**Supplementary information**

**Supplementary figure 1: Study flowchart for HOMAGE cohort**

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**Supplementary Figure 2: Population attributable risk associated with modifiable risk variables in people with or without MI in HOMAGE**

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PAR: population attributable risk; x-axis: PAR percentage; y-axis: modifiable risk factors; error bars: confidence interval

**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/m2, 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 | | | | | | | | | | | |

**Supplementary Table 3: 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** | | | | **P-value interaction** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **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 | 0.803 |
| **Age class**  (ref: age <55 years) |  |  | <0.001 |  | <0.001 |  |  | <0.001 |  | <0.001 | <0.001 |
| 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 | 0.107 |
| **Smoking status**  (ref: non-smokers) |  |  | 0.258 |  | 0.002 |  |  | 0.011 |  |  | < 0.001 |
| 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 | - | - | 0.164 |
| **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 | < 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 | 0.139 |
| **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 | 0.016 |
| **eGFR class (ml/min/1,73 m²)**  (ref: ≥75) |  |  | <0.001 |  | 0.002 |  |  | <0.001 |  | 0.006 | 0.002 |
| < 60 |  | 3.71 (1.89 - 7.3) | <0.001 | 3.13 (1.54 - 6.37) | 0.002 |  | 1.7 (1.23 - 2.35) | 0.001 | 1.3 (0.9 - 1.87) | 0.159 |  |
| 60 - 75 |  | 2.05 (1.01 - 4.16) | 0.046 | 2 (0.96 - 4.14) | 0.063 |  | 0.93 (0.66 - 1.31) | 0.68 | 0.81 (0.55 - 1.18) | 0.264 |  |
| 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.  Interaction were tested in models containing only the interaction and main effects (i.e. with no adjustment variables). | | | | | | | | | | |  |

**Supplementary Table 4: 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, after forcing the adjustment for beta-blockers and ACEi/ARBs use.**

| **Variable** | **Group** | **Multivariable MI+**  **c-index = 0.704** | | **Multivariable MI-**  **c-index = 0.699** | | **Interaction in**  **multivariable model** |
| --- | --- | --- | --- | --- | --- | --- |
|  |  | HR (CI) | P-value | HR (CI) | P-value | P-value interaction |
| Sex |  |  | 0.014 |  | 0.029 | 0.763 |
|  | M | Reference |  | Reference |  |  |
|  | F | 0.64 (0.45 - 0.91) | 0.014 | 0.72 (0.54 - 0.97) | 0.029 |  |
| Age class |  |  | <0.001 |  | <0.001 | 0.004 |
|  | <= 55 yrs | Reference |  | Reference |  |  |
|  | > 75 yrs | 7.11 (2.1 - 24.06) | 0.002 | 4.59 (1.97 - 10.7) | <0.001 |  |
|  | 55-65 yrs | 0.87 (0.23 - 3.31) | 0.839 | 1.4 (0.61 - 3.21) | 0.429 |  |
|  | 65-75 yrs | 2.99 (0.93 - 9.62) | 0.066 | 3.13 (1.39 - 7.03) | 0.006 |  |
| BMI (5 kg/cm²) |  | 1.02 (0.83 - 1.26) | 0.838 | 1.16 (1.02 - 1.32) | 0.024 | 0.032 |
| Smoking status |  |  | 0.008 |  | 0.105 | 0.055 |
|  | Non-smoker | Reference |  | Reference |  |  |
|  | Smoker | 1.92 (1.27 - 2.91) | 0.002 | 1.4 (1.02 - 1.92) | 0.039 |  |
|  | Ex-smoker | 1.2 (0.51 - 2.79) | 0.675 | 1.27 (0.87 - 1.85) | 0.214 |  |
| Diabetes |  |  | 0.003 |  | 0.137 | 0.395 |
|  | No | Reference |  | Reference |  |  |
|  | Yes | 2.37 (1.35 - 4.14) | 0.003 | 1.32 (0.91 - 1.91) | 0.137 |  |
| SBP class |  |  | 0.908 |  | <0.001 | 0.005 |
|  | <= 160 mmHg | Reference |  | Reference |  |  |
|  | > 160 mmHg | 0.98 (0.69 - 1.39) | 0.908 | 1.75 (1.34 - 2.27) | <0.001 |  |
| Heart rate (10 bpm) |  | 1.17 (1.01 - 1.34) | 0.033 | 1.11 (1 - 1.23) | 0.041 | 0.55 |
| Blood glucose (mmol/L) |  | 0.9 (0.78 - 1.04) | 0.154 | 1.07 (1.01 - 1.15) | 0.033 | 0.013 |
| eGFR class |  |  | 0.022 |  | 0.004 | 0.04 |
|  | >= 75 ml/min/1,73 m² | Reference |  | Reference |  |  |
|  | 60-75 ml/min/1,73 m² | 1.79 (0.83 - 3.86) | 0.136 | 0.78 (0.53 - 1.17) | 0.233 |  |
|  | < 60 ml/min/1,73 m² | 2.57 (1.23 - 5.38) | 0.012 | 1.31 (0.9 - 1.93) | 0.162 |  |
| ACEi and/or ARB use |  |  | <0.001 |  | 0.011 | 0.774 |
|  | No | Reference |  | Reference |  |  |
|  | Yes | 2.12 (1.47 - 3.05) | <0.001 | 1.44 (1.09 - 1.9) | 0.011 |  |
| Beta-blockers use |  |  | 0.748 |  | 0.604 | 0.711 |
|  | No | Reference |  | Reference |  |  |
|  | Yes | 1.06 (0.73 - 1.56) | 0.748 | 0.92 (0.68 - 1.25) | 0.604 |  |

**Supplementary Table 5: 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 | | | | | | |

Table 6: Multivariable Fine-Gray competing risks models for HF event with or without prior MI (with non-HF death as competing risk) using variables selected in both backwards procedure)

|  | **Multivariable MI+  c-index = 0.826** | |  | | **Multivariable MI-  c-index = 0.704** | | | **Multiplicative interaction in multivariable model** | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Variable** | **HR (CI)** | **P-value** | |  | **HR (CI)** | **P-value** | **P-value interaction** | |
| Sex (male) | 1.79 (1.26 - 2.54) | 0.001 | |  | 1.16 (0.88 - 1.54) | 0.29 | 0.323 | |
| Age class  (ref: age ≤ 55 yrs) |  | <0.001 | |  |  | <0.001 | < 0.001 | |
| 55-65 | 0.61 (0.18 - 2.06) | 0.423 | |  | 1.66 (0.75 - 3.67) | 0.214 |  | |
| 65-75 | 4.05 (1.61 - 10.22) | 0.003 | |  | 4.33 (2.03 - 9.21) | <0.001 |  | |
| > 75 | 12.06 (4.64 - 31.32) | <0.001 | |  | 7.92 (3.62 - 17.32) | <0.001 |  | |
| BMI (5 kg/m²) | 1.03 (0.85 - 1.26) | 0.734 | |  | 1.16 (1.03 - 1.31) | 0.014 | 0.022 | |
| Smoking status  (ref: Non-smoker) |  | 0.001 | |  |  | 0.127 | 0.019 | |
| Smoker | 1.73 (1.18 - 2.54) | 0.005 | |  | 1.17 (0.87 - 1.58) | 0.297 |  | |
| Ex-smoker | 0.47 (0.23 - 0.95) | 0.035 | |  | 0.83 (0.61 - 1.13) | 0.242 |  | |
| Diabetes | 2.71 (1.56 - 4.7) | <0.001 | |  | 1.12 (0.79 - 1.59) | 0.521 | 0.672 | |
| SBP class > 160 mmHg | 0.8 (0.56 - 1.13) | 0.204 | |  | 1.42 (1.11 - 1.82) | 0.006 | 0.002 | |
| Heart rate (10 bpm) | 1.1 (0.97 - 1.24) | 0.144 | |  | 1.09 (0.99 - 1.21) | 0.089 | 0.247 | |
| Blood glucose (mmol/L) | 0.86 (0.73 - 1.02) | 0.076 | |  | 1.09 (1.02 - 1.17) | 0.012 | 0.01 | |
| eGFR class  (ref: ≥ 75 ml/min/1,73 m²) |  | 0.004 | |  |  | 0.002 | 0.015 | |
| 60-75 | 1.91 (0.86 - 4.27) | 0.114 | |  | 0.76 (0.52 - 1.1) | 0.141 |  | |
| < 60 | 3.28 (1.46 - 7.37) | 0.004 | |  | 1.3 (0.9 - 1.88) | 0.155 |  | |

**Supplementary References**

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