

Supplementary Material

Supplementary Table 1. Association of hsCRP and IL6 quintiles with 3P-MACE

Biomarker	Events n/N (%)	HR (95%CI)	P-value
hsCRP, mg/L			
Q1: 0.4 (0.2, 0.3, 0.6, 0.7)	183/1340 (13.7)	Referent	-
Q2: 1.0 (0.7, 0.8, 1.2, 1.4)	212/1325 (16.0)	1.16 (0.96-1.42)	0.13
Q3: 1.9 (1.4, 1.6, 2.2, 2.6)	219/1328 (16.5)	1.25 (1.03-1.52)	0.027
Q4: 3.6 (2.6, 3.1, 4.3, 5.1)	245/1331 (18.4)	1.42 (1.17-1.72)	<0.001
Q5: 8.8 (5.1, 6.5, 12.7, 84)	259/1290 (20.1)	1.57 (1.30-1.90)	<0.001
IL6, pg/mL			
Q1: 0.5 (0.1, 0.4, 0.6, 0.7)	130/1324 (9.8)	Referent	-
Q2: 0.9 (0.7, 0.8, 0.9, 1.0)	184/1323 (13.9)	1.47 (1.18-1.84)	0.001
Q3: 1.2 (1.0, 1.1, 1.3, 1.4)	226/1323 (17.1)	1.90 (1.53-2.35)	<0.001
Q4: 1.7 (1.4, 1.6, 1.9, 2.1)	274/1321 (20.7)	2.44 (1.98-3.01)	<0.001
Q5: 3.0 (2.1, 2.5, 4.0, 13)	304/1323 (23.0)	2.85 (2.32-3.50)	<0.001

Legend: hsCRP, high sensitivity C-reactive protein; IL6, interleukin-6; 3P-MACE, composite of cardiovascular death, stroke, or myocardial infarction; Q, quintile with median (min, percentile₂₅₋₇₅, max) biomarker values.

Statin-by-biomarkers interaction tests: IL6-by-statin interaction P =0.82 and hsCRP-by-statin interaction P =0.48, supporting similar associations in among statin users (n =979) and nonusers (n =5632).

Median (percentile₂₅₋₇₅) 3P-MACE follow-up time was 13.8 (9.2 to 14.6) years.

Supplementary Table 2. Participants characteristics by IL6 and hsCRP data-driven category combinations

Variable/Categories	Low IL6 Low hsCRP	High IL6 Low hsCRP	Low IL6 High hsCRP	High IL6 High hsCRP	P- value
N.	1109	2331	213	2961	
Age, years	56 (50, 65)	65 (55, 72)	57 (51, 64)	63 (54, 70)	<0.001
Male sex	621 (56.0%)	1312 (56.3%)	74 (34.7%)	1106 (37.4%)	<0.001
Race					<0.001
Caucasian	472 (42.6%)	923 (39.6%)	98 (46.0%)	1072 (36.2%)	
Chinese	261 (23.5%)	362 (15.5%)	25 (11.7%)	145 (4.9%)	
African American	220 (19.8%)	550 (23.6%)	53 (24.9%)	982 (33.2%)	
Hispanic	156 (14.1%)	496 (21.3%)	37 (17.4%)	762 (25.7%)	
Framingham score, points	7.9 (3.9, 13.7)	13.7 (6.7, 25.3)	7.3 (3.9, 13.2)	13.2 (6.3, 24.8)	<0.001
Hypertension	297 (26.8%)	1026 (44.0%)	77 (36.2%)	1552 (52.4%)	<0.001
Diabetes <i>mellitus</i>	66 (6.0%)	297 (12.7%)	11 (5.2%)	458 (15.5%)	<0.001
Smoking					
No	631 (57.2%)	1193 (51.3%)	106 (49.8%)	1399 (47.4%)	<0.001
Past	385 (34.9%)	856 (36.8%)	69 (32.4%)	1106 (37.5%)	
Current	88 (8.0%)	276 (11.9%)	38 (17.8%)	445 (15.1%)	
Heart rate, bpm	60 (55, 66)	61 (56, 68)	62 (57, 67)	64 (58, 71)	<0.001
SBP, mmHg	124 (114, 137)	132 (121, 146)	127 (117, 140)	135 (124, 148)	<0.001
DBP, mmHg	73 (67, 80)	75 (69, 82)	73 (67, 81)	75 (69, 82)	<0.001
Waist circumference, cm	89 (82, 97)	96 (88, 104)	91 (83, 98)	103 (94, 113)	<0.001
BMI, kg/m ²	24.8 (22.5, 27.3)	26.7 (24.0, 29.7)	26.1 (23.4, 28.4)	29.9 (26.7, 34.0)	<0.001
Triglycerides, mg/dL	97 (69, 138)	107 (76, 156)	111 (78, 157)	121 (86, 175)	<0.001
Total cholesterol, mg/dL	193 (172, 215)	189 (169, 212)	198 (178, 228)	194 (171, 217)	<0.001
LDL cholesterol, mg/dL	115 (98, 137)	114 (95, 134)	118 (95, 139)	117 (96, 138)	0.042
HDL cholesterol, mg/dL	52 (44, 62)	48 (40, 59)	53 (44, 66)	47 (40, 57)	<0.001
eGFR, ml/min/1.73m ²	81.4 (71.2, 91.0)	77.3 (66.0, 87.9)	79.9 (70.8, 89.2)	76.7 (65.8, 89.1)	<0.001
Lp(a), mg/dL	15.3 (7.6, 35.3)	15.9 (6.9, 39.8)	18.6 (6.8, 41.0)	19.1 (7.9, 42.8)	<0.001
hsCRP, mg/L	0.7 (0.4, 1.1)	1.0 (0.6, 1.4)	3.0 (2.5, 4.1)	4.5 (3.0, 7.9)	<0.001
IL6, pg/mL	0.5 (0.4, 0.6)	1.1 (0.9, 1.6)	0.6 (0.5, 0.6)	1.7 (1.2, 2.5)	<0.001
Ao valve calcium (Agatston)					<0.001
0	1028 (92.7%)	1973 (84.6%)	203 (95.3%)	2529 (85.5%)	
1-99	63 (5.7%)	221 (9.5%)	8 (3.8%)	275 (9.3%)	
≥100	18 (1.6%)	137 (5.9%)	2 (0.9%)	155 (5.2%)	
ACEi/ARB	116 (10.5%)	407 (17.5%)	18 (8.5%)	646 (21.8%)	<0.001
Beta-blocker	78 (7.0%)	231 (9.9%)	9 (4.2%)	313 (10.6%)	<0.001
Statins	144 (13.0%)	399 (17.1%)	25 (11.7%)	411 (13.9%)	<0.001

Legend: SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; eGFR, estimated glomerular filtration rate; Lp, lipoprotein; hsCRP, high-sensitivity C-reactive protein; IL6, interleukin-6; Ao, aortic; ACEi/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blocker.

Low biomarker: CRP <2 mg/L or IL6 <0.7 pg/mL.

High biomarker: CRP ≥2 mg/L or IL6 ≥0.7 pg/mL.

Supplementary Table 3. Outcome associations of hsCRP and IL6 continuous and data-driven categories

Outcome/ Biomarker	Low biomarker Events n/N (%) IR per 100py	High biomarker Events n/N (%) IR per 100py	High vs. Low HR (95%CI) ¹ P-value	High vs. Low HR (95%CI) ² P-value
High-sensitivity C-reactive protein (hsCRP)				
3P-MACE	523/3440 (15.2) 1.3 (1.2-1.4)	595/3174 (18.8) 1.7 (1.5-1.8)	1.25 (1.11-1.41) P <0.001	1.05 (0.92-1.19) P =0.48
CVD/HF	245/3440 (7.1) 0.6 (0.5-0.7)	293/3174 (9.2) 0.8 (0.7-0.9)	1.28 (1.08-1.52) P =0.004	1.01 (0.84-1.21) P =0.95
CVD	135/3440 (3.9) 0.3 (0.3-0.4)	160/3174 (5.0) 0.4 (0.3-0.5)	1.26 (1.01-1.59) P =0.045	0.96 (0.74-1.23) P =0.72
ACM	599/3431 (17.5) 1.3 (1.2-1.4)	644/3162 (20.4) 1.6 (1.5-1.7)	1.16 (1.04-1.30) P =0.009	0.86 (0.76-0.97) P =0.015
Interleukin-6 (IL6)				
3P-MACE	130/1322 (9.8) 0.8 (0.7-0.9)	988/5292 (18.7) 1.7 (1.6-1.8)	1.52 (1.26-1.83) P <0.001	1.39 (1.14-1.69) P =0.001
CVD/HF	48/1322 (3.6) 0.3 (0.2-0.4)	490/5292 (9.3) 0.8 (0.7-0.8)	1.84 (1.36-2.48) P <0.001	1.67 (1.22-2.28) P =0.001
CVD	30/1322 (2.3) 0.2 (0.1-0.2)	265/5292 (5.0) 0.4 (0.3-0.4)	1.47 (1.01-2.16) P =0.046	1.37 (0.92-2.04) P =0.13
ACM	130/1320 (9.9) 0.7 (0.6-0.8)	1113/5273 (21.1) 1.6 (1.6-1.7)	1.62 (1.35-1.95) P <0.001	1.59 (1.31-1.93) P <0.001

Legend: hsCRP, high sensitivity C-reactive protein; IL6, interleukin-6; HR, hazard ratio; CI, confidence interval; 3P-MACE, composite of cardiovascular death, stroke, or myocardial infarction; CVD, cardiovascular death; HF, heart failure; ACM, all-cause mortality.

Low biomarker: CRP <2 mg/L or IL6 <0.7 pg/mL.

High biomarker: CRP ≥2 mg/L or IL6 ≥0.7 pg/mL.

¹ Model adjusted Framingham risk score.

² Model adjusted Framingham risk score plus IL6 if hsCRP was the independent variable or model adjusted Framingham risk score plus hsCRP if IL6 was the independent variable.

Supplementary Table 4. Outcome associations of hsCRP and IL6 data-driven category combinations

Outcome/ Biomarker combinations	Low IL6-Low hsCRP Events n/N (%) IR per 100py	High IL6-Low hsCRP Events n/N (%) IR per 100py	Low IL6-High hsCRP Events n/N (%) IR per 100py	High IL6-High hsCRP Events n/N (%) IR per 100py	High IL6-Low hsCRP vs. Low- Low HR (95%CI) ¹ P-value	Low IL6-High hsCRP vs. Low- Low HR (95%CI) ¹ P-value	High IL6-High hsCRP vs. Low- Low HR (95%CI) ¹ P-value
3P-MACE	107/1109 (9.7) 0.8 (0.6-0.9)	416/2331 (17.9) 1.6 (1.4-1.7)	23/213 (10.8) 0.9 (0.6-1.3)	572/2961 (19.3) 1.7 (1.6-1.9)	1.43 (1.15-1.77) P =0.001	1.18 (0.75-1.86) P =0.46	1.67 (1.36-2.06) P <0.001
CVD/HF	42/1109 (3.8) 0.3 (0.2-0.4)	203/2331 (8.7) 0.7 (0.6-0.8)	6/213 (2.8) 0.2 (0.1-0.5)	287/2961 (9.7) 0.8 (0.7-0.9)	1.59 (1.14-2.23) P =0.007	0.76 (0.32-1.79) P =0.53	1.91 (1.38-2.65) P <0.001
CVD	25/1109 (2.3) 0.2 (0.1-0.2)	110/2331 (4.7) 0.4 (0.3-0.4)	5/231 (2.4) 0.2 (0.1-0.4)	155/2961 (5.2) 0.4 (0.4-0.5)	1.34 (0.87-2.08) P =0.19	1.08 (0.42-2.84) P =0.87	1.62 (1.06-2.48) P =0.026
ACM	113/1107 (10.2) 0.7 (0.6-0.9)	486/2324 (20.9) 1.6 (1.5-1.8)	17/213 (8.0) 0.6 (0.4-0.9)	627/2949 (21.3) 1.7 (1.5-1.9)	1.50 (1.22-1.84) P <0.001	0.81 (0.48-1.34) P =0.41	1.63 (1.33-2.00) P <0.001

Legend: hsCRP, high sensitivity C-reactive protein; IL6, interleukin-6; HR, hazard ratio; CI, confidence interval; 3P-MACE, composite of cardiovascular death, stroke, or myocardial infarction; CVD, cardiovascular death; HF, heart failure; ACM, all-cause mortality.

Low biomarker: CRP <2 mg/L or IL6 <0.7 pg/mL.

High biomarker: CRP ≥2 mg/L or IL6 ≥0.7 pg/mL.

¹ Model adjusted Framingham risk score.

Supplementary Table 5. Associations of hsCRP and IL6 (data-driven categories) with aortic valve calcium

Ao valve calcium*/ Biomarker	Low biomarker Events n/N (%)	High biomarker Events n/N (%)	High vs. Low OR (95%CI)¹ P-value
High-sensitivity C-reactive protein (hsCRP)			
0	3001/3440 (87.2)	2732/3172 (86.1)	Referent
1-99	284/3440 (8.3)	283/3172 (8.9)	1.04 (0.87-1.24) P =0.68
≥100	155/3440 (4.5)	157/3172 (5.0)	1.04 (0.82-1.31) P =0.76
Interleukin-6 (IL6)			
0	1231/1322 (93.1)	4502/5290 (85.1)	Referent
1-99	71/1322 (5.4)	496/5290 (9.4)	1.32 (1.01-1.72) P =0.042
≥100	20/1322 (1.5)	292/5290 (5.5)	2.43 (1.53-3.88) P <0.001

Legend: hsCRP, high sensitivity C-reactive protein; IL6, interleukin-6; OR, odds ratio (multinomial logistic regression); CI, confidence interval; Ao, aortic.

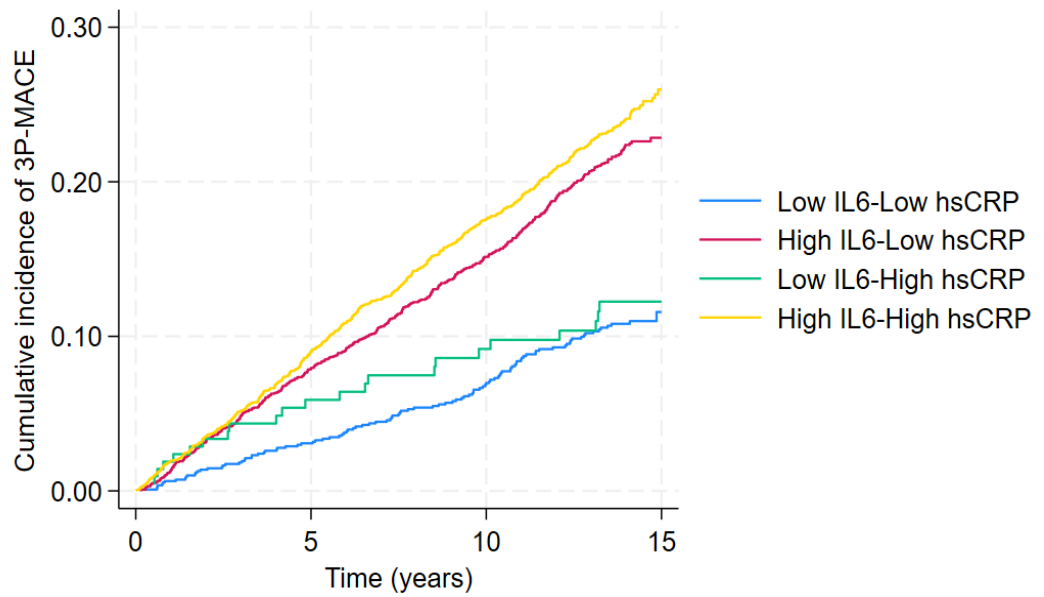
*Agatston units

Low biomarker: CRP <2 mg/L or IL6 <0.7 pg/mL.

High biomarker: CRP ≥2 mg/L or IL6 ≥0.7 pg/mL.

¹ Model adjusted Framingham risk score.

Supplementary Figure 1. 3P-MACE association of hsCRP and IL6 data-driven category combinations



Number at risk				
Low IL6-Low hsCRP	1107	1020	929	107
High IL6-Low hsCRP	2324	2002	1674	176
Low IL6-High hsCRP	213	193	170	33
High IL6-High hsCRP	2949	2470	2034	243

Legend: hsCRP, high sensitivity C-reactive protein; IL6, interleukin-6; 3P-MACE, composite of cardiovascular death, stroke, or myocardial infarction.

Low biomarker: CRP <2 mg/L or IL6 <0.7 pg/mL.

High biomarker: CRP ≥2 mg/L or IL6 ≥0.7 pg/mL.