Comparing and contrasting risk factors for Heart failure in patients with and without history of myocardial infarction:

Data from HOMAGE and the UK Biobank

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Abstract

Introduction: Myocardial infarction (MI) is among the commonest attributable risk factors for heart failure (HF). We compared clinical characteristics associated with the progression to heart failure and with subsequent outcome in patients with or without a history of MI.

Methods: Patients enrolled in the longitudinal new onset HF cohort in the HOMAGE cohort (N=26 478, 7 241 [27%] history of MI) were analyzed. Predictors of new onset HF, defined as first hospitalization for HF, and its subsequent association with mortality, were identified using survival analysis in patients with and without prior MI. The UK Biobank (N=500,001, 4555 [0.9%] patients with history of MI) was used for external validation.

Results: Older age, lower renal function, male sex and higher heart rate were significant risk factors of HF onset both in patients with and without prior MI. In contrast, smoking was significantly associated with HF onset only in patients with history of MI whereas higher BMI, SBP and blood glucose were significantly associated with HF onset only in patients without prior MI (all p for interactions<0.05). The increase in subsequent mortality following HF onset was greater in patients with prior MI (HR: 11.41 (8.54 -15.22) p<0.001) than in those without prior MI (HR: 5.97 (4.66–7.65) p<0.001) (p for interaction<0.001). In the UK biobank, higher BMI, HbA1c, diabetes and hypertension had a stronger association with HF onset in participants without prior MI compared to participants with MI (all p for interactions<0.05).

Conclusion: The importance of clinical risk factors and the increase in subsequent mortality risk following HF onset is dependent on whether the patient has had a prior MI. diabetes and hypertension are associated with new onset HF only in the absence of MI history. Risk management based on MI history may be useful in guiding more targeted intervention.

Abbreviations: BMI; Body Mass Index; CI: Confidence Interval; CV: Cardiovascular; HF: Heart failure; HR: Hazard Ratio; MI: Myocardial Infarction; SBP: Systolic Blood Pressure; eGFR: estimated Glomerular Filtration Rate

Keywords: heart failure, myocardial infarction, cardiovascular diseases, survival

Introduction

Heart failure (HF) is one of the leading causes of morbidity and mortality throughout the world. With ≥ 37 million people already affected worldwide, the number will continue to rise for the next 20 years(1, 2). Increasing life expectancy and prevalence of risk factors such as hypertension, diabetes, obesity and coronary artery disease, especially in younger populations, will further add to the steadily increasing number of HF patients(3). Despite advances in treatment, mortality rates remain particularly high with poor 5-year survival(4). Hence, early identification and management of risk factors is critical for preventing or delaying the onset of HF.

The implementation of preventive measures relies on the correct identification of individuals at higher risk. Several scores have been developed with the aim of identifying populations at higher risk taking into account variables such as age, sex, body mass index (BMI), lipid levels, kidney function and other comorbidities including diabetes and hypertension(5, 6). These scores assess HF risk irrespectively of the presence of prior myocardial infarction (MI) i.e., these risk score assess the HF risk based on a fixed value assigned to each risk factor including MI. However, the strength of a relation between a risk factor and outcome might depend upon whether a patient has previously had an MI.

Different etiologies, risk factors and pathophysiological mechanisms, in combination with concomitant diseases, renders HF a complex and heterogeneous syndrome with several phenotypes(7, 8). However, HF with history of prior MI appears distinct from HF without prior MI in many aspects including: ischemic injury, inflammation and neurohormonal pathways involved in cardiac remodeling(9). Importantly, ischemic / non-ischemic HF is often the only characterization reported in large registries regarding HF etiology, thus emphasizing the cardinal importance of MI history. Given the different pathophysiological background of HF with and without prior MI, classical risk factors (such as age, blood pressure, diabetes, dyslipidemia, kidney disease, etc.) may contribute differentially to HF onset in patients with and without MI. Similarly, given the difference in patient phenotypes, the association

between HF onset and subsequent outcome may vary meaningfully between patients with and without prior MI. History of MI is known to be associated with worse outcomes in patients with overt HF and could be related to MI history rather than the intrinsic prognosis of ischemic HF(10, 11); Surprisingly, data evaluating the impact of MI history on the prognosis impact of HF onset (i.e. the impact on subsequent outcome) are scarce (12, 13).

We compared the clinical characteristics associated with the progression to HF and with subsequent outcome in patients with or without a history of MI in patients at higher risk of HF in the HOMAGE database and validated our results in the UK Biobank population-based cohort.

Methods

Derivation cohort: Patients included in the Heart 'OMics' in AGEing (HOMAGE) merged database were studied. Briefly, the HOMAGE database included 52 631 study participants from 21 studies from eight European countries which enrolled subjects with overt cardiovascular (CV) disease or at risk of CV disease or healthy individuals. A detailed description of the database is provided elsewhere(14, 15).

Among this large database, patients identified to be at a higher risk for HF (i.e. without HF but with significant risk for HF based on their comorbidities/clinical history) were included in the analysis reported here(14, 15). Patients included were originally from four separate cohorts (ASCOT, DYDA, HVC, PROSPER) in which included patients had higher risk of HF and provided sufficient follow-up to assess the incidence of HF onset. (Supplementary figure 1)

Outcomes: The primary objective of the study was to identify whether the risk factors for HF onset differed depending on the presence (MI+) or absence of prior MI (MI-). For this objective, the selected outcome was time to HF onset as defined by hospitalization for HF. The endpoints for each study were adjudicated in the respective cohort and trials and the committee within the HOMAGE consortium

retrospectively assessed the quality of endpoint adjudication for each study (supplementary table 1) (5, 15).

The secondary objective of the study was to determine the effect of HF onset on the risk of subsequent mortality depending on the presence or absence of a history of MI. For this objective, all-cause mortality was the primary outcome.

Validation cohort: The results of our analysis were replicated in UK Biobank, a large population-based, prospective observational study with 502,493 middle-aged and elderly participants from the United Kingdom. The health outcomes were ascertained through data linkage to hospitalization records and incident HF was defined according to the International Classification of Diseases-10 codes. Subjects with prevalent heart failure at baseline were excluded from this analysis. Brief study design and baseline characteristics of the study participants included from the UK Biobank are presented in the supplementary material and supplementary table 2.

All of the studies were conducted in accordance with Good Clinical Practice guidelines and applicable national regulations and all study participants provided written informed consent.

Statistical analysis: For the descriptive analyses, continuous variables are expressed as mean ± standard deviation (SD) for normally distributed data or as median (Q1-Q3) for skewed data. Categorical variables are expressed as proportions (%).

Univariable Cox regression models were used to calculate the hazard ratio (HR) for HF onset associated with each risk factor. Due to differences in duration of follow-up between each cohort, the cohorts were added as strata in the Cox regression models for the HOMAGE database. Age, systolic blood pressure (SBP) and estimated glomerular filtration rate (eGFR) were categorized due to non-linearity. A backward selection procedure was applied to determine the variables to be included in the multivariable models. Total cholesterol, body weight and height were not included in the backward selection due to their high

collinearity with other variables (only low density lipoprotein-cholesterol (LDL-c) and BMI were considered). Interactions between each risk factor and history of MI were examined, adding interaction terms to survival models. The discriminative value of multivariable models for HF onset was assessed using Harrell's c-index. For validation analysis, a dedicated adjustment was performed to calculate hazard ratios of risk factor associated with HF onset in UK Biobank.

Kaplan-Meier survival curves were plotted to estimate the risk of death and risk differences following HF onset in patients with and without prior MI. In addition, time-dependent Cox models were fitted to assess the association of HF onset with subsequent mortality according to the presence/absence of MI history. The models were adjusted for sex, age, smoking status, BMI, diabetes, SBP, heart rate, blood glucose and eGFR. Blood glucose and diabetes were kept in the models as VIF were < 2. Statistical analyses were performed using R 3.6.1 and 3.5.3 (URL https://www.R-project.org/). A p value of less than 0.05 was considered statistically significant.

Results

HOMAGE cohort results

A total of 26 478 subjects was included for analysis, out of whom 7 241 (27%) had a history of MI. During a median follow-up time of 5.2 (3.5–5.9) years, 2.44% (N=177/7 241) of participants with a history of MI and 1.92% (N=370/19 237) without a history of MI developed HF.

Baseline characteristics (Table 1)

Participants with HF onset were older than those without, irrespective of prior MI status. Participants without prior MI who developed HF had higher SBP than participants without HF (167.5 (23.0) for HF versus 161.3 (19.9) for non-HF) whereas the opposite was observed in patients with MI history (154.0 (23.8) for HF vs. 159.2 (19.3) for non-HF) (Table 1).

Predictors of HF with or without history of MI (Table 2)

In multivariable analysis, male sex, older age, higher heart rate and worse renal function were significantly associated with increased risk of HF onset both in participants with, and those without, prior MI. However, there was a significantly lower risk associated with with eGFR > 75ml/min/1.73 m² only amongst those with prior MI (HR= 0.32 (0.16-0.65) p=0.002).The association was not significant amongst those with no prior MI (HR=0.77 (0.53-1.11) p=0.16).

Active smoking status was significantly associated with HF onset (HR=2.00 (1.36 - 2.94) p<0.001) in participants with a history of MI, while the association was neutral in univariable analysis in those with no prior MI. Similarly, diabetes was a predictor of HF onset only in those with prior MI . In contrast, higher BMI, higher SBP and higher blood glucose levels were significantly associated with HF onset and retained in multivariable models in only participants without prior MI but not in participants with prior MI.

Head-to-head comparison of HF risk factors in multivariable models

When predictors of HF were simultaneously included in multivariable models to allow a direct comparison of the magnitude of associations in participants with and without prior MI (Figure 1), a similar pattern of results was observed: SBP, blood glucose and BMI were more strongly associated with incident HF in participants without prior MI (p value for interaction respectively 0.003, 0.006 and 0.027) whereas smoking status (p value for interaction 0.021) and worse renal function (p value for interaction 0.022)were associated with incident HF in patients with prior MI

Effect of HF on mortality depending on history of MI (Figure 2)

In adjusted time-dependent Cox analysis, HF increased the risk of mortality in patients with prior MI (HR=11.41, 8.54 -15.22, p<0.001) to a greater extent than in those without prior MI (HR=5.97, 4.66 -

7.65, p<0.001). The differential impact of HF on subsequent survival was confirmed by a dedicated interaction analysis (p for interaction <0.001).

At 3-year follow-up, the absolute risk increase of mortality related to HF onset was of greater magnitude in those with prior MI (51.3% (41.5 - 61.1)) than in those without prior MI (35.7% (29.7-41.7)).

Validation analysis in the UK Biobank study

From the UK Biobank study, 500,001 subjects were included in the validation analysis, of whom 4555 (0.91%) had a history of MI at baseline. The validation cohort participants were younger (~9 years) and fewer participants had hypertension and diabetes compared to participants in the HOMAGE database. Among people with prior MI, 14.9% (680/4555) developed incident HF while 2.7% (13536/495446) participants without prior MI developed HF over a median (Q1 – Q3) follow-up of 11.8 (11.1-12.5) years. Increasing age, worse renal function and smoking were significantly associated with increased risk of HF in people with and without prior MI. A higher BMI, HbA1c, diabetes and hypertension had a stronger association with HF onset in participants without prior MI compared to participants with prior MI (p-interaction: 0.0005, 0.03, 0.03 and 0.0005 respectively – Table 3). In addition, male sex was significantly and markedly associated with a higher risk of HF onset only in participants with prior MI but not in participants without MI (p for interaction <0.0001).

Discussion

In this pooled cohort study of patients at higher risk of developing HF, we found that the pattern of association of risk factors with HF was dependent on the presence of prior MI. Increasing age, poorer renal function, male sex and higher heart rate were associated with HF onset irrespective of MI history, and should consequently be perceived as stable and ubiquitous risk factors for HF onset. However, blood pressure/hypertension, BMI and blood glucose/HbA1c were more strongly associated with HF onset in participants without prior MI both in the HOMAGE cohort and UK Biobank cohort. Our results are in

line with previous reports suggesting that metabolic factors and hypertension are more associated with heart failure with normal ejection fraction than heart failure due to reduced ejection fraction HFpEF (16, 17). Importantly, despite the differences in baseline characteristics and risk factors in the HOMAGE (participants at high risk of HF) and UK Biobank study (population-based cohort), we saw a strikingly similar pattern of association between metabolic- and hypertension- related factors and new onset HF onset. In addition, the increase in subsequent risks for mortality following HF onset was of greater magnitude in patients with prior MI on both an additive and relative scale.

These results consequently suggest that, as in patients with overt HF, prior MI should be a variable systematically emphasized in epidemiological studies focusing on the prediction of HF onset. Importantly, metabolic- and hypertension- related factors have a greater impact on HF onset in the absence of prior MI, and their prevention/treatment should consequently be particularly optimized in people who have not had an MI.

Risk factors more associated with HF onset in the participants with prior MI

Smoking status and diabetes were strong predictors of HF onset in the prior MI group in the HOMAGE cohort. Our results are in keeping with previous studies where diabetes was found to be an important determinant of HF onset in post-MI patients(18-20). Our study furthermore found that smoking was more strongly related to HF onset in the patients with prior MI than in the patients without prior MI. Previous papers have also demonstrated that smoking is associated with new onset HF following MI, even though the smokers seemingly had a better risk profile than non-smokers(21, 22), possibly due to increased myocardial injury and myocardial hemorrhage (21). This differential impact may not be captured in risk scores calculated with multivariable risk models where diabetes is associated with a fixed risk estimate. However, smoking status was similarly associated with incident HF regardless of prior MI in the validation cohort , perhaps due to differences in the baseline smoking behavior of the participants the

two cohorts. For example, in the UK Biobank a smaller proportion of participants were smokers compared to the HOMAGE cohort.

In the present analysis, higher SBP (in HOMAGE) and history of hypertension (in the UK Biobank study) was not associated with an increased risk of incident HF in patients with a prior MI. Previous studies have shown that lower BP could be related to greater LV dilation following MI, thus increasing the risk of subsequent HF(23, 24). Following an MI, lower SBP and pulse pressure would consequently be associated with an increased risk of events, including HF. In addition, there is a BP paradox in patients with heart failure due to reduced ejection fraction (HFrEF): higher BP appears to be 'protective' (25, 26). However, the paradox has been described only *after* HF onset, whereas we focus here on the pre-HF period. In the analysis presented herein, we put emphasis on the role of low BP in the risk assessment of HF onset in patients with prior MI.

Risk factors more strongly associated with HF onset in participants without prior MI

Our study highlighted hypertension as a strong risk factor for HF onset in patients without prior MI. Similarly, an analysis of the Framingham Heart study cohort previously demonstrated that hypertension is the most important risk factor associated with HF onset(27). Our results highlight that the magnitude of the association between blood pressure and incident HF is far greater in patients without prior MI than in patients with prior MI. There was no relation between SBP and incident HF in patients with prior MI, perhaps because low SBP was due to reduced left ventricular function and hence, greater risk of HF onset (23).

Metabolic factors such as BMI and blood glucose were stronger predictors of HF onset in patients without prior MI in our study. Similarly, the validation analysis found that hypertension, diabetes and higher BMI were more strongly related to HF onset without prior MI. Similar findings were observed in a study combining data from middle-aged men and women from four different American cardiovascular disease

cohorts(28), in which participants who did not have any of the three risk factors (hypertension, obesity and diabetes) had a substantially lesser risk of HF, thus placing greater emphasis on metabolic factors in the genesis of HF in patients without MI. In the presence of a prior MI, a lower prevalence of metabolic risk factors is perhaps sufficient to trigger remodeling and tip the patient in to HF.

Impact of HF on mortality depending on history of MI

incident HF increases 5-year mortality by more than 50%(4, 29, 30). However, very few studies have explored the incremental risk of mortality associated with HF onset according to MI history. We found that the increase in mortality following HF onset was of greater magnitude both on a relative (higher HR) and additive scale (higher risk difference) in participants with prior MI than in participants without. History of MI is thus an important modifier of the effect of HF onset on subsequent prognosis, possibly due to different HF profiles. Indeed, following MI, the proportion of patients with HF due to reduced ejection fraction is likely to be far higher, and it is this that confers the greater risk.

Risk scores and risk prediction models

A number of scores have been developed for predicting the risk of HF. The Framingham Study CHF (1999) risk score based on key clinical features was the first to provide estimates of the 4-year probability of heart failure(31). Subsequently, the ARIC heart failure risk calculator, the Health ABC risk score, the PCP-HF calculator and the HOMAGE score were developed based on clinical and laboratory features(5, 6, 32, 33). Importantly, however, none of these scores differentiates HF prediction according to the history of MI. Having access to a large dataset enabled us to assess interactions with MI history efficiently. Interaction p values were significant for many factors suggesting substantial differences between the effect of each risk factor in patients with or without prior MI – something that has not been previously emphasized.

Limitations

There are several limitations to our study. First, the results are subject to biases inherent to all observational cohort studies. Second, the included cohorts featured certain differences in the inclusion criteria and length of the follow up-period. For example, the DYDA study considered MI as an exclusion criterion while the ASCOT cohort had a longer follow-up time than the other 3 cohorts. However, all models were adjusted for clinical characteristics. Third, the diagnosis of HF was not based on the Framingham criteria but rather on hospitalization of HF. Hence, non-hospitalized HF patients were not labeled as HF in the current analysis. Moreover, differences in HF hospitalization due to different hospital admissions policy, treating physicians, adherence to guidelines for therapy occur in different cohorts. Further, we do not have data regarding how long ago MI happened before the recruitment in the cohort and if there were recurrent MIs during follow-up. Fourth, it is possible that the some of the patients enrolled had had clinically silent MIs and were consequently included in the no prior MI group, thus diluting the difference between the two groups. In addition, the overall SBP in the HOMAGE database was high due to the phenotype of patients included in the original cohorts aggregated within the HOMAGE consortium. Therefore, we used a cut-off of 160 mm Hg in the HOMAGE cohort given the structure of the data. However, the results were similar in the UK Biobank using the classic definition for hypertension. Finally, LVEF at the time of HF onset was not available; we cannot consequently provide HFrEF- or HFpEF- specific associations. Whether the pattern of association we observed is primarily driven by a subtype of HF (i.e. HFrEF or HFpEF) should be further studied in future.

Research and clinical implications

Our results suggest that "classical" risk factors for HF carry a different weighting depending on the clinical setting. This fact has not been sufficiently emphasized previously. In light of our results, a history of prior MI should be particularly highlighted in epidemiological studies focusing on predictors of HF onset, as is done in studies performed in patients with overt HF. In addition, the modifying effect of MI on HF predictors should be systematically assessed in future reports. A personalized HF risk stratification

may help in designing preventive strategies depending on the clinical setting. In patients without MI, hypertension treatment and the control of metabolic features appear to be of much greater importance. These results could help in the prioritization of healthcare interventions in the prevention of HF.

Conclusions

The importance of clinical risk factors and the increase in subsequent mortality risk following HF onset is dependent on the presence or absence of a history of prior MI. These results suggest that patients should be differentiated in terms of risk assessment based on their history of prior MI and may ultimately benefit from different targeted interventions to prevent HF.

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and the Northwest Regional Development Agency. It has also had funding from the Welsh Assembly Government and the British Heart Foundation.

Table 1: Baseline characteristics in relation to history of MI and the occurrence of HF during follow-up in the HOMAGE cohort

			Patients with a history of MI		Patients without a history of MI		
	Overall (N= 26 478)	**N available**	**No HF onset during FU** (N=7 064)	**HF onset** (N=177)	**No HF onset during FU** (N=18 867)	**HF onset** (N=370)	**p**
Clinical data							
Sex (Female)	8095 (30.6)	26478	2822 (39.9)	66 (37.3)	5090 (27.0)	117 (31.6)	<0.001
Age (years)	65.6 (9.3)	26478	63.9 (10.3)	73.4 (7.6)	66.1 (8.8)	71.1 (7.7)	<0.001
Smoking status		26413					<0.001
Non-smoker	11146 (42.2)		3513 (49.8)	114 (64.4)	7368 (39.2)	151 (41.4)	
Smoker	7734 (29.3)		1806 (25.6)	43 (24.3)	5789 (30.8)	96 (26.3)	
Ex-smoker	7533 (28.5)		1733 (24.6)	20 (11.3)	5662 (30.1)	118 (32.3)	
Alcohol consumption	17547 (67.5)	25993	4751 (68.0)	98 (56.0)	12480 (67.6)	218 (61.6)	0.001
Hypertension	23711 (89.5)	26478	6087 (86.2)	115 (65.0)	17185 (91.1)	324 (87.6)	<0.001
Diabetes	6779 (25.6)	26478	1096 (15.5)	34 (19.2)	5513 (29.2)	136 (36.8)	<0.001
SBP (mmHg)	160.8 (19.9)	26407	159.2 (19.3)	154.0 (23.8)	161.3 (19.9)	167.5 (23.0)	<0.001
Heart rate (bpm)	70.8 (12.6)	26352	70.6 (12.9)	68.8 (11.8)	70.9 (12.5)	71.8 (13.0)	0.022
BMI (kg/m²)	27.8 [25.2, 30.8]	26477	27.7 [25.2, 30.7]	27.2 [25.4, 30.5]	27.8 [25.2, 30.8]	28.3 [25.3, 31.6]	0.042
Laboratory data							
Blood glucose (mmol/L)	5.5 [5.0, 6.4]	24546	5.4 [4.9, 6.0]	5.3 [4.8, 5.9]	5.6 [5.0, 6.6]	5.6 [5.0, 7.4]	<0.001
Total cholesterol (mmol/L)	5.8 (1.1)	26435	5.9 (1.1)	5.7 (1.0)	5.8 (1.1)	5.8 (1.0)	<0.001
LDL-cholesterol (mmol/L)	3.7 (0.9)	24273	3.8 (0.9)	3.7 (0.8)	3.7 (0.9)	3.7 (0.9)	<0.001
HDL-cholesterol (mmol/L)	1.2 [1.0, 1.5]	26431	1.3 [1.1, 1.5]	1.2 [1.0, 1.4]	1.2 [1.0, 1.5]	1.2 [1.0, 1.5]	<0.001
Triglycerides (mmol/L)	1.5 [1.1, 2.1]	24648	1.5 [1.1, 2.1]	1.4 [1.1, 2.0]	1.5 [1.1, 2.1]	1.5 [1.2, 2.1]	0.286
Serum creatinine (µmol/L)	96.0 [86.0, 108.0]	20252	96.0 [85.0, 108.0]	113.0 [92.2, 132.8]	97.0 [86.0, 108.0]	99.0 [87.0, 117.0]	<0.001
eGFR CKD-EPI (ml/min/1,73 m²)	65.3 [55.1, 75.6]	20252	64.9 [54.8, 75.3]	48.9 [41.4, 62.7]	65.7 [55.6, 76.0]	59.6 [47.3, 71.0]	<0.001
Medications							
Use of ACEI/ARBs	7947 (34.8)	22821	1933 (33.1)	62 (36.0)	5814 (35.3)	138 (40.4)	0.003
Use of beta blockers	8017 (35.1)	22821	2256 (38.6)	54 (31.4)	5610 (34.1)	97 (28.4)	<0.001

ACEI: Angiotensin-converting enzyme inhibitor; ARBs: Angiotensin receptor blocker; BMI; Body Mass Index; FU: follow-up; HF: Heart failure; MI: Myocardial Infarction; SBP: Systolic Blood Pressure; eGFR: estimated Glomerular Filtration Rate (calculated using CKD-EPI formula)

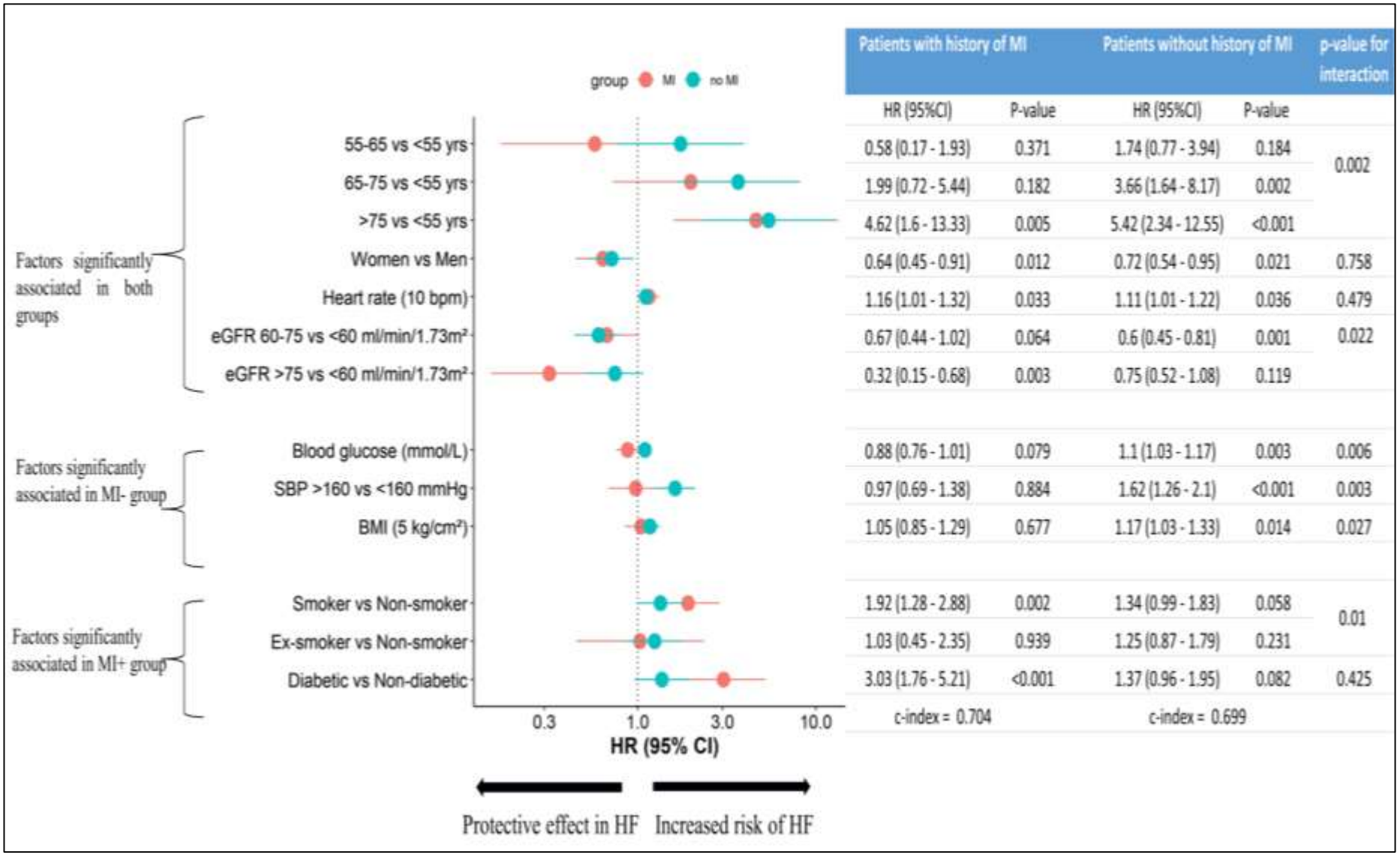
Table 2: Univariable and multivariable (using backward selection) Cox regression models for HF event with or without history of MI in the HOMAGE cohort

Variable	Patients with history of MI				Patients without history of MI			
	Univariable model		Multivariable model c-index = 0.708		Univariable model		Multivariable model c-index = 0.692	
	HR (95%CI)	P-value	HR (95%CI)	P-value	HR (95%CI)	P-value	HR (95%CI)	P-value
Sex (Female)	0.85 (0.63 - 1.15)	0.296	0.63 (0.45 - 0.88)	0.008	1.00 (0.79 - 1.27)	0.996	0.71 (0.54 - 0.93)	0.015
Age class (ref: age <55 years)								
55-65 yrs	0.92 (0.39 - 2.17)	0.842	0.79 (0.26 - 2.41)	0.681	1.52 (0.84 - 2.77)	0.167	1.52 (0.7 - 3.27)	0.29
65-75 yrs	3.47 (1.66 - 7.26)	0.001	2.94 (1.13 - 7.64)	0.027	3.34 (1.89 - 5.92)	<0.001	3.22 (1.52 - 6.84)	0.002
> 75 yrs	7.58 (3.5 - 16.4)	<0.001	6.84 (2.52 - 18.59)	<0.001	5.84 (3.24 - 10.52)	<0.001	4.83 (2.2 - 10.6)	<0.001
BMI (5 kg/cm²)	1.12 (0.95 - 1.33)	0.189	-	-	1.15 (1.04 - 1.28)	0.006	1.15 (1.02 - 1.31)	0.027
Smoking status (ref: non-smokers)								
Smoker	1.36 (0.94 - 1.96)	0.105	2.00 (1.36 - 2.94)	<0.001	0.91 (0.7 - 1.18)	0.47	-	-
Ex-smoker	1.26(0.71 - 2.23)	0.428	1.21 (0.61 - 2.41)	0.583	1.38 (1.05 - 1.83)	0.022	-	-
Diabetes	1.88 (1.29 - 2.75)	0.001	1.96 (1.29 - 2.99)	0.002	1.95 (1.57 - 2.43)	<0.001	-	-
SBP class >160 mmHg	1.03 (0.76 - 1.41)	0.84	-	-	1.74 (1.4 - 2.15)	<0.001	1.59 (1.23 - 2.05)	<0.001
Heart rate (10 bpm)	1.13 (1 - 1.27)	0.047	1.16 (1.02 - 1.32)	0.02	1.1 (1.01 - 1.19)	0.026	1.12 (1.02 - 1.23)	0.022
Blood glucose (mmol/L)	1.05 (0.96 - 1.15)	0.314	-	-	1.13 (1.09 - 1.17)	<0.001	1.14 (1.09 - 1.18)	<0.001
eGFR class (ml/min/1,73 m²) (ref: <60)								
60 - 75	0.55 (0.37 - 0.83)	0.004	0.64 (0.43 - 0.96)	0.029	0.55 (0.41 - 0.72)	<0.001	0.62 (0.46 - 0.83)	0.001
≥75	0.27 (0.14 - 0.53)	<0.001	0.32 (0.16 - 0.65)	0.002	0.59 (0.42 - 0.81)	0.001	0.77 (0.53 - 1.11)	0.159

BMI; Body Mass Index; FU: follow-up; HF: Heart failure; MI: Myocardial Infarction; SBP: Systolic Blood Pressure; eGFR: estimated Glomerular Filtration Rate

Values for univariable association not shown for alcohol intake, hypertension, HDL, LDL cholesterol because they were not retained in backward selection procedure of multivariable analysis in both the group

Figure 1: Forest plot of the head-to-head comparison of risk factors for HF onset in multivariable survival models in participants with and without a history of MI in the HOMAGE cohort



	Patients with history of MI		Patients without history of MI		p-value for interaction
	HR (95%CI)	P-value	HR (95%CI)	P-value	
55-65 vs <55 yrs	0.58 (0.17 - 1.93)	0.371	1.74 (0.77 - 3.94)	0.184	0.002
65-75 vs <55 yrs	1.99 (0.72 - 5.44)	0.182	3.66 (1.64 - 8.17)	0.002	
>75 vs <55 yrs	4.62 (1.6 - 13.33)	0.005	5.42 (2.34 - 12.55)	<0.001	
Women vs Men	0.64 (0.45 - 0.91)	0.012	0.72 (0.54 - 0.95)	0.021	0.758
Heart rate (10 bpm)	1.16 (1.01 - 1.32)	0.033	1.11 (1.01 - 1.22)	0.036	0.479
eGFR 60-75 vs <60 ml/min/1.73m²	0.67 (0.44 - 1.02)	0.064	0.6 (0.45 - 0.81)	0.001	0.022
eGFR >75 vs <60 ml/min/1.73m²	0.32 (0.15 - 0.68)	0.003	0.75 (0.52 - 1.08)	0.119	
Blood glucose (mmol/L)	0.88 (0.76 - 1.01)	0.079	1.1 (1.03 - 1.17)	0.003	0.006
SBP >160 vs <160 mmHg	0.97 (0.69 - 1.38)	0.884	1.62 (1.26 - 2.1)	<0.001	0.003
BMI (5 kg/cm²)	1.05 (0.85 - 1.29)	0.677	1.17 (1.03 - 1.33)	0.014	0.027
Smoker vs Non-smoker	1.92 (1.28 - 2.88)	0.002	1.34 (0.99 - 1.83)	0.058	0.01
Ex-smoker vs Non-smoker	1.03 (0.45 - 2.35)	0.939	1.25 (0.87 - 1.79)	0.231	
Diabetic vs Non-diabetic	3.03 (1.76 - 5.21)	<0.001	1.37 (0.96 - 1.95)	0.082	0.425
	c-index = 0.704		c-index = 0.699		

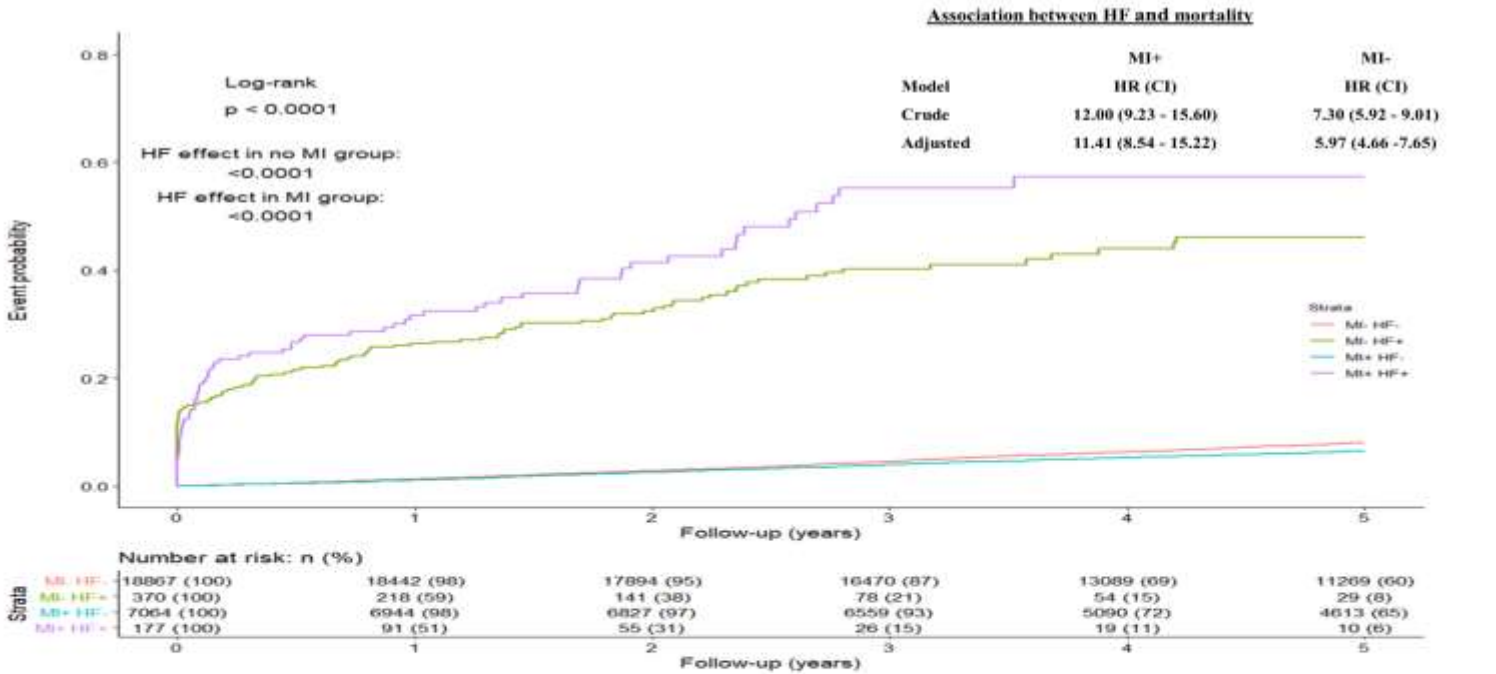
CI: Confidence Interval; HR: Hazard Ratio; MI: Myocardial Infarction; SBP: Systolic Blood Pressure; eGFR: estimated Glomerular Filtration Rate

Table 3: Multivariable Cox regression models for HF event with or without history of MI in UK biobank study

	Patients with history of MI		Patients without history of MI		P- value of interaction
	HR (95% CI)	P	HR (95% CI)	P	
Age in year	1.04 (1.03-1.05)	< 0.0001	1.12 (1.11-1.12)	< 0.0001	< 0.0001
Male	1.00 (0.83-1.21)	0.97	2.06 (1.99-2.13)	< 0.0001	< 0.0001
eGFR	0.73 (0.67-0.81)	< 0.0001	0.67 (0.66-0.69)	< 0.0001	< 0.0001
HbA1c	1.13 (1.07-1.20)	< 0.0001	1.19 (1.17-1.20)	< 0.0001	0.03
Hypertension	1.14 (1.08-1.22)	0.29	1.61 (1.54-1.69)	< 0.0001	0.0005
BMI	1.22 (1.12-1.33)	< 0.0001	1.49 (1.46-1.51)	< 0.0001	0.0005
Smoker	1.88 (1.48-2.38)	< 0.0001	1.97 (1.87-2.08)	< 0.0001	0.59
Ex-smoker	1.36 (1.13-1.63)	0.0009	1.32 (1.27-1.37)	< 0.0001	0.74
Type2 diabetes	1.50 (1.22-1.84)	0.0001	1.81 (1.72-1.91)	< 0.0001	0.03

Continuous variables were standardized to per-SD increase
Detailed adjustment model is presented in supplementary table 3

Figure 2: Mortality risk estimates in patients with and without HF onset according to MI history status



Model	MI+ HR (CI)	MI- HR (CI)
Crude	12.00 (9.23 - 15.60)	7.30 (5.92 - 9.01)
Adjusted	11.41 (8.54 - 15.22)	5.97 (4.66 -7.65)

Risk estimates at 1-4 years depending on HF and MI history

Variable	Risk at 1 year (CI 95 %)	Risk at 2 years (CI 95 %)	Risk at 3 years (CI 95 %)	Risk at 4 years (CI 95 %)
HF- MI+	1.1 (0.9 - 1.3)	2.5 (2.2 - 2.9)	3.9 (3.5 - 4.4)	5.3 (4.7 - 5.8)
HF+ MI+	31.6 (24.1 - 38.4)	41.5 (32.7 - 49.1)	55.2 (44.3 - 64)	57.4 (45.9 - 66.4)
HF+ MI-	26.4 (21.6 - 30.9)	32.4 (27 - 37.4)	40.2 (33.9 - 46)	44 (36.9 - 50.3)
HF- MI-	1.3 (1.1 - 1.4)	2.8 (2.6 - 3)	4.5 (4.2 - 4.8)	6.3 (5.9 - 6.6)

Risk difference estimates on mortality at 1-4 years in HF patients depending on history of MI

Comparison group	Reference group	Risk difference at 1 year (95%CI)	Risk difference at 2 years (95%CI)	Risk difference at 3 years (95%CI)	Risk difference at 4 years (95%CI)
HF+ MI-	HF-MI-	25.1 (20.5 - 29.7)	29.6 (24.4 - 34.8)	35.7 (29.7 - 41.7)	37.8 (31.1 - 44.4)
HF+MI+	HF- MI+	30.5 (23.4 - 37.6)	38.9 (30.8 - 47.1)	51.3 (41.5 - 61.1)	52.1 (41.9 - 62.3)

CI: Confidence Interval; HF: Heart failure; *HR: Hazard Ratio;* MI: Myocardial Infarction

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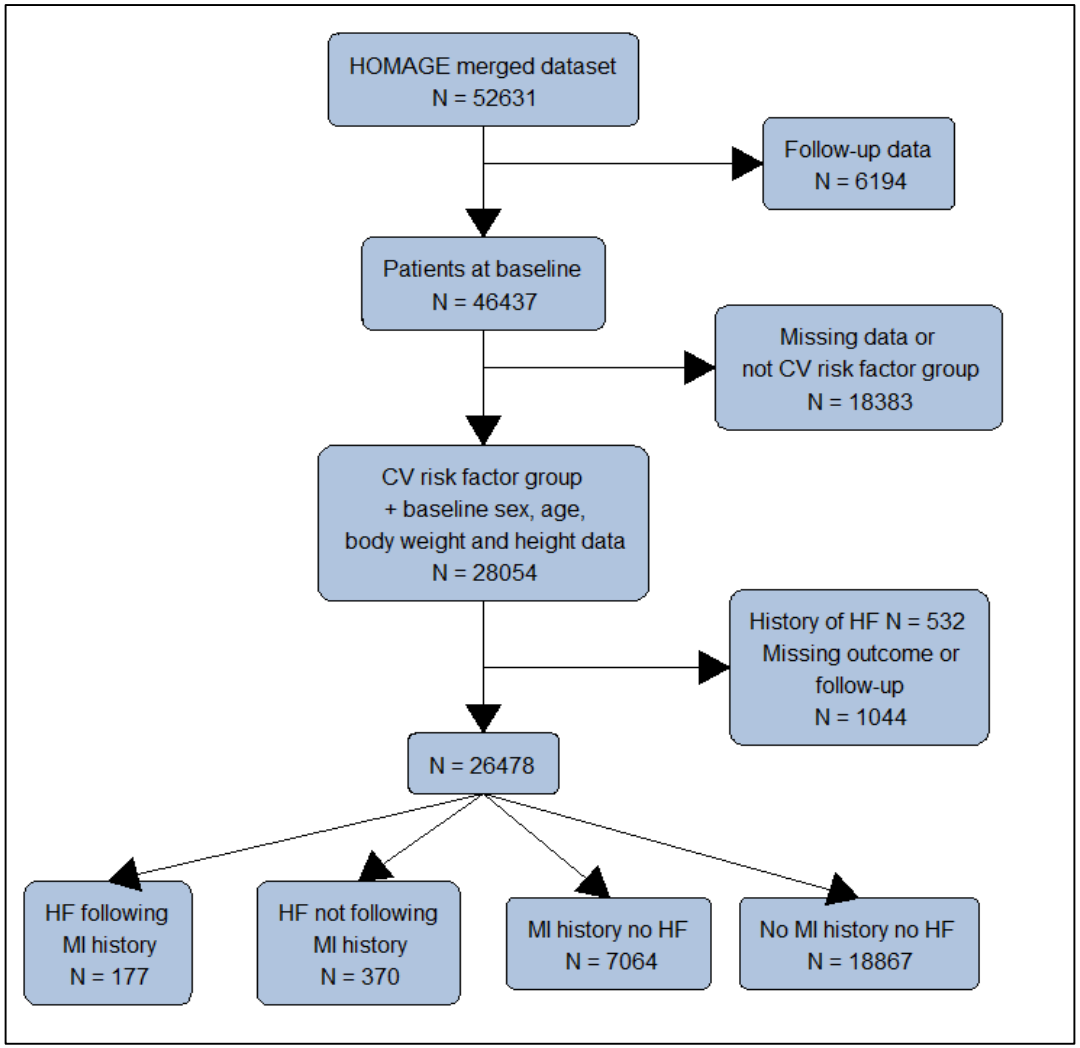
Supplementary information

Supplementary figure 1: Study flowchart for HOMAGE cohort



Supplementary table 1: Definition of HF in the included cohorts (1,2,3)

Name of the cohort	Criteria for diagnosing HF
ASCOT trial	HF onset was confirmed by clinical signs and symptoms or diagnosis by attending physician
PROSPER trial	HF onset was confirmed by review of hospital records
HVC	Investigator judgement
DYDA trial	Investigator judgement Systolic LVD was defined as LV ejection fraction (LVEF) ≤50% or Midwall fractional shortening ≤15%. Diastolic LVD was defined as E/A ratio (transmitral flow by Doppler) between 0.75 and 1.5 and deceleration time of E wave >140 msec.
UK Biobank	International Classification of Diseases-10 codes

Study description of UK Biobank

Study design and participants

Between 2007 and 2010, UK Biobank recruited 502,493 participants (aged 37–73 years) from the general population. Participants attended one of 22 assessment centres across England, Scotland, and Wales where they completed a self-administered, touch-screen questionnaire and face-to-face interview, and trained staff took a series of measurements including: height, weight, and blood pressure. Ethnicity, education level, sleep duration, smoking status, and alcohol intake were self-reported. Townsend area deprivation index was derived from postcode of residence using aggregated data on unemployment, car and home ownership, and household overcrowding.(4) Blood pressure was measured by a trained nurse. Hours of physical activity were self-reported using the validated International Physical Activity Questionnaire.(5) Height was measured to the nearest

centimetre, using a Seca 202 stadiometer, body weight to the nearest 0.1 kg, using a Tania BC-418 body composition analyser, and waist circumference (WC) and hip circumference to the nearest 1 mm using a standard scale. BMI was calculated as weight/height2 and the World Health Organization's criteria were used to classify BMI into: underweight (<18.5), normal weight (18.5 to <25), overweight (25 to <30), and obese (≥30). Biochemistry measures were performed at a dedicated central laboratory between 2014 and 2017. All of these tests were externally verified with acceptable distribution. Details of these measurements and assay performances can be found in the UK Biobank online showcase and protocol (6).

Outcome ascertainment

Clinical endpoints were ascertained through data linkage in the UK Biobank. Date and cause of death was obtained from death certificates held within the National Health Service Information Centre (England and Wales) and the National Health Service Central Register Scotland (Scotland). Date and cause of hospital admissions were obtained through record linkage to Health Episode Statistics (England and Wales) and Scottish Morbidity Records (Scotland). Detailed information about the linkage procedures can be found at http://content.digital.nhs.uk/services. At the time of analysis, mortality data were available up to 30 June 2020 and hospital admission data were available up to 31 May 2020 for participants in England and 31 March 2017 for those in Scotland and Wales.

Supplementary Table 2: Baseline characteristics in relation to history of MI and the occurrence of HF during follow-up in UK Biobank (validation cohort)

		Prior MI at baseline		No MI at baseline		
	Overall	No incident HF	Incident HF	No incident HF	Incident HF	P
Total n (%)	(N=500001)	(N=3875)	(N=680)	(N=481910)	(N=13536)	
Age, years, mean (SD)	56.50 (8.09)	60.87 (6.41)	62.21 (5.75)	56.31 (8.09)	61.95 (6.32)	< 0.0001
Male	227224 (45.45)	3150 (81.29)	550 (80.88)	215100 (44.64)	8424 (62.23)	< 0.0001
Smoking						< 0.0001
Never	272630 (54.85)	1301 (33.84)	174 (25.82)	265718 (55.46)	5437 (40.54)	
Smoker	52653 (10.59)	523 (13.61)	126 (18.69)	49881 (10.41)	2123 (15.83)	
Ex-smoker	171788 (34.56)	2020 (52.55)	374 (55.49)	163544 (34.13)	5850 (43.62)	
Units/week of alcohol intake	16.28 (18.90)	18.42 (20.90)	17.09 (20.92)	16.20 (18.74)	18.34 (23.27)	< 0.0001
BMI, kg/m^2, mean (SD)	27.42 (4.79)	27.34 (4.74)	29.82 (5.89)	28.80 (4.45)	29.90 (5.34)	< 0.0001
Hypertension	252917 (52.87)	3288 (85.87)	588 (87.89)	238693 (51.81)	10348 (78.46)	< 0.0001
SBP, mmHg, mean (SD)	137.84 (18.67)	137.68 (18.59)	144.53 (20.02)	135.32 (18.33)	135.23 (19.73)	< 0.0001
Diabetes	28084 (6.03)	606 (16.67)	183 (28.28)	24862 (5.54)	2433 (19.23)	< 0.0001
HbA1c, nmol/mol, mean (SD)	36.09 (6.76)	39.66 (8.80)	42.66 (12.16)	35.94 (6.52)	39.99 (11.17)	< 0.0001
eGFR, mean (SD)	91.86 (17.14)	81.17 (17.11)	73.67 (19.40)	92.37 (16.86)	77.61 (19.15)	< 0.0001
Cholesterol lowering medication	85126 (17.03)	3604 (93.01)	625 (91.91)	75386 (15.64)	5511 (40.71)	< 0.0001
Total cholesterol, mmol/L, mean (SD)	5.70 (1.14)	4.29 (0.91)	4.32 (0.98)	5.72 (1.13)	5.31 (1.25)	< 0.0001
LDL-c, mmol/L,mean (SD)	3.56 (0.87)	2.57 (0.66)	2.60 (0.72)	3.58 (0.86)	3.30 (0.93)	< 0.0001
HDL-c, mmol/L,mean (SD)	1.45 (0.38)	1.18 (0.29)	1.16 (0.30)	1.46 (0.38)	1.33 (0.38)	< 0.0001
Triglyceride, mmol/L,mean (SD)	1.75 (1.04)	1.87 (1.07)	1.88 (0.99)	1.74 (1.03)	1.95 (1.16)	< 0.0001

BMI; Body Mass Index; FU: follow-up; HF: Heart failure; MI: Myocardial Infarction; SBP: Systolic Blood Pressure; eGFR: estimated Glomerular Filtration Rate
T2DM defined by either self-report diagnosis, medication, or A1c>48 nmol/mol
Hypertension defined by self-report diagnosis, medication, or SBP>140 mmHg

Table 3: Multivariable Cox proportional model for the risk of HF onset depending on the MI history in the validation cohort (UK Biobank)

	Prevalent MI at baseline		No MI at baseline		P value of interaction
	HR (95% CI)	P	HR (95% CI)	P	
Model 0					
Age in year	1.04 (1.03-1.05)	< 0.0001	1.12 (1.11-1.12)	< 0.0001	< 0.0001
Male	1.00 (0.83-1.21)	0.97	2.06 (1.99-2.13)	< 0.0001	< 0.0001
Non-white ethnicity	1.49 (1.11-1.98)	0.007	0.96 (0.89-1.04)	0.37	0.04
Model 1					
Deprivation	1.20 (1.12-1.29)	< 0.0001	1.31 (1.28-1.33)	< 0.0001	0.61
Model 2					
MET-min/week	0.85 (0.77-0.93)	0.0008	0.89 (0.88-0.91)	< 0.0001	0.13
TV viewing	1.13 (1.06-1.21)	0.0003	1.24 (1.22-1.26)	< 0.0001	0.003
Fruit/veg intake	0.98 (0.91-1.06)	0.6	0.96 (0.94-0.97)	< 0.0001	0.46
Red meat intake	1.10 (1.02-1.18)	0.008	1.07 (1.06-1.09)	< 0.0001	0.69
Processed meat intake	1.06 (0.90-1.24)	0.51	1.21 (1.16-1.25)	< 0.0001	0.053
Low oily fish intake	1.15 (0.91-1.47)	0.25	1.29 (1.22-1.36)	< 0.0001	0.69
Former smoker	1.36 (1.13-1.63)	0.0009	1.32 (1.27-1.37)	< 0.0001	0.74
Current smoker	1.88 (1.48-2.38)	< 0.0001	1.97 (1.87-2.08)	< 0.0001	0.59
Alcohol intake	0.98 (0.90-1.06)	0.56	1.01 (1.00-1.03)	0.12	0.1
Model 3					
BMI	1.22 (1.12-1.33)	< 0.0001	1.49 (1.46-1.51)	< 0.0001	0.0005
WHR	1.28 (1.14-1.44)	< 0.0001	1.57 (1.54-1.61)	< 0.0001	< 0.0001
Model 4					
Grip strength	0.80 (0.71-0.89)	< 0.0001	0.75 (0.73-0.77)	< 0.0001	0.49
Hypertension	1.15 (0.89-1.50)	0.29	1.61 (1.54-1.69)	< 0.0001	0.0005
SBP	0.97 (0.89-1.06)	0.53	1.06 (1.04-1.08)	< 0.0001	0.15
CRP	1.14 (1.08-1.22)	< 0.0001	1.16 (1.14-1.17)	< 0.0001	0.02
Type 2 diabetes	1.50 (1.22-1.84)	0.0001	1.81 (1.72-1.91)	< 0.0001	0.03
HbA1c	1.13 (1.07-1.20)	< 0.0001	1.19 (1.17-1.20)	< 0.0001	0.03
Cystatin C	1.30 (1.21-1.39)	< 0.0001	1.39 (1.37-1.41)	< 0.0001	0.0002
eGFR	0.73 (0.67-0.81)	< 0.0001	0.67 (0.66-0.69)	< 0.0001	< 0.0001
GGT	1.12 (1.05-1.19)	0.0003	1.14 (1.12-1.16)	< 0.0001	0.02

Adjusted for all factors in the prior model. E.g. factors in Model 1 adjusted for factors in Model 0
Continuous variables were standardised to per-SD increase

Supplementary References

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