Risk Factors for Incident Heart Failure in Age and Sex Specific Strata: a Population-Based cohort using linked Electronic Health Records

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Supplementary material

Supplementary Figure 1 – Flowchart of study population

Legend: CALIBER = Cardiovascular disease research using Linked Bespoke studies and Electronic health Records

Supplementary Figure 2 – Kaplan Meier time-to-event for incident HF

Legend: Kaplan Meier time-to-event curve stratified for age: 55 - 65 year, 65 - 75 years and > 75 years.

Supplementary Figure 3 - Risk factors associated with incident heart failure

Legend: Independent HRs for all individuals, further adjusted for ethnicity, blood pressure lowering medication and lipid regulating drugs. Lowest quintile of social deprivation assessed by index of multiple deprivation, HR (95% CI) = Hazard Ratio (95% Confidence Interval), SBP = Systolic Blood Pressure, DBP = Diastolic Blood Pressure, total WBC count = total White Blood Cell count. Hazard ratios were considered statistically significant if p-value < 0.001 (Bonferroni corrected threshold).

Supplementary Figure 4 - Risk factors associated with incident heart failure in men stratified by age and prior MI

Legend: Independent HRs in a subset of individuals with and without prior MI, further adjusted for ethnicity, blood pressure lowering medication and lipid regulating drugs. Lowest quintile of social deprivation assessed by index of multiple deprivation, MI = Myocardial Infarction, HR (95% CI) = Hazard Ratio (95% Confidence Interval), SBP = Systolic Blood Pressure, DBP = Diastolic Blood Pressure, total WBC count = total White Blood Cell count. Patient events with prior MI: Age category 55-64 years n (events) = 2,426 (285) , age category 65-74 years n (events) = 1,362 (340), age category >75 years n (events) = 1,090 (372). Patient events without prior MI: Age category 55-64 years n

(events) = 255,272 (5,123), age category 65-74 years n (events) = 87,054 (7,707), age category >75 years n (events) = 57,441 (9,487). Hazard ratios were considered statistically significant if p-value < 0.001 (Bonferroni corrected threshold).

Supplementary Figure 5 - Risk factors associated with incident heart failure in women stratified by age and prior MI

Legend: Independent HRs in subset of individuals with and without prior MI, further adjusted for ethnicity, blood pressure lowering medication and lipid regulating drugs. Lowest quintile of social deprivation assessed by index of multiple deprivation, MI = Myocardial Infarction, HR (95% CI) = Hazard Ratio (95% Confidence Interval), SBP = Systolic Blood Pressure, DBP = Diastolic Blood Pressure, total WBC count = total White Blood Cell count. Patient events with prior MI: Age category 55-64 years n (events) = 638 (76), age category 65-74 years n (events) = 688 (175), age category >75 years n (events) = 1,153 (349). Patient events without prior MI: Age category 55-64 years n (events) = 256,726 (2,808), age category 65-74 years n (events) = 100,504 (6,449), age category >75 years n (events) = 107,333 (14,822). Hazard ratios were considered statistically significant if p-value < 0.001 (Bonferroni corrected threshold).

Supplementary Figure 6 - Risk factors associated with incident heart failure in men stratified by age and blood pressure lowering medication

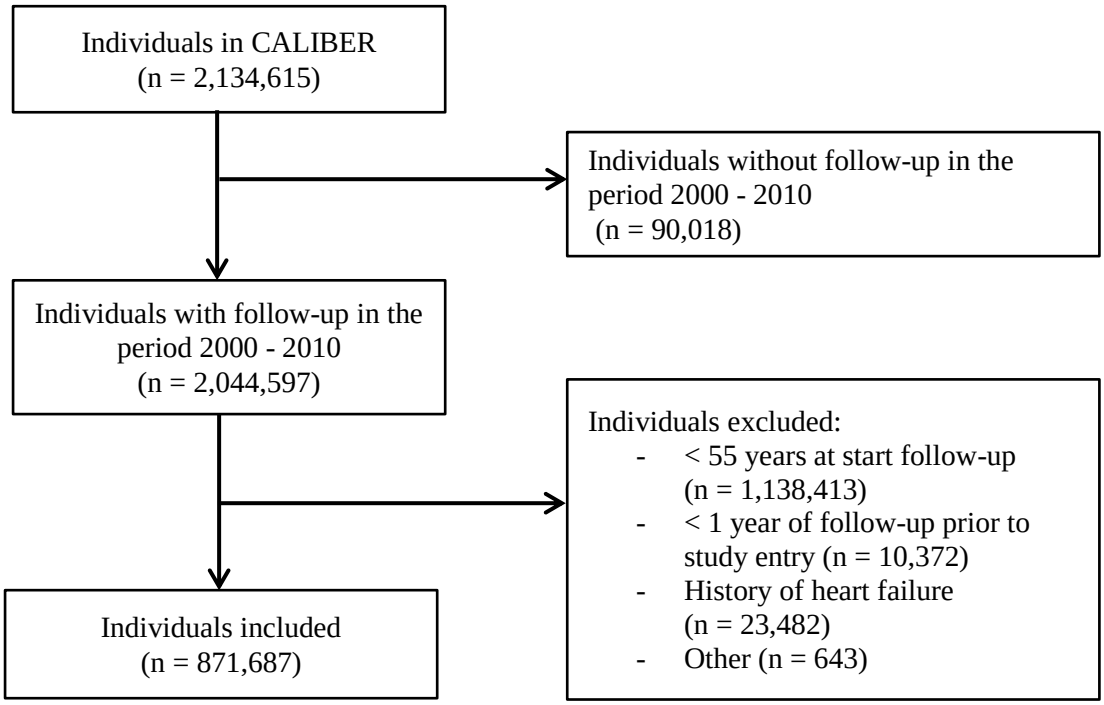
Legend: Independent HRs in subset of individuals with and without blood pressure lowering medication, further adjusted for ethnicity and lipid regulating drugs. Lowest quintile of social deprivation assessed by index of multiple deprivation, HR (95% CI) = Hazard Ratio (95% Confidence Interval), SBP = Systolic Blood Pressure, DBP = Diastolic Blood Pressure, total WBC count = total White Blood Cell count. Patient events with blood pressure lowering medication: Age category 55-64 years n (events) = 68,524 (2,921), age category 65-74 years n (events) = 36,768 (5,090), age category >75 years n (events) = 28,700 (6,725). Patient events without blood pressure lowering medication: Age category 55-64 years n (events) = 189,174 (2,487), age category 65-74 years n (events) = 51,648

(2,957), age category >75 years n (events) = 29,831 (3,134). Hazard ratios were considered statistically significant if p-value < 0.001 (Bonferroni corrected threshold).

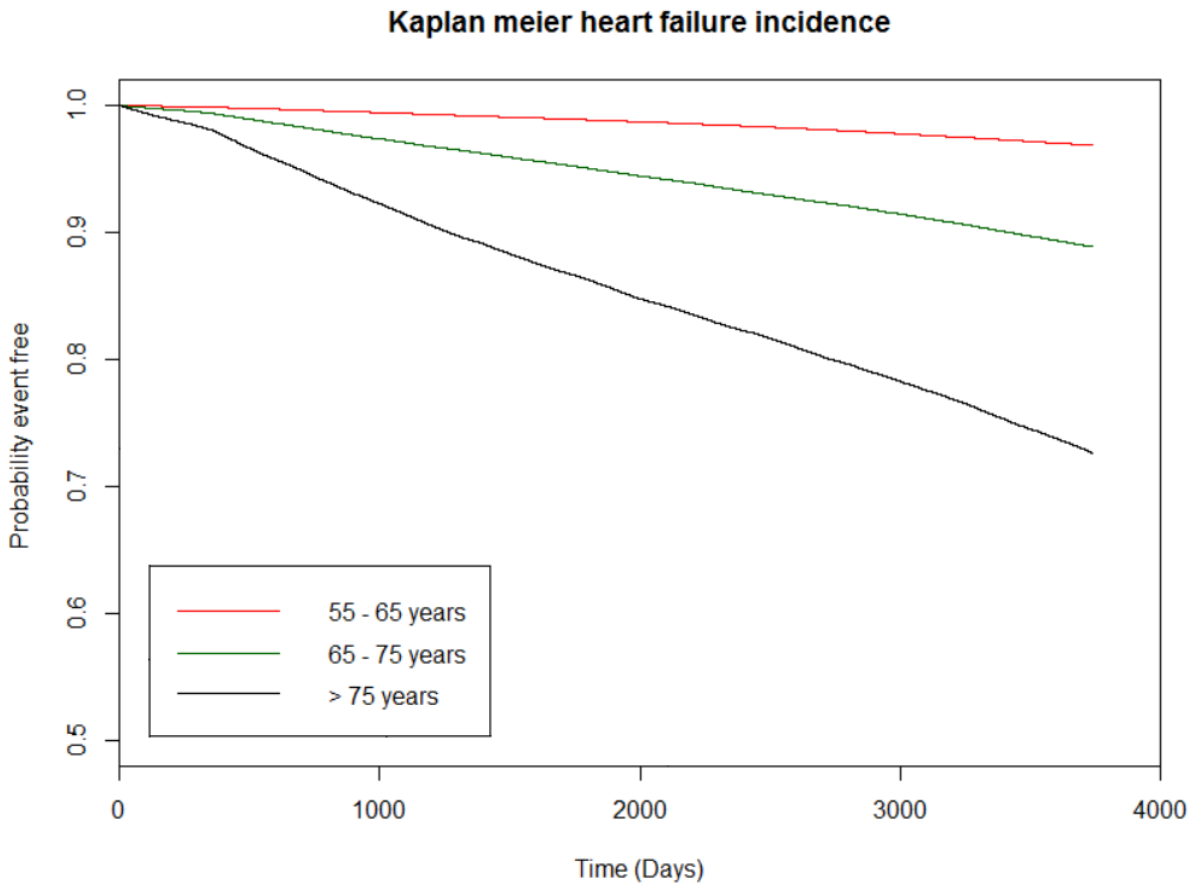
Supplementary Figure 7 - Risk factors associated with incident heart failure in women stratified by age and blood pressure lowering medication

Legend: Independent HRs in subset of individuals with and without blood pressure lowering medication, further adjusted for ethnicity and lipid regulating drugs. Lowest quintile of social deprivation assessed by index of multiple deprivation, HR (95% CI) = Hazard Ratio (95% Confidence Interval), SBP = Systolic Blood Pressure, DBP = Diastolic Blood Pressure, total WBC count = total White Blood Cell count. Patient events with blood pressure lowering medication: Age category 55-64 years n (events) = 69,912 (1659), age category 65-74 years n (events) = 43,712 (4490), age category >75 years n (events) = 60,311 (11,428). Patient events without blood pressure lowering medication: Age category 55-64 years n (events) = 187,452 (1,219), age category 65-74 years n (events) = 57,480 (2,134), age category >75 years n (events) = 48,175 (3,743). Hazard ratios were considered statistically significant if p-value < 0.001 (Bonferroni corrected threshold).

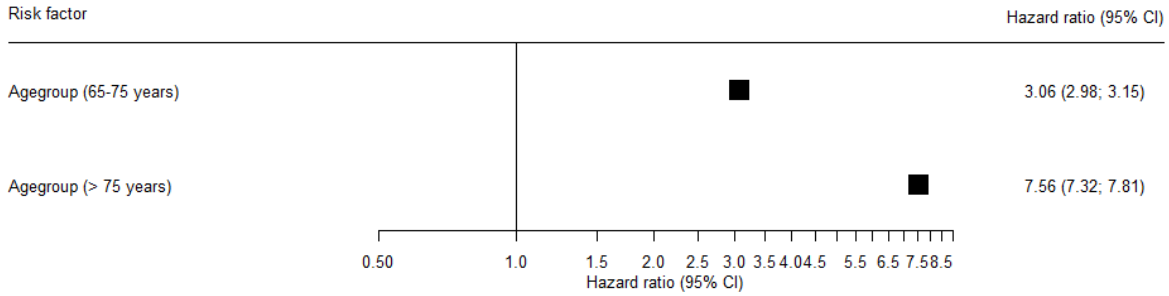
Supplementary Figure 1

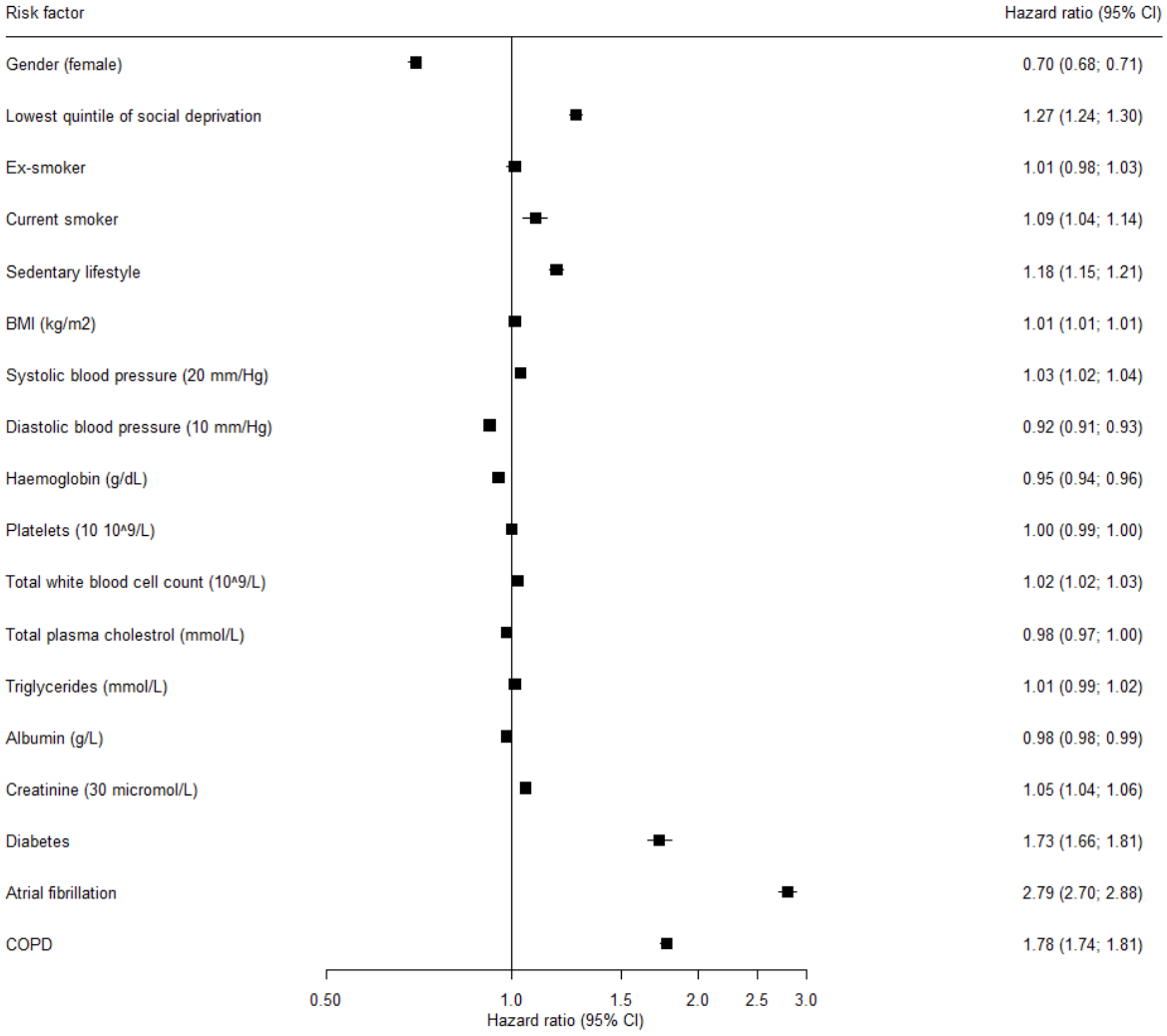


Supplementary Figure 2

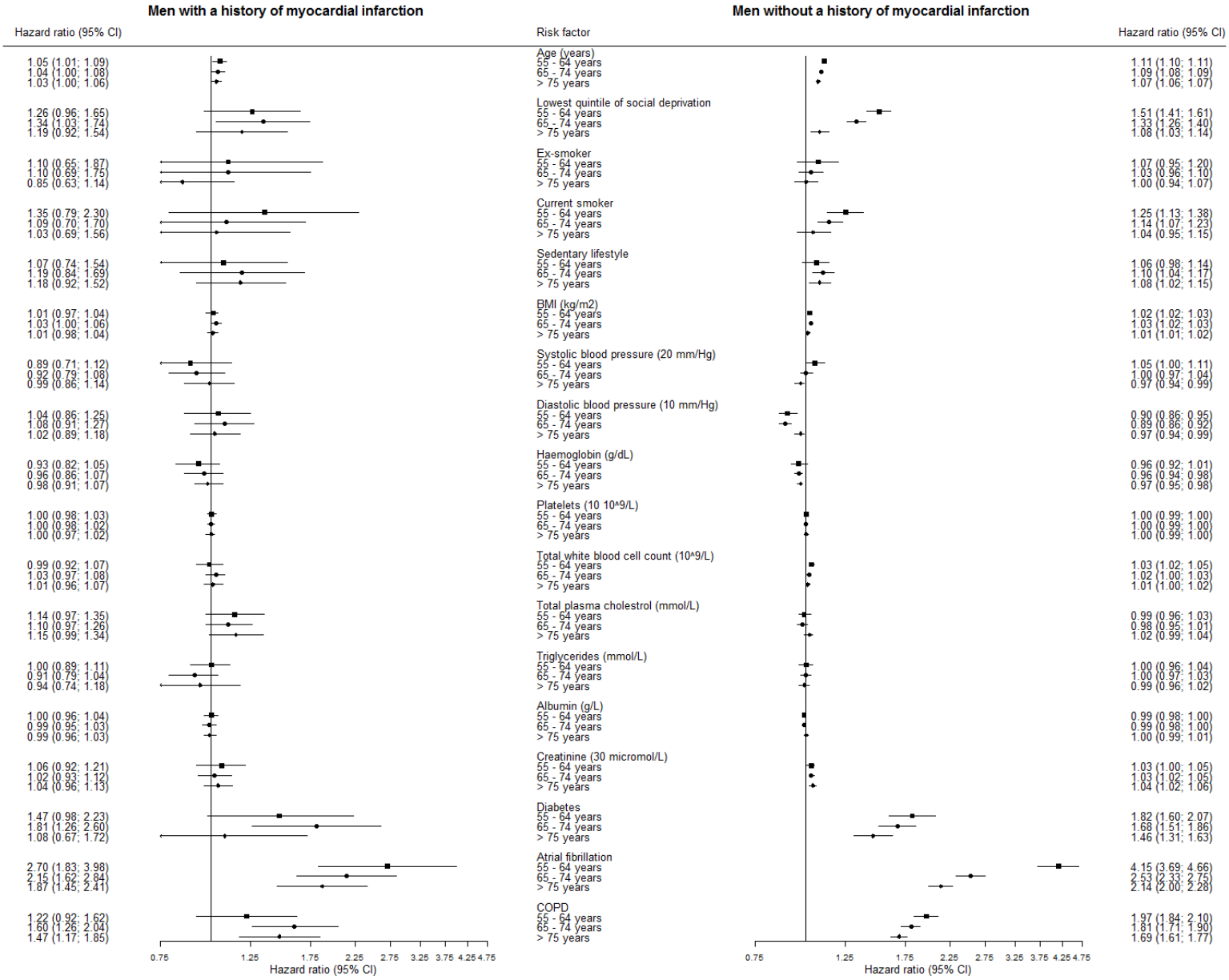


Supplementary Figure 3

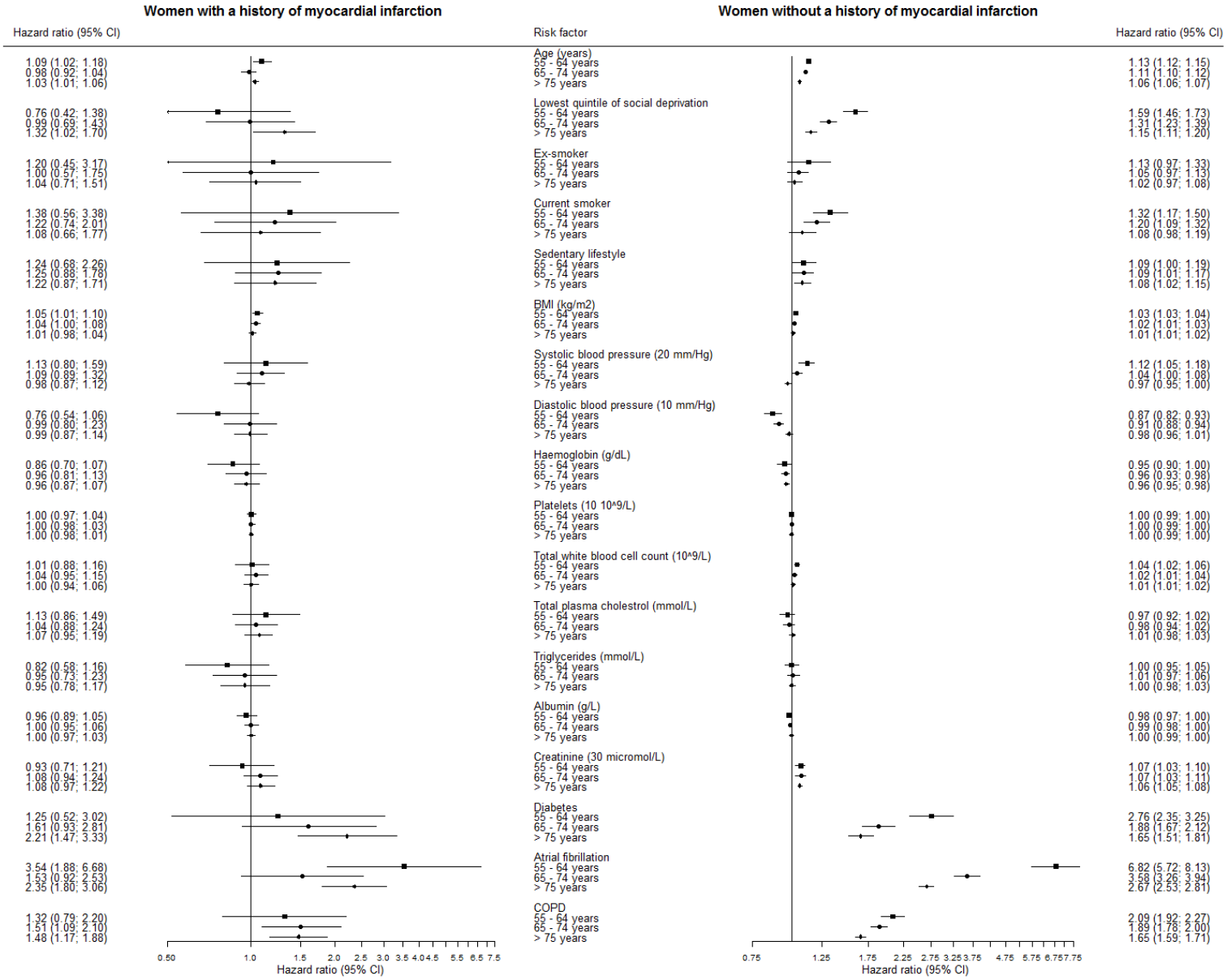




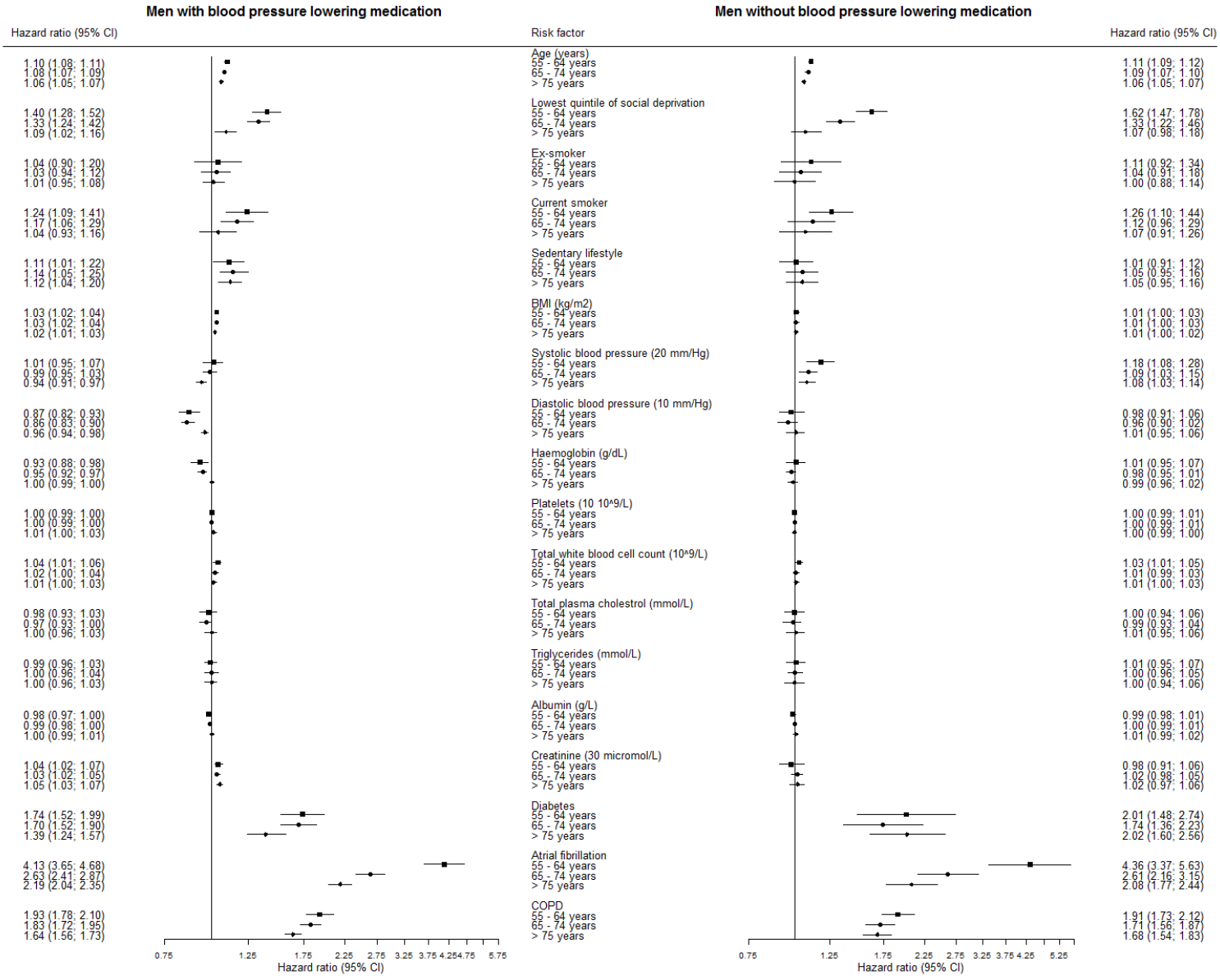
Supplementary Figure 4



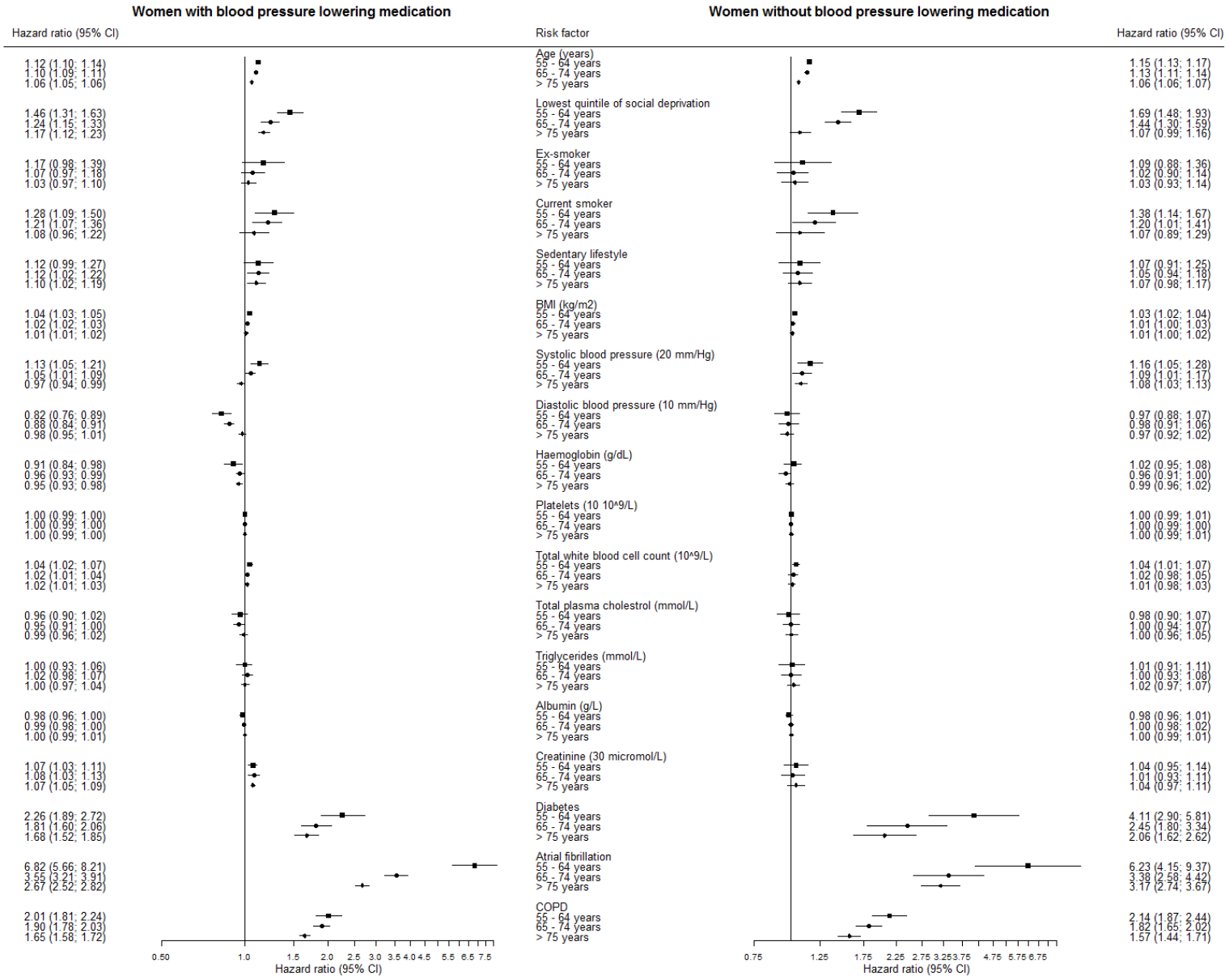
Supplementary Figure 5



Supplementary Figure 6



Supplementary Figure 7



Supplementary Table 1 - Overview of READ and ICD-10 codes used to identify heart failure and myocardial infarction in CPRD and HES data sources

	CPRD READ codes	HES ICD 10
Heart failure	G580400, G210.00, G210000, G210100, G211100, G21z100, G230.00, G232.00, G234.00, G1yz100, 1O1..00, 662W.00, 662p.00, 8B29.00, 8H2S.00, 9Or0.00, G400.00, G41z.11, G554000**,** G554011, G58..00, G58..11, G580.00, G580.11, G580.12, G580.13, G580.14, G580000, G580100, G580200, G580300, G581.00, G581.11, G581.13, G581000, G582.00, G58z.00, G58z.12, G5yy900, G5yyA00, R2y1000	I110, I130, I132, I260, I50
Non-fatal acute myocardial infarction	G30X000, G307100, 323..00, 3233.00, 3234.00, 3235.00, 3236.00, 323Z.00, 889A.00, G30..00, G30..12, G30..13, G30..15, G30..16, G300.00, G301.00, G301000, G301100, G301z00, G302.00, G303.00, G304.00, G305.00, G306.00, G307.00, G307000, G308.00, G309.00, G30B.00, G30X.00, G30y.00, G30y000, G30y100, G30y200, G30yz00, G30z.00, G31y100, G38..00, G380.00, G381.00, G384.00, G38z.00, Gyu3400	I21

Details of how these codes are defined can be found online at http://www.caliberresearch.org/portal/. CPRD = Clinical Practice Research Datalink; HES = Hospital Episode Statistics.

Supplementary Table 2 – Complete cases baseline characteristics stratified by age in men

	55 – 64 years		65 – 74 years		> 75 years		% missing HF	% missing
	HF subjects	Non HF subjects	HF subjects	Non HF subjects	HF subjects	Non HF subjects	**subjects**	**non HF subjects**
Number of patients	5408	252290	8047	80369	9859	48672	23314	381331
Demographics								
Ethnicity (% Caucasian)	96.3	95.1	96.8	95.8	98.3	97.4	18.3	42.0
Most deprived fifth (%)*	26.1	17.1	22.8	18.0	19.4	19.2	0.24	0.35
Lifestyle (%) †								
Smoking							75.3	62.9
Current Smoking	41.7	27.9	23.0	18.0	12.3	12.2	n/a	n/a
Ex-smoker	31.6	29.9	40.4	38.1	40	40.7	n/a	n/a
Never smoked	26.7	42.3	36.6	43.9	47.7	47.2	n/a	n/a
Sedentary lifestyle	51.1	37.1	55.2	40.9	64.1	57.1	79.2	80.3
Clinical measures in mean (sd)								
or median [IQR] †								
Body Mass Index (kg/m^2)	29.5 (5.7)	27.9 (4.7)	28.0 (4.6)	26.8 (4.1)	26.2 (4.1)	25.4 (3.9)	55.7	58.6
Total cholesterol (mmol/L)	5.3 (1.4)	5.4 (1.1)	5.1 (1.0)	5.2 (1.0)	5.0 (1.1)	4.9 (1.1)	66.8	68.4
Triglycerides (mmol /L)	2.1 (1.4)	1.9 (1.3)	1.8 (1.1)	1.7 (1.0)	1.6 (1.0)	1.5 (0.9)	78.9	76.6
LDL cholesterol (mmol/L)	3.3 (1.0)	3.3 (1.0)	3.2 (1.0)	3.2 (1.0)	3.1 (1.1)	2.9 (1.0)	85.2	80.6
HDL cholesterol (mmol/L)	1.2 (0.4)	1.3 (0.4)	1.3 (0.6)	1.3 (0.4)	1.3 (0.5)	1.3 (0.4)	84.1	79.3
SBP (mmHg)	142.9 (19.9)	139.1 (17.2)	147.1 (19.4)	146.0 (18.4)	148.3 (19.9)	147.0 (19.5)	23.2	34.1

DBP (mmHg)	83.7 (10.5)	83.6 (9.6)	81.4 (9.6)	82.1 (9.5)	79.8 (9.8)	79.7 (9.7)	23.2	34.1
Heamoglobin (g/dL)	14.5 (1.6)	14.8 (1.2)	14.0 (1.7)	14.3 (1.5)	13.4 (1.7)	13.5 (1.7)	68.5	71.2
Platelets (10^9/L)	239.0 [87.0]	243.0 [76.5]	224.5 [83.0]	230.0 [80.0]	223.0 [85.3]	230.0 [88.0]	73.2	73.8
Albumin (g/L)	41.2 (4.0)	42.6 (3.6)	40.6 (3.9)	41.2 (3.8)	39.4 (4.1)	39.3 (4.4)	75.8	74.1
Creatinine (micromol/L)	96.5 [25.5]	93.0 [19.0]	103.0 [28.0]	98.0 [22.5]	112.0 [38.8]	105.0 [31.0]	60.0	66.1
eGFR (mL/min/1.73 m^2)	70.2 (18.0)	74.0 (14.6)	62.5 (16.4)	66.1 (14.9)	55.0 (16.0)	59.4 (16.1)	61.4	75.5
Sodium (mmol/L)	139.0 (8.0)	139.7 (7.5)	139.0 (8.1)	139.5 (8.1)	138.8 (8.9)	138.9 (9.6)	64.5	68.0
Potassium (mmol/L)	4.4 (0.8)	4.4 (1.1)	4.6 (4.9)	4.4 (1.9)	4.5 (3.4)	4.4 (2.8)	64.5	68.0
Total WBC count (10^9 / L)	8.0 (2.8)	7.1 (2.2)	7.7 (2.7)	7.2 (2.5)	7.7 (3.2)	7.4 (2.6)	72.9	73.9
Comorbidity (%) §								
Atrial fibrillation	6.5	0.9	8.8	2.4	11.1	4.6	n/a	n/a
COPD	22.4	10.2	25.4	13.8	27.7	18.1	n/a	n/a
Diabetes mellitus	5.5	1.6	5.3	2.3	3.7	2.4	n/a	n/a
Myocardial infarction	5.3	0.9	4.2	1.3	3.8	1.5	n/a	n/a
Hypertension	68.5	44.8	78.8	60.2	83.4	65.4	15.1	31.1
Obesity	19.5	11.4	13.6	7.9	6.8	4.3	55.7	58.6
Medication use (%) ¤								
Blood pressure lowering medication	37.3	15.9	48.7	26.4	59.0	34.9	n/a	n/a
Lipid regulating drugs	29.6	13.6	26.2	17.2	11.5	10.7	n/a	n/a

*assessed by index of multiple deprivation † measurement closest to and within 3 years before baseline. § denotes prior medical history of given comorbidity 3 years before baseline. SD = Standard Deviation; LDL = Low Density Lipoprotein; HDL = High Density Lipoprotein; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; total WBC count = total White Blood Cell count; eGFR = estimated Glomerular Filtration Rate; COPD = Chronic Obstructive Pulmonary Disease.

Supplementary Table 3 - Complete cases baseline characteristics stratified by age in women

	55 – 64 years		65 – 74 years		> 75 years		% missing HF	% missing
	HF subjects	Non HF subjects	HF subjects	Non HF subjects	HF subjects	Non HF subjects	**subjects**	**non HF subjects**
Number of patients	2878	254486	6624	94568	15171	93315	24673	442369
Demographics								
Ethnicity (% Caucasian)	95.0	94.5	96.7	96.0	98.8	98.1	19.9	38.9
Most deprived fifth (%)*	29.4	16.3	25.3	18.5	22.1	19.0	0.24	0.36
Lifestyle (%) †								
Smoking							78.1	62.4
Current Smoking	34.8	22.0	22.3	13.9	8.2	7.1	n/a	n/a
Ex-smoker	25.7	21.2	26.1	22.9	23.1	21.4	n/a	n/a
Never smoked	39.6	56.8	51.7	63.2	68.7	71.6	n/a	n/a
Sedentary lifestyle	62.6	41.8	68.0	51.3	78.0	69.8	82.1	78.4
Clinical measures in mean (sd)								
or median [IQR] †								
Body Mass Index (kg/m^2)	31.3 (7.7)	27.8 (5.8)	29.0 (6.3)	27.0 (5.3)	26.2 (5.2)	25.1 (4.8)	61.0	54.6
Total cholesterol (mmol/L)	5.6 (1.2)	5.8 (1.1)	5.7 (1.2)	5.8 (1.2)	5.7 (1.3)	5.6 (1.2)	77.0	72.8
Triglycerides (mmol /L)	2.0 (1.1)	1.6 (1.0)	2.0 (1.2)	1.7 (0.9)	1.8 (1.1)	1.6 (0.9)	86.2	80.0
LDL cholesterol (mmol/L)	3.4 (1.1)	3.5 (1.0)	3.5 (1.1)	3.5 (1.1)	3.4 (1.2)	3.3 (1.2)	90.0	83.3
HDL cholesterol (mmol/L)	1.5 (0.5)	1.6 (0.5)	1.5 (0.5)	1.6 (0.5)	1.5 (0.5)	1.6 (0.5)	89.4	82.0
SBP (mmHg)	145.2 (19.8)	136.7 (17.7)	151.5 (20.1)	148.2 (18.9)	152.9 (21.0)	150.2 (20.8)	23.1	25.9

DBP (mmHg)	83.2 (9.9)	81.5 (9.3)	82.6 (9.9)	82.6 (9.3)	81.4 (9.9)	80.8 (10.0)	23.1	25.9
Heamoglobin (g/dL)	13.3 (1.6)	13.5 (1.1)	13.1 (1.5)	13.3 (1.3)	12.7 (1.5)	12.7 (1.5)	64.0	65.7
Platelets (10^9/L)	265.8 [94.0]	270.0 [82.0]	259.0 [93.0]	263.0 [87.5]	256.0 [95.8]	264.0 [96.5]	69.7	69.0
Albumin (g/L)	40.4 (3.9)	42.0 (3.5)	40.2 (3.8)	40.9 (3.7)	39. (4.2)	39.0 (4.4)	75.8	73.1
Creatinine (micromol/L)	81.0 [23.0]	77.0 [16.5]	87.0 [25.5]	81.5 [20.0]	94.0 [32.5]	87.0 [27.0]	60.0	65.2
eGFR (mL/min/1.73 m^2)	64.2 (17.8)	68.9 (14.3)	56.5 (15.6)	61.1 (14.5)	50.5 (15.1)	55.0 (15.3)	61.7	74.1
Sodium (mmol/L)	139.3 (7.4)	139.9 (6.9)	138.9 (9.1)	139.4 (9.5)	138.2 (9.4)	138.3 (10.1)	63.9	66.7
Potassium (mmol/L)	4.3 (0.6)	4.3 (2.4)	4.5 (8.2)	4.4 (2.5)	4.3 (1.2)	4.3 (2.7)	63.9	66.7
Total WBC count (10^9 / L)	7.8 (2.5)	6.7 (2.1)	7.6 (2.4)	7.0 (2.3)	7.6 (2.7)	7.3 (2.5)	69.6	69.0
Comorbidity (%) §								
Atrial fibrillation	5.4	0.4	7.7	1.4	10.9	3.7	n/a	n/a
COPD	29.4	13.1	27.4	14.1	24.6	15.2	n/a	n/a
Diabetes mellitus	6.5	1.1	4.9	1.7	3.4	1.9	n/a	n/a
Myocardial infarction	2.6	0.2	2.6	0.5	2.3	0.9	n/a	n/a
Hypertension	72.6	46.6	81.5	63.3	86.8	70.4	11.5	21.9
Obesity	26.4	14.5	17.2	10.4	7.4	4.8	61.0	54.6
Medication use (%) ¤								
Blood pressure lowering medication	47.2	18.9	58.6	31.8	69.1	44.2	n/a	n/a
Lipid regulating drugs	22.9	9.4	21.6	14.3	8.8	8.7	n/a	n/a

*assessed by index of multiple deprivation † measurement closest to and within 3 years before baseline. § denotes prior medical history of given comorbidity 3 years before baseline. SD = Standard Deviation; LDL = Low Density Lipoprotein; HDL = High Density Lipoprotein; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; total WBC count = total White Blood Cell count; eGFR = estimated Glomerular Filtration Rate; COPD = Chronic Obstructive Pulmonary Disease.

Supplementary Table 4 - Complete case analysis for risk factors associated with incident heart failure stratified by age in men

	55 – 64 years	**65 – 74 years**	**> 75 years**	**Total**
n (events)	25,932 (478)	5,569 (498)	2,765 (346)	34,266 (1,322)
Risk Factors	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**
Age (years)	1.05 (1.06; 1.15)	1.09 (1.03; 1.16)	1.08 (1.03; 1.12)	1.08 (1.05; 1.11)
Most deprived fifth †	1.09 (1.21; 2.12)	1.65 (1.13; 2.42)	1.40 (0.91; 2.15)	1.34 (1.07; 1.67)
Ex-smokers	1.27 (0.77: 1.67)	0.77 (0.53; 1.13)	0.95 (0.64; 1.41)	0.98 (0.78; 1.23)
Current-smokers	1.67 (0.71; 1.67)	1.17 (0.69; 2.01)	1.50 (0.75; 2.98)	1.45 (1.09; 1.94)
Sedentary lifestyle	1.11 (1.13; 2.53)	1.31 (0.92; 1.87)	1.78 (1.15; 2.74)	1.34 (1.09; 1.64)
Body Mass Index (kg/m^2)	1.06 (1.01; 1.05)	1.01 (0.97; 1.05)	1.04 (0.99; 1.09)	1.05 (1.02; 1.07)
SBP (per 20 mm/hg)	0.85 (0.85; 1.26)	1.06 (0.85; 1.32)	0.82 (0.64; 1.06)	0.90 (0.79; 1.04)
DBP (per 10 mm/hg)	0.86 (0.76; 1.02)	0.82 (0.66; 1.01)	0.97 (0.75; 1.24)	0.87 (0.76; 0.99)
Haemoglobin (g/dL)	0.86 (0.91; 1.01)	0.92 (0.82; 1.04)	0.91 (0.79; 1.04)	0.90 (0.84; 0.97)
Platelets (per 10 10^9/L)	0.98 (0.96; 1.00)	0.98 (0.95; 1.01)	0.97 (0.94; 1.00)	0.98 (0.96; 0.99)
Total WBC count (10^9 / L)	1.14 (1.06; 1.16)	1.01 (0.92; 1.10)	1.03 (0.94; 1.14)	1.07 (1.03; 1.12)
Total cholesterol (mmol/L)	0.99 (0.87; 1.12)	0.94 (0.78; 1.13)	0.96 (0.78; 1.19)	0.97 (0.87; 1.08)
Triglycerides (mmol /L)	0.87 (0.90; 1.13)	1.17 (0.97; 1.42)	0.91 (0.69; 1.19)	0.95 (0.86; 1.05)
Albumin (g/L)	0.95 (0.92; 0.99)	0.92 (0.88; 0.97)	0.99 (0.94; 1.05)	0.95 (0.93; 0.98)
Creatinine (per 30 µmol/L)	1.13 (1.03; 1.17)	1.04 (0.99; 1.09)	1.23 (1.06; 1.43)	1.05 (1.02; 1.08)
Diabetes	0.72 (0.37; 1.38)	1.27 (0.70; 2.32)	1.31 (0.67; 2.56)	1.01 (0.70; 1.44)
Atrial fibrillation	2.47 (1.32; 4.60)	2.59 (1.54; 4.36)	1.93 (1.13; 3.29)	2.34 (1.90; 4.24)
COPD	1.87 (1.32; 2.65)	1.23 (0.80;1.90)	1.20 (0.76; 1.88)	1.43 (1.14; 1.79)

Further adjusted for ethnicity, blood pressure lowering medication and lipid regulating drugs. † Assessed by index of multiple deprivation, HR (95% CI) = Hazard Ratio (95% Confidence Interval), SBP = Systolic Blood Pressure, DBP = Diastolic Blood Pressure, total WBC count = total White Blood Cell count. Hazard ratios were considered statistically significant if p-value < 0.001 (Bonferroni corrected threshold).

Supplementary Table 5 - Complete case analysis for risk factors associated with incident heart failure stratified by age in women

	55 – 64 years	**65 – 74 years**	**> 75 years**	**Total**
n (events)	26,036 (227)	5,846 (325)	4078 (423)	35,960 (984)
Risk Factors	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**
Age (years)	1.09 (1.02; 1.16)	1.08 (1.00; 1.18)	1.08 (1.04; 1.13)	1.09 (1.06; 1.12)
Most deprived fifth †	1.17 (0.70; 1.95)	1.60 (0.96; 2.64)	1.26 (0.84; 1.90)	1.34 (1.04; 1.76)
Ex-smokers	0.79 (0.44: 1.43)	1.76 (1.00; 3.09)	1.38 (0.95; 2.02)	1.25 (0.95; 1.64)
Current-smokers	0.99 (0.54; 1.82)	2.28 (1.13; 4.60)	1.48 (0.71; 3.11)	1.50 (1.03; 2.19)
Sedentary lifestyle	1.63 (1.00; 2.68)	1.35 (0.79; 2.30)	1.39 (0.90; 2.15)	1.42 (1.08; 1.87)
Body Mass Index (kg/m^2)	1.02 (0.98; 1.05)	1.04 (0.99; 1.09)	1.00 (0.97; 1.04)	1.02 (1.00; 1.04)
SBP (per 20 mm/hg)	0.88 (0.63; 1.24)	0.82 (0.61; 1.12)	1.00 (0.81; 1.24)	0.93 (0.80; 1.09)
DBP (per 10 mm/hg)	0.96 (0.71; 1.29)	0.85 (0.63; 1.14)	0.98 (0.79; 1.20)	0.92 (0.80; 1.06)
Haemoglobin (g/dL)	0.94 (0.77; 1.14)	0.98 (0.79; 1.22)	0.94 (0.82; 1.09)	0.93 (0.84; 1.03)
Platelets (per 10 10^9/L)	1.00 (0.96; 1.03)	0.96 (0.93; 1.00)	0.98 (0.96; 1.01)	0.98 (0.96; 1.00)
Total WBC count (10^9 / L)	1.08 (1.00; 1.16)	0.97 (0.85; 1.12)	1.05 (0.99; 1.11)	1.04 (1.00; 1.09)
Total cholesterol (mmol/L)	1.10 (0.88; 1.38)	0.91 (0.72; 1.15)	0.96 (0.81; 1.14)	0.99 (0.89; 1.11)
Triglycerides (mmol /L)	1.02 (0.84; 1.25)	1.16 (0.90; 1.50)	0.90 (0.68; 1.19)	1.01 (0.88; 1.15)
Albumin (g/L)	0.90 (0.84; 0.97)	0.96 (0.90; 1.02)	0.97 (0.92; 1.03)	0.95 (0.94; 0.99)
Creatinine (per 30 µmol/L)	1.06 (0.93; 1.21)	0.99 (0.72; 1.36)	1.07 (0.92; 1.24)	1.04 (0.94; 1.16)
Diabetes	2.76 (1.46; 5.24)	2.59 (1.17; 5.75)	1.43 (0.66; 3.11)	2.28 (1.52; 3.41)
Atrial fibrillation	6.09 (2.52; 14.73)	5.94 (2.85; 12.33)	1.34 (0.71; 2.54)	2.50 (1.66; 3.78)
COPD	2.31 (1.43; 3.75)	4.15 (2.55; 6.75)	1.85 (1.21; 2.81)	2.39 (1.84; 3.09)

Further adjusted for ethnicity, blood pressure lowering medication and lipid regulating drugs. † Assessed by index of multiple deprivation, HR (95% CI) = Hazard Ratio (95% Confidence Interval), SBP = Systolic Blood Pressure, DBP = Diastolic Blood Pressure, total WBC count = total White Blood Cell count. Hazard ratios were considered statistically significant if p-value < 0.001 (Bonferroni corrected threshold).

Supplementary Table 6 - Evaluation of heterogeneity at practice level for the association of risk factors with heart failure stratified by age in men

	55 – 64 years	**65 – 74 years**	**> 75 years**
n (events)	257,698 (5,408)	88,416 (8,047)	58,531 (9,859)
Risk Factors	**HR (95% CI)***	**HR (95% CI)***	**HR (95% CI)***
Age (years)	1.10 (1.09; 1.11)	1.08 (1.08; 1.09)	1.07 (1.06; 1.07)
Most deprived fifth †	1.41 (1.31; 1.51)	1.27 (1.19; 1.35)	1.08 (1.02; 1.15)
Ex-smokers	1.08 (0.96; 1.21)	1.03 (0.97; 1.10)	1.00 (0.94; 1.06)
Current-smokers	1.27 (1.15; 1.41)	1.15 (1.07; 1.23)	1.06 (0.96; 1.16)
Sedentary lifestyle	1.06 (0.99; 1.14)	1.10 (1.04; 1.17)	1.08 (1.01; 1.15)
Body Mass Index (kg/m^2)	1.02 (1.01; 1.03)	1.02 (1.02; 1.03)	1.01 (1.01; 1.02)
SBP (per 20 mm/hg)	1.03 (0.98; 1.08)	0.99 (0.96; 1.02)	0.96 (0.93; 0.99)
DBP (per 10 mm/hg)	0.91 (0.87; 0.95)	0.90 (0.87; 0.92)	0.97 (0.94; 0.99)
Haemoglobin (g/dL)	0.96 (0.92; 1.01)	0.96 (0.95; 0.98)	0.97 (0.95; 0.99)
Platelets (per 10 10^9/L)	1.00 (0.99; 1.00)	1.00 (0.99; 1.00)	1.00 (0.99; 1.00)
Total WBC count (10^9 / L)	1.03 (1.02; 1.05)	1.02 (1.00; 1.03)	1.01 (1.00; 1.02)
Total cholesterol (mmol/L)	0.99 (0.95; 1.03)	0.98 (0.95; 1.01)	1.02 (0.99; 1.05)
Triglycerides (mmol /L)	1.00 (0.96; 1.03)	0.99 (0.96; 1.02)	0.99 (0.96; 1.02)
Albumin (g/L)	0.99 (0.97; 1.00)	0.99 (0.98; 1.00)	1.00 (0.99; 1.01)
Creatinine (per 30 µmol/L)	1.03 (1.01; 1.05)	1.03; 1.01; 1.05)	1.04 (1.02; 1.06)
Diabetes	1.80 (1.59; 2.04)	1.69 (1.53; 1.87)	1.44 (1.30; 1.60)
Atrial fibrillation	4.09 (3.66; 4.58)	2.52 (2.33; 2.73)	2.16 (2.02; 2.30)
COPD	1.94 (1.81; 2.07)	1.82; 1.73; 1.92)	1.69 (1.62; 1.77)

*Estimates of random effects accounting for practice level heterogeneity, further adjusted for ethnicity, blood pressure lowering medication and lipid regulating drugs. † Assessed by index of multiple deprivation, HR (95% CI) = Hazard Ratio (95% Confidence Interval), SBP = Systolic Blood Pressure, DBP = Diastolic Blood Pressure, total WBC count = total White Blood Cell count. Hazard ratios were considered statistically significant if p-value < 0.001 (Bonferroni corrected threshold).

Supplementary Table 7 - Evaluation of heterogeneity at practice level for the association of risk factors with heart failure stratified by age in women

	55 – 64 years	**65 – 74 years**	**> 75 years**
n (events)	257,364 (2,878)	101,192 (6,624)	108,486 (15,171)
Risk Factors	**HR (95% CI)***	**HR (95% CI)***	**HR (95% CI)***
Age (years)	1.14 (1.12; 1.15)	1.11 (1.10; 1.12)	1.06 (1.06; 1.07)
Most deprived fifth †	1.46 (1.33; 1.60)	1.27 (1.19; 1.36)	1.12 (1.07; 1.18)
Ex-smokers	1.14 (0.97; 1.34)	1.05 (0.97; 1.14)	1.03 (0.98; 1.09)
Current-smokers	1.34 (1.19; 1.51)	1.21 (1.10; 1.32)	1.09 (0.99; 1.20)
Sedentary lifestyle	1.09 (1.00; 1.19)	1.08 (1.01; 1.16)	1.08 (1.01; 1.14)
Body Mass Index (kg/m^2)	1.03 (1.03; 1.04)	1.02 (1.02; 1.03)	1.01 (1.01; 1.01)
SBP (per 20 mm/hg)	1.11 (1.04; 1.17)	1.03 (1.00; 1.07)	0.97 (0.95; 0.99)
DBP (per 10 mm/hg)	0.87 (0.82; 0.92)	0.91 (0.88; 0.94)	0.98 (0.96; 1.01)
Haemoglobin (g/dL)	0.95 (0.90; 1.01)	0.96 (0.93; 0.98)	0.97 (0.95; 0.98)
Platelets (per 10 10^9/L)	1.00 (0.99; 1.00)	1.00 (0.99; 1.00)	1.00 (0.99; 1.00)
Total WBC count (10^9 / L)	1.04 (1.02; 1.06)	1.02 (1.01; 1.04)	1.01 (1.01; 1.02)
Total cholesterol (mmol/L)	0.97 (0.92; 1.02)	0.98 (0.94; 1.01)	1.01 (0.98; 1.03)
Triglycerides (mmol /L)	1.00 (0.95; 1.05)	1.01 (0.96; 1.05)	1.00 (0.97; 1.02)
Albumin (g/L)	0.98 (0.97; 1.00)	0.99 (0.98; 1.00)	1.00 (0.99; 1.00)
Creatinine (per 30 µmol/L)	1.06 (1.03; 1.10)	1.06 (1.02; 1.11)	1.06 (1.04; 1.08)
Diabetes	2.71 (2.31; 3.18)	1.89 (1.68; 2.13)	1.66 (1.52; 1.82)
Atrial fibrillation	6.90 (5.82; 8.19)	3.51 (3.20; 3.85)	2.70 (2.56; 2.84)
COPD	2.11 (1.94; 2.29)	1.94 (1.83; 2.05)	1.65 (1.59; 1.72)

* Estimates of random effects accounting for practice level heterogeneity, further adjusted for ethnicity, blood pressure lowering medication and lipid regulating drugs. † Assessed by index of multiple deprivation, HR (95% CI) = Hazard Ratio (95% Confidence Interval), SBP = Systolic Blood Pressure, DBP = Diastolic Blood Pressure, total WBC count = total White Blood Cell count. Hazard ratios were considered statistically significant if p-value < 0.001 (Bonferroni corrected threshold).

Supplementary Table 8 - Associations of risk factors with incident heart failure stratified by age and end points from different sources of EHR in men

	55 – 64 years		65 – 74 years		> 75 years	
	CPRD	**HES**	**CPRD**	**HES**	**CPRD**	**HES**
n (events)	254,731 (2,441)	255,257 (2,967)	84,150 (3,781)	84,635 (4,266)	53,146 (4,474)	54,057 (5,385)
Risk Factors	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**
Age (years)	1.12 (1.11; 1.13)	1.09 (1.08; 1.11)	1.09 (1.08; 1.11)	1.08 (1.07; 1.09)	1.05 (1.04; 1.06)	1.08 (1.07; 1.09)
Most deprived fifth †	1.41 (1.28; 1.56)	1.58 (1.45; 1.72)	1.24 (1.14; 1.34)	1.44 (1.33; 1.54)	1.00 (0.93; 1.08)	1.15 (1.08; 1.23)
Ex-smokers	1.08 (0.92; 1.27)	1.07 (0.93; 1.24)	1.02 (0.92; 1.13)	1.04 (0.96; 1.14)	0.99 (0.90; 1.08)	1.00 (0.93; 1.08)
Current-smokers	1.23 (1.07; 1.42)	1.31 (1.14; 1.51)	1.10 (0.97; 1.25)	1.21 (1.09; 1.34)	1.05 (0.91; 1.21)	1.06 (0.94; 1.20)
Sedentary lifestyle	1.09 (0.98; 1.22)	1.03 (0.93; 1.14)	1.10 (1.00; 1.22)	1.12 (1.03; 1.22)	1.07 (0.97; 1.19)	1.10 (1.02; 1.19)
Body Mass Index (kg/m^2)	1.03 (1.02; 1.04)	1.02 (1.01; 1.03)	1.03 (1.02; 1.04)	1.02 (1.01; 1.03)	1.01 (1.01; 1.02)	1.01 (1.01; 1.02)
SBP (per 20 mm/hg)	1.01 (0.94; 1.08)	1.06 (0.99; 1.12)	0.95 (0.91; 1.00)	1.04 (1.00; 1.09)	0.99 (0.95; 1.03)	0.94 (0.91; 0.98)
DBP (per 10 mm/hg)	0.91 (0.85; 0.97)	0.90 (0.85; 0.96)	0.90 (0.86; 0.94)	0.89 (0.85; 0.93)	0.97 (0.93; 1.02)	0.96 (0.92; 0.99)
Haemoglobin (g/dL)	0.97 (0.93; 1.02)	0.95 (0.89; 1.02)	0.96 (0.94; 0.99)	0.96 (0.93; 0.99)	0.97 (0.94; 1.00)	0.96 (0.94; 0.98)
Platelets (per 10 10^9/L)	1.00 (0.99; 1.01)	1.00 (0.99; 1.00)	1.00 (0.99; 1.00)	1.00 (0.99; 1.00)	0.99 (0.99; 1.00)	1.00 (0.99; 1.00)
Total WBC count (10^9 / L)	1.03 (1.01; 1.06)	1.03 (1.01; 1.05)	1.02 (1.00; 1.04)	1.02 (1.00; 1.03)	1.02 (1.00; 1.03)	1.01 (0.99; 1.02)
Total cholesterol (mmol/L)	0.98 (0.92; 1.04)	1.00 (0.95; 1.06)	0.99 (0.94; 1.03)	0.98 (0.94; 1.02)	1.03 (1.00; 1.07)	1.01 (0.98; 1.05)
Triglycerides (mmol /L)	1.01 (0.96; 1.05)	1.00 (0.95; 1.04)	0.98 (0.93; 1.04)	1.00 (0.97; 1.04)	0.99 (0.95; 1.04)	0.99 (0.95; 1.03)
Albumin (g/L)	0.99 (0.98; 1.00)	0.99 (0.97; 1.01)	0.99 (0.97; 1.00)	0.99 (0.98; 1.00)	0.99 (0.98; 1.01)	1.00 (0.99; 1.01)
Creatinine (per 30 µmol/L)	1.03 (0.99; 1.06)	1.04 (1.01; 1.06)	1.02; 1.00; 1.05)	1.03; 1.02; 1.05)	1.04 (1.01; 1.07)	1.05 (1.02; 1.08)
Diabetes	1.75 (1.45; 2.10)	1.88 (1.60; 2.22)	1.49 (1.27; 1.73)	1.97 (1.72; 2.24)	1.27 (1.07; 1.50)	1.63 (1.42; 1.87)
Atrial fibrillation	4.61 (3.93; 5.39)	3.83 (3.28; 4.48)	2.82 (2.52; 3.15)	2.45 (2.19; 2.75)	2.22 (2.02; 2.44)	2.25 (2.07; 2.46)
COPD	2.00 (1.82; 2.20)	1.90 (1.74; 2.08)	2.02 (1.88; 2.17)	1.68 (1.56; 1.80)	1.91 (1.79; 2.03)	1.59 (1.50; 1.69)

***** Further adjusted for ethnicity, blood pressure lowering medication and lipid regulating drugs. † Assessed by index of multiple deprivation, EHR = Electronic Health Records, CPRD = Clinical Practice Research Datalink, HES = Hospital Episode Statistics, HR (95% CI) = Hazard Ratio (95% Confidence Interval), SBP = Systolic Blood Pressure, DBP = Diastolic Blood Pressure, total WBC count = total White Blood Cell count. Hazard ratios were considered statistically significant if p-value < 0.001 (Bonferroni corrected threshold).

Supplementary table 9 - Associations of risk factors with incident heart failure stratified by age and end points from different sources of EHR in women

	55 – 64 years		65 – 74 years		> 75 years	
	CPRD	**HES**	**CPRD**	**HES**	**CPRD**	**HES**
n (events)	255,703 (1,216)	256,148 (1,662)	97,522 (2,954)	98,238 (3,670)	100,096 (6,781)	101,705 (8,390)
Risk Factors	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**
Age (years)	1.16 (1.14; 1.18)	1.12 (1.10; 1.13)	1.11 (1.10; 1.13)	1.11 (1.11; 1.13)	1.05 (1.05; 1.06)	1.07 (1.07; 1.08)
Most deprived fifth †	1.53 (1.34; 1.75)	1.61 (1.44; 1.80)	1.25 (1.15; 1.37)	1.36 (1.26; 1.47)	1.07 (1.01; 1.14)	1.24 (1.17; 1.30)
Ex-smokers	1.13 (0.88; 1.43)	1.16 (0.98; 1.36)	1.02 (0.90; 1.16)	1.08 (0.98; 1.18)	1.02 (0.94; 1.11)	1.03 (0.97; 1.09)
Current-smokers	1.30 (1.04; 1.64)	1.39 (1.20; 1.61)	1.17 (1.02; 1.36)	1.26 (1.11; 1.42)	1.02 (0.89; 1.18)	1.15 (1.02; 1.30)
Sedentary lifestyle	1.14 (0.97; 1.32)	1.07 (0.95; 1.20)	1.06 (0.94; 1.18)	1.12 (1.03; 1.21)	1.08 (1.00; 1.17)	1.09 (1.01; 1.18)
Body Mass Index (kg/m^2)	1.03 (1.02; 1.05)	1.04 (1.03; 1.05)	1.02 (1.01; 1.03)	1.02 (1.01; 1.03)	1.01 (1.00; 1.02)	1.01 (1.01; 1.02)
SBP (per 20 mm/hg)	1.09 (1.00; 1.19)	1.13 (1.05; 1.22)	1.04 (0.99; 1.10)	1.04 (0.99; 1.09)	0.98 (0.95; 1.01)	0.97 (0.94; 1.00)
DBP (per 10 mm/hg)	0.88 (0.80; 0.97)	0.86 (0.80; 0.93)	0.92 (0.88; 0.97)	0.89 (0.85; 0.93)	1.01 (0.97; 1.04)	0.96 (0.93; 0.99)
Haemoglobin (g/dL)	0.97 (0.89; 1.05)	0.93 (0.88; 0.99)	0.97 (0.93; 1.01)	0.94 (0.91; 0.97)	0.97 (0.95; 0.99)	0.96 (0.93; 0.98)
Platelets (per 10 10^9/L)	1.00 (0.99; 1.01)	1.00 (0.99; 1.01)	1.00 (0.99; 1.00)	1.00 (0.99; 1.01)	1.00 (0.99; 1.00)	1.00 (0.99; 1.00)
Total WBC count (10^9 / L)	1.04 (1.01; 1.08)	1.04 (1.01; 1.07)	1.03 (1.01; 1.05)	1.02 (1.00; 1.04)	1.01 (1.00; 1.03)	1.02 (1.00; 1.03)
Total cholesterol (mmol/L)	0.94 (0.88; 1.01)	0.99 (0.92; 1.06)	0.97 (0.92; 1.03)	0.98 (0.93; 1.03)	1.02 (0.99; 1.06)	1.00 (0.97; 1.03)
Triglycerides (mmol /L)	1.00 (0.92; 1.09)	1.00 (0.94; 1.06)	1.01 (0.95; 1.07)	1.01 (0.96; 1.06)	0.99 (0.96; 1.03)	1.00 (0.97; 1.04)
Albumin (g/L)	0.98 (0.97; 1.00)	0.98 (0.96; 1.00)	0.99 (0.98; 1.01)	1.00 (0.98; 1.01)	0.99 (0.99; 1.00)	1.00 (0.99; 1.01)
Creatinine (per 30 µmol/L)	1.07 (1.02; 1.12)	1.06 (1.02; 1.11)	1.05 (1.00; 1.09)	1.08 (1.03; 1.14)	1.06 (1.03; 1.09)	1.08 (1.05; 1.10)
Diabetes	2.49 (1.94; 3.18)	2.90 (2.36; 3.57)	1.60 (1.33; 1.93)	2.21 (1.90; 2.57)	1.54 (1.34; 1.77)	1.90 (1.69; 2.13)
Atrial fibrillation	7.38 (5.76; 9.46)	7.03 (5.60; 8.82)	3.83 (3.35; 4.39)	3.55 (3.13; 4.03)	2.76 (2.55; 2.98)	2.95 (2.75; 3.16)
COPD	2.21 (1.95; 2.51)	2.01 (1.80; 2.24)	2.08 (1.92; 2.26)	1.80 (1.67; 1.94)	1.98 (1.87; 2.09)	1.47 (1.40; 1.55)

***** Further adjusted for ethnicity, blood pressure lowering medication and lipid regulating drugs. † Assessed by index of multiple deprivation, EHR = Electronic Health Records, CPRD = Clinical Practice Research Datalink, HES = Hospital Episode Statistics, HR (95% CI) = Hazard Ratio (95% Confidence Interval), SBP = Systolic Blood Pressure, DBP = Diastolic Blood Pressure, total WBC count = total White Blood Cell count. Hazard ratios were considered statistically significant if p-value < 0.001 (Bonferroni corrected threshold).