.7–27.5)	27.1 (20.8–32.9)	51.6 (44.2–58.0)	47.2 (36.2–56.3)

All PAFs estimated in a model adjusted for age, sex (where applicable), height, hypertension (SBP ≥140 mmHg), overweight (BMI ≥25 kg/m^2), current smoking, prevalent diabetes and history of coronary events. Total PAF differs from the sum of PAFs due to overlap between risk factors.
BMI, body mass index; MDCS, Malmö Diet and Cancer Study; MPP, Malmö Preventive Project; PAF, population attributable fraction; SBP, systolic blood pressure.

intensive blood pressure control (<120 mm Hg) was associated with a decreased risk of acutely decompensated HF,[25] not only highlighting the importance of systolic blood pressure control and its relationship with HF, but also suggesting that lower blood pressure targets may achieve an even greater impact. Prevalent coronary artery disease was associated with preferential development of AF with HF compared with AF alone in MDCS, but not in the MPP cohort. The latter finding was likely due to the younger baseline age and low prevalence of participants with pre-existing coronary disease at baseline in MPP (0.4%).

Our study must be interpreted in light of several limitations. First, the study cohorts were composed primarily of individuals of European descent, and the results may not be entirely generalisable to individuals of other ethnicities or race. Second, patient characteristics were only available at baseline and thus we were unable to perform time-updated analyses to confirm the observed associations. However, our findings were consistent with prior reports,[22] and the associations remained robust even after sensitivity analysis. Third, clinical endpoint data such as the occurrence of incident AF or HF were obtained from Swedish administrative registries, potentially leading to misclassification bias. However, clinical endpoints in the MPP and MDCS cohorts have been recently shown to be highly accurate (>95%).[11] Any misclassification that may have occurred was likely non-differential, and would have biassed our results towards the null. Finally, the occurrence of clinical endpoints was determined in the hospital setting, therefore any AF or HF cases that did not lead to hospitalisation would not have been detected. However, this would have also biassed our results towards the null.

In summary, in this analysis of two large, prospective, population-based cohorts free of AF and HF at baseline, BMI >25 kg/m^2, systolic blood pressure >140 mm Hg and active cigarette smoking were more strongly associated with the development of the combination of AF and HF, than AF alone. These modifiable risk factors accounted for greater than 50% of the PAR. Randomised trials are needed to assess whether modification of these three risk factors can reduce the incidence of AF with HF and subsequently decrease mortality.

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Contributors Dr JW is the first and corresponding author. He was involved in study design and conception, data analysis and interpretation, drafting and revising of the manuscript and final approval. He is the guarantor. Dr LJ is the senior author and was involved in study design and conception, data analysis and interpretation, manuscript revision and final approval. Drs DC and Healey were involved in study design, data interpretation, manuscript revision and final approval.

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Patient consent for publication Not required.

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Data availability statement Data are available upon reasonable request. Please contact Drs JA Wong or L Johnson for details.

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