Supplemental Material

Table S1. Distribution of risk factors in the different surveys stratified by sex. The Tromsø Study.

	Women (n = 5704)			Men (n =4405)		
	4th survey (1994-1995)	5th survey (2001-2002)	6th survey (2007-2008)	4th survey (1994-1995)	5th survey (2001-2002)	6th survey (2007-2008)
Number of observations	3194	2948	3902	2922	2168	2824
Age (years), mean (SD)	60.3 (10.4)	65.4 (9.8)	63.6 (9.3)	59.1 (10.2)	65.5 (9.4)	63.5 (9.1)
BMI (kg/m^2), mean (SD)	25.9 (4.5)	26.8 (4.6)	26.8 (4.6)	26.0 (3.3)	26.7 (3.4)	27.3 (3.7)
Carotid plaque, %	44.0	53.0	41.2	51.0	65.5	50.0
TPA (mm^2), median (IQR)*	13.2	15.7	16.6	17.1	20.3	21.9
	(7.7, 22.5)	(8.7, 39.7)	(10.0, 27.4)	(9.8, 29.8)	(11.3, 35.8)	(12.9, 36.6)
CRP (mg/L), median (IQR)	1.13	1.53	1.36	1.27	1.59	1.37
	(0.56, 2.41)	(0.80, 3.14)	(0.71, 2.70)	(0.66, 2.67)	(0.86, 3.12)	(0.77, 2.55)
Systolic blood pressure (mmHg), mean (SD)	145 (24)	145 (23)	140 (25)	145 (20)	144 (20)	142 (20)
Diastolic blood pressure (mmHg), mean (SD)	82 (13)	81 (13)	76 (10)	85 (12)	83 (12)	82 (10)
Hypertension (SD), %	54.9	59.9	56.9	57.9	61.6	60.6
Antihypertensive medication, %	12.2	23.5	28.9	11.0	23.3	26.2
Total cholesterol (mmol/L), mean (SD)	6.9 (1.3)	6.5 (1.2)	5.9 (1.1)	6.5 (1.2)	6.1 (1.1)	5.6 (1.1)
HDL cholesterol (mmol/L), mean (SD)	1.7 (0.4)	1.6 (0.4)	1.7 (0.4)	1.4 (0.4)	1.4 (0.4)	1.4 (0.4)
Lipid-lowering medication, %	1.8	10.9	16.0	1.5	14.9	17.4
Diabetes mellitus, %	3.8	7.3	7.2	3.6	9.8	8.2
Smoking, %	31.1	24.7	18.7	35.4	25.3	16.6

BMI, body mass index; TPA, total plaque area; CRP, C-reactive protein; HDL, high-density lipoprotein; n, number of participants; IQR, interquartile range; SD, standard deviation. *If prevalent carotid plaque. In total 10 109 participants were included in the study, of these 4932 attended one, 2505 attended two and 2672 attended three surveys.

Table S2. Sex stratified incidence rates (IRs) and hazard ratios (HRs) with 95% confidence intervals (CIs) of first-ever ischemic stroke from time-varying Cox models across risk categories of C-reactive protein (CRP). The Tromsø Study.

CRP	n [*]	Events	IR[†] (95% CI)	Model 1[‡] HR (95% CI)	Model 2[§] HR (95% CI)
Men					
< 1 mg /L	2820	83	4.5 (3.7, 5.6)	Reference	Reference
1–3 mg/L	3209	130	6.3 (5.3, 7.5)	1.19 (0.90, 1.57)	1.06 (0.80, 1.41)
> 3 mg/L	1743	132	12.5 (10.5, 14.8)	2.24 (1.70, 2.95)	1.84 (1.39, 2.45)
Women					
< 1 mg /L	3870	78	3.1 (2.5, 3.8)	Reference	Reference
1–3 mg/L	3815	131	5.2 (4.3, 6.1)	1.36 (1.02, 1.80)	1.23 (0.92, 1.64)
> 3 mg/L	2211	117	8.1 (6.8, 9.7)	2.14 (1.61, 2.86)	1.79 (1.32, 2.43)

[*]Observations. [†]Crude IRs per 1000 person-years. [‡] Age as time-scale. [§]Age as time-scale, adjusted for total cholesterol, high-density lipoprotein cholesterol, diabetes mellitus, systolic blood pressure, smoking, body mass index, lipid-lowering medication and antihypertensive medication.

Table S3. Sex stratified incidence rates (IRs) and hazard ratios (HRs) with 95% confidence intervals (CIs) of first-ever myocardial infarction from time-varying Cox models across risk categories of C-reactive protein (CRP). The Tromsø Study.

CRP	n [*]	Events	IR[†] (95% CI)	Model 1[‡] HR (95% CI)	Model 2[§] HR (95% CI)
Men					
< 1 mg /L	2758	149	8.4 (7.1, 9.8)	Reference	Reference
1–3 mg/L	3156	282	14.1 (12.5, 15.8)	1.52 (1.25, 1.86)	1.31(1.07, 1.61)
> 3 mg/L	1708	202	19.6 (17.1, 22.5)	2.03 (1.64, 2.51)	1.56 (1.25, 1.94)
Women					
< 1 mg /L	3847	113	4.5 (3.7, 5.4)	Reference	Reference
1–3 mg/L	3782	185	7.4 (6.4, 8.5)	1.35 (1.07, 1.70)	1.14 (0.90, 1.46)
> 3 mg/L	2203	148	10.3 (8.7, 12.1)	1.83 (1.43, 2.33)	1.36 (1.04, 1.76)

[*]Observations. [†]Crude IRs per 1000 person-years. [‡] Age as time-scale. [§] Age as time-scale, adjusted for total cholesterol, high-density lipoprotein cholesterol, diabetes mellitus, systolic blood pressure, smoking, body mass index, lipid-lowering medication and antihypertensive medication.

Table S4. Sex stratified incidence rates (IRs) and hazard ratios (HRs) with 95% confidence intervals (CIs) of first-ever ischemic stroke from time-varying Cox models across categories of total plaque area (TPA) before and after adjustment for C-reactive protein (CRP). The Tromsø Study.

TPA	n [*]	Events	IR[†] (95% CI)	Model 1[‡] HR (95% CI)	Model 1[‡] + CRP HR (95% CI)	Absolute attenuation of HR after inclusion of CRP in the model[§]	Percentage attenuation of HR after inclusion of CRP in the model	Model 2[‖] HR (95% CI)
Men								
No plaque	3543	89	3.9 (3.2, 4.8)	Reference	Reference	–	–	Reference
TPA<median	2115	93	6.9 (5.6, 8.4)	1.27 (0.94, 1.70)	1.25 (0.93, 1.68)	0.02	7.4	1.16 (0.87, 1.56)
TPA>median	2114	163	12.4 (10.7, 14.5)	1.81 (1.38, 2.37)	1.72 (1.31, 2.24)	0.09	11.1	1.45 (1.11, 1.91)
Women								
No plaque	5402	88	2.5 (2.0, 3.1)	Reference	Reference	–	–	Reference
TPA<median	2247	84	5.6 (4.5, 6.9)	1.46 (1.08, 1.98)	1.46 (1.07, 1.97)	0.00	–	1.41 (1.04, 1.91)
TPA>median	2247	154	10.2 (8.7, 11.9)	2.03 (1.54, 2.67)	1.96 (1.49, 2.58)	0.07	6.8	1.72 (1.30, 2.28)

[*]Observations. [†]Crude IRs per 1000 person-years. [‡] Age as time-scale. [§] Change in HR from Model 1 to Model 1 + CRP. CRP was log-transformed. [‖] Age as time-scale, adjusted for total cholesterol, high-density lipoprotein cholesterol, diabetes mellitus, systolic blood pressure, smoking, body mass index, lipid -lowering medication, antihypertensive medication and CRP (log-transformed).

Table S5. Sex stratified incidence rates (IRs) and hazard ratios (HRs) with 95% confidence intervals (CIs) of first-ever myocardial infarction from time-varying Cox models across categories of total plaque area (TPA) before and after adjustment for C-reactive protein (CRP). The Tromsø Study.

TPA	n [*]	Events	IR[†] (95% CI)	Model 1[‡] HR (95% CI)	Model 1[‡] + CRP HR (95% CI)	Absolute attenuation of HR after inclusion of CRP in the model[§]	Percentage attenuation of HR after inclusion of CRP in the model	Model 2[‖] HR (95% CI)
Men								
No plaque	3493	178	8.0 (6.9, 9.2)	Reference	Reference	–	–	Reference
TPA<median	2043	173	13.2 (11.4, 15.3)	1.36 (1.10, 1.68)	1.35 (1.09, 1.67)	0.01	2.7	1.22 (0.98, 1.51)
TPA>median	2065	282	22.2 (19.7, 24.9)	1.99 (1.63, 2.43)	1.91 (1.56, 2.32)	0.08	8.1	1.57 (1.29, 1.93)
Women								
No plaque	5388	122	3.5 (2.9, 4.2)	Reference	Reference	–	–	Reference
TPA<median	2221	118	7.9 (6.6, 9.2)	1.61 (1.25, 2.08)	1.60 (1.24, 2.07)	0.01	1.6	1.46 (1.13, 1.89)
TPA>median	2223	206	13.9 (12.1, 15.9)	2.34 (1.85, 2.95)	2.28 (1.81, 2.88)	0.06	4.5	1.75 (1.38, 2.23)

[*]Observations. [†]Crude IRs per 1000 person-years. [‡] Age as time-scale. [§] Change in HR from Model 1 to Model 1 + CRP. CRP was log-transformed. [‖] Age as time-scale, adjusted for total cholesterol, high-density lipoprotein cholesterol, diabetes mellitus, systolic blood pressure, smoking, body mass index, lipid-lowering medication, antihypertensive medication and CRP (log-transformed).

Table S6. Incidence rates (IRs) and hazard ratios (HRs) with 95% confidence intervals (CIs) of first-ever ischemic stroke (IS) and myocardial infarction (MI) from time-varying Cox models across constellations of C-reactive protein (CRP) and categories of total plaque area (TPA). The Tromsø Study.

			Ischemic stroke				Myocardial infraction	
	n[*]	Incident IS	IR[†] (95% CI)	HR[‡] (95% CI)	n[*]	Incident MI	IR[†] (95% CI)	HR[‡] (95% CI)
Both sexes[§]								
No plaque & CRP <1 mg/L	3784	51	2.1 (1.6, 2.7)	Ref.	3762	72	2.9 (2.3, 3.7)	Ref.
No plaque & CRP 1-3mg/L	3436	71	3.2 (2.5, 4.0)	1.25 (0.87, 1.79)	3409	140	6.4 (5.4, 7.5)	1.86 (1.40, 2.48)
No plaque & CRP >3 mg/L	1725	55	5.0 (3.8, 6.5)	1.93 (1.32, 2.82)	1710	88	8.0 (6.5, 9.9)	2.36 (1.73, 3.22)
TPA<median & CRP <1 mg/L	1608	41	3.9 (2.9, 5.3)	1.22 (0.81, 1.84)	1581	82	8.0 (6.5, 10.0)	1.96 (1.43, 2.69)
TPA<median & CRP 1-3 mg/L	1756	79	6.8 (5.4, 8.4)	1.86 (1.30, 2.65)	1724	108	9.4 (7.8, 11.4)	2.10 (1.55, 2.83)
TPA<median & CRP >3 mg/L	997	57	9.0 (6.9, 11.6)	2.50 (1.70, 3.65)	980	101	16.3 (13.4, 18.8)	3.72 (2.74, 5.05)
TPA>median & CRP <1 mg/L	1298	69	8.0 (6.3, 10.1)	1.85 (1.28, 2.68)	1262	108	13.0 (10.7, 15.7)	2.67 (1.97, 3.62)
TPA>median & CRP 1-3 mg/L	1832	111	9.2 (7.7, 11.1)	2.04 (1.45, 2.86)	1805	219	18.8 (16.5, 21.5)	3.71 (2.83, 4.88)
TPA>median & CRP >3 mg/L	1232	137	18.2 (15.4, 21.5)	4.07 (2.93, 5.66)	1219	161	21.2 (18.2, 24.8)	4.17 (3.14, 5.54)
Men								
No plaque & CRP <1 mg/L	1441	26	2.8 (1.9, 4.0)	Ref.	1422	37	4.0 (1.7, 3.2)	Ref.
No plaque & CRP 1-3mg/L	1444	34	3.7(2.6, 5.1)	1.10 (0.66, 1.84)	1424	87	9.6 (7.8, 11.9)	2.20 (1.49, 3.23)
No plaque & CRP >3 mg/L	658	29	7.0 (4.9, 10.1)	2.08 (1.22, 3.53)	647	54	13.5 (10.3, 17.6)	3.01 (1.98, 4.57)
TPA<median & CRP <1 mg/L	778	24	4.8 (3.2, 7.1)	1.19 (0.68, 2.08)	760	53	10.9 (8.3, 14.2)	2.20 (1.44, 3.36)
TPA<median & CRP 1-3 mg/L	873	41	7.3 (5.4, 9.9)	1.64 (1.00, 2.69)	854	65	11.8 (9.3, 15.1)	2.27 (1.51, 3.42)
TPA<median & CRP >3 mg/L	463	28	9.8 (6.8, 14.2)	2.14 (1.25, 3.66)	450	55	20.3 (15.6, 26.4	3.85 (2.53, 5.87)
TPA>median & CRP <1 mg/L	601	33	8.6 (6.1, 12.2)	1.62 (0.96, 2.73)	576	59	16.3 (12.6, 21.0)	2.82 (1.86, 4.28)
TPA>median & CRP 1-3 mg/L	892	55	9.7 (7.4, 12.6)	1.78 (1.11, 2.86)	878	130	23.6 19.9, 28.1)	4.06 (2.80, 5.90)
TPA>median & CRP >3 mg/L	622	75	20.9 (16.7, 26.2)	3.81 (2.42, 6.01)	611	93	25.9 (21.2, 31.8)	4.39 (2.98, 6.48)
Women								
No plaque & CRP <1 mg/L	2343	25	1.7 (1.1, 2.4)	Ref.	2340	35	2.3 (1.7, 3.2)	Ref.
No plaque & CRP 1-3mg/L	1992	37	2.8 (2.1, 3.9)	1.42 (0.86, 2.37)	1985	53	4.1 (3.1, 5.3)	1.44 (0.94, 2.21)
No plaque & CRP >3 mg/L	1067	26	3.7 (2.5, 5.5)	1.81 (1.04, 3.14)	1063	34	4.9 (3.5, 6.9)	1.66 (1.04, 2.67)
TPA<median & CRP <1 mg/L	830	17	3.1 (1.9, 5.0)	1.21 (0.65, 2.25)	821	29	5.5 (3.9, 7.9)	1.59 (0.98, 2.60)
TPA<median & CRP 1-3 mg/L	883	38	6.3 (4.6, 8.7)	2.06 (1.24, 3.51)	870	43	7.2 (5.4, 9.7)	1.85 (1.18, 2.89)
TPA<median & CRP >3 mg/L	534	29	8.2 (5.7, 11.8)	2.92 (1.70, 5.01)	530	46	13.2 (9.9, 17.7)	3.41 (2.19, 5.31)
TPA>median & CRP <1 mg/L	697	36	7.5 (5.4, 10.3)	2.09 (1.24, 3.51)	686	49	10.4 (7.9, 13.8)	2.41 (1.55, 3.74)
TPA>median & CRP 1-3 mg/L	940	56	8.9 (6.8, 11.5)	2.31 (1.43, 3.76)	927	89	14.5 (11.8, 17.9)	3.17 (2.13, 4.73)
TPA>median & CRP >3 mg/L	610	62	15.7 (12.3, 20.2)	4.28 (2.66, 6.89)	610	68	17.0 (13.4, 21.6)	3.80 (2.51, 5.76)

* Observations

† Crude incidence rates per 1000 person-years.

‡ Adjusted for age (**§** and sex).

Table S7. Additive interaction of C-reactive protein (CRP) and categories of total plaque area (TPA) on risk of first-ever ischemic stroke and myocardial infarction. The Tromsø Study.

	Ischemic stroke	Myocardial infarction
Exposure	*HR[*] (95% CI)*	*HR* (95% CI)*
CRP >3 mg/L & no plaque	1.93 (1.32, 2.82)	2.36 (1.73, 3.22)
TPA >median & CRP <1 mg/L	1.85 (1.28, 2.68)	2.67 (1.97, 3.62)
CRP >3 mg/L & TPA>median	4.07 (2.93, 5.66)	4.17 (3.14, 5.54)
Measure	*Estimate (95% CI)*	*Estimate (95% CI)*
Relative excess risk due to interaction (RERI)	1.29 (0.32, 2.25)	0.13 (-0.82, 1.08)
Attributable proportion (AP)	0.32 (0.10, 0.53)	0.03 (-0.20, 0.26)
Synergy index	1.72 (1.06, 2.81)	1.04 (0.77, 1.42)

HR, hazard ratio; CI, confidence interval. [*]Age and sex adjusted.

Table S8. Hazard ratios (HRs) with 95% confidence intervals (CIs) per standard deviation increase in C-reactive protein (CRP)[*] across categories of total plaque area (TPA). Assessment of multiplicative interaction. The Tromsø Study.

	Ischemic stroke		Myocardial infarction	
	HR[†] (95% CI)	HR[‡] (95% CI)	HR[†] (95% CI)	HR[‡] (95% CI)
Overall	**1.32** **(1.23, 1.41)**	**1.25** **(1.16, 1.34)**	**1.25** **(1.18, 1.32)**	**1.13** **(1.06, 1.20)**
TPA				
No plaque	**1.23** **(1.08, 1.41)**	1.15 (0.99, 1.33)	**1.27** **(1.15, 1.41)**	1.11 (0.99, 1.25)
TPA < median	**1.27** **(1.11, 1.56)**	**1.22** **(1.05, 1.41)**	**1.23** **(1.11, 1.37)**	**1.13** **(1.01, 1.28)**
TPA > median	**1.34** **(1.22, 1.48)**	**1.29** **(1.17, 1.43)**	**1.17** **(1.08, 1.27)**	**1.11** **(1.02, 1.21)**
Interaction p-value	0.65	0.66	0.44	0.45

[*]Log-transformed.

[†] Adjusted for age and sex.

[‡] Adjusted for age, sex, smoking, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, diabetes mellitus, body mass index, lipid lowering medication and antihypertensive medication. Bold; p<0.05 for HR.

Table S9. Crude incidence rates (IRs) and hazard ratios (HRs) with 95% confidence intervals (CIs) of first-ever ischemic stroke from time-fixed[*] Cox models across risk categories of C-reactive protein (CRP). The Tromsø Study.

CRP	n [**]	Events	IR[†] (95% CI)	Model 1[‡] HR (95% CI)	Model 2[§] HR (95% CI)
Both sexes[‖]					
< 1 mg /L	4158	211	4.2 (3.7–4.8)	Reference	Reference
1–3 mg/L	3898	258	5.9 (5.3–6.7)	1.25 (1.05–1.50)	1.14 (0.95–1.37)
> 3 mg/L	2053	202	9.6 (8.4–11.1)	2.05 (1.69–2.50)	1.71 (1.40–2.09)
Men					
< 1 mg /L	1738	103	4.9 (4.0–5.9)	Reference	Reference
1–3 mg/L	1769	138	7.1 (6.0–8.4)	1.32 (1.03–1.71)	1.21(0.93–1.57)
> 3 mg/L	898	104	11.5 (9.5–14.0)	2.12 (1.61–2.78)	1.76 (1.33–2.35)
Women					
< 1 mg /L	2420	108	3.7 (3.1–4.5)	Reference	Reference
1–3 mg/L	2129	120	5.0 (4.2–6.0)	1.18 (0.90–1.54)	1.08 (0.82–1.41)
> 3 mg/L	1155	98	8.2 (6.7–10.0)	2.00 (1.52–2.63)	1.671.25–2.23)

[*]Values of exposure variables at time of study entrance. [**]Participants. [†]Crude IRs per 1000 person-years. [‡] Adjusted for age ([‖] and sex). [§]Adjusted for age, smoking, total cholesterol, high-density lipoprotein cholesterol, diabetes mellitus, systolic blood pressure, body mass index, lipid-lowering medication, antihypertensive medication ([‖] and sex).

Table 10. Crude incidence rates (IRs) and hazard ratios (HRs) with 95% confidence intervals (CIs) of first-ever myocardial infarction from time-fixed[*] Cox models across risk categories of C-reactive protein (CRP). The Tromsø Study.

CRP	n [**]	Events	IR[†] (95% CI)	Model 1[‡] HR (95% CI)	Model 2[§] HR (95% CI)
Both sexes[‖]					
< 1 mg /L	4158	339	6.8 (6.2–7.6)	Reference	Reference
1–3 mg/L	3898	452	10.6 (9.7–11.7)	1.38 (1.20–1.59)	1.16 (1.00–1.34)
> 3 mg/L	2053	288	13.9 (12.4–15.6)	1.78 (1.53–2.09)	1.32 (1.12–1.56)
Men					
< 1 mg /L	1738	194	9.4 (8.2–10.8)	Reference	Reference
1–3 mg/L	1769	272	14.6 (12.9–16.4)	1.41 (1.18–1.70)	1.22 (1.01–1.47)
> 3 mg/L	898	167	18.9 (16.2–22.0)	1.80 (1.46–2.21)	1.37 (1.11–1.70)
Women					
< 1 mg /L	2420	145	5.0 (4.3–5.9)	Reference	Reference
1–3 mg/L	2129	180	7.6 (6.5–8.8)	1.33 (1.07–1.65)	1.08 (0.86–1.36)
> 3 mg/L	1155	121	10.2 (8.5–12.2)	1.79 (1.40–2.28)	1.28 (0.99–1.66)

[*]Values of exposure variables at time of study entrance. [**]Participants. [†]Crude IRs per 1000 person-years. [‡] Adjusted for age ([‖] and sex). [§]Adjusted for age, smoking, total cholesterol, high-density lipoprotein cholesterol, diabetes mellitus, systolic blood pressure, body mass index, lipid-lowering medication, antihypertensive medication ([‖] and sex).

Table S11. Crude incidence rates (IRs) and hazard ratios (HRs) with 95% confidence intervals (CIs) of first-ever ischemic stroke from time-fixed[*] Cox models across categories of total plaque area (TPA), before and after adjustment for C-reactive protein (CRP). The Tromsø Study.

TPA	n[**]	Events	IR[†] (95% CI)	Model 1[‡] HR (95% CI)	Model 1[‡] + CRP HR (95% CI)	Absolute attenuation of HR after inclusion of CRP in the model[§]	Percentage attenuation of HR after inclusion of CRP in the model	Model 2[‖] HR (95% CI)
Both sexes[#]								
No plaque	5711	233	3.5 (3.1–4.0)	Reference	Reference	–	–	Reference
TPA<median	2198	175	6.7 (5.8–7.8)	1.33 (1.09–1.62)	1.33 (1.09–1.62)	0	–	1.28 (1.05–1.56)
TPA>median	2200	263	11.5 (10.2–13.0)	2.00 (1.67–2.42)	1.92 (1.60–2.31)	0.08	8.0	1.69 (1.39–2.04)
Men								
No plaque	2284	114	4.3 (3.6–5.2)	Reference	Reference	–	–	Reference
TPA<median	1060	96	6.9 (6.2–9.3)	1.27 (0.97–1.68)	1.27 (0.96–1.67)	0.00	–	1.20 (0.91–1.59)
TPA>median	1061	135	12.8 (10.8-15.1)	1.91 (1.47–2.48)	1.79 (1.38–2.32)	0.12	13.2	1.57 (1.20–2.05)
Women								
No plaque	3427	119	3.0 (2.5–3.6)	Reference	Reference	–	–	Reference
TPA<median	1139	79	5.9 (4.7–7.3)	1.39 (1.04–1.85)	1.39 (1.05–1.86)	0.00	–	1.37 (1.03–1.83)
TPA>median	1138	128	10.4 (8.8–12.4)	2.10 (1.62–2.73)	2.05 (1.57–2.66)	0.05	4.5	1.83 (1.40–2.40)

[*]Values of exposure variables at time of study entrance. [**]Participants. [†]Crude IRs per 1000 person-years. [‡]Adjusted for age ([#] and sex). [§]Absolute attenuation of HR after inclusion of CRP in the model (i.e. change in HR from Model 1 to Model 1 + CRP). CRP was log-transformed. [‖] Adjusted for age, CRP (log-transformed), smoking, total cholesterol, high-density lipoprotein cholesterol, diabetes mellitus, systolic blood pressure, body mass index, lipid-lowering medication, antihypertensive medication ([#] and sex).

Table S12. Crude incidence rates (IRs) and hazard ratios (HRs) with 95% confidence intervals (CIs) of first-ever myocardial infarction from time-fixed[*] Cox models across categories of total plaque area (TPA), before and after adjustment for C-reactive protein (CRP). The Tromsø Study.

TPA	n[**]	Events	IR[†] (95% CI)	Model 1[‡] HR (95% CI)	Model 1[‡] + CRP HR (95% CI)	Absolute attenuation of HR after inclusion of CRP in the model[§]	Percentage attenuation of HR after inclusion of CRP in the model	Model 2[‖] HR (95% CI)
Both sexes[#]								
No plaque	5711	385	5.9 (5.4–6.6)	Reference	Reference	–	–	Reference
TPA<median	2200	394	11.8 (10.5–13.2)	1.45 (1.24–1.69)	1.44 (1.24–1.68)	0.01	2.2	1.31 (1.12–1.52)
TPA>median	2198	300	17.6 (16.5–19.5)	1.97 (1.70–2.29)	1.90 (1.64–2.20)	0.07	7.2	1.49 (1.28–1.73)
Men								
No plaque	2284	229	9.0 (7.9–10.2)	Reference	Reference	–	–	Reference
TPA<median	1061	172	14.0 (12.1–16.3)	1.24 (1.01–1.51)	1.23 (1.00–1.50)	0.01	4.2	1.12(0.92–1.37)
TPA>median	1060	232	22.6 (19.8-25.6)	1.80 (1.49–2.18)	1.72 (1.41–2.08)	0.08	10.0	1.43 (1.17–1.74)
Women								
No plaque	3427	156	4.0 (3.4–4.7)	Reference	Reference	–	–	Reference
TPA<median	1139	128	14.0 (12.1–16.3)	1.81(1.43–2.30)	1.81 (1.43–2.30)	0.00	–	1.64 (1.29–2.08)
TPA>median	1138	162	12.6 (19.8-25.6)	2.22 (1.76–2.79)	2.17 (1.72–2.73)	0.05	4.1	1.63 (1.29–2.06)

[*]Values of exposure variables at time of study entrance. [**]Participants. [†]Crude IRs per 1000 person-years. [‡]Adjusted for age ([#] and sex). [§]Absolute attenuation of HR after inclusion of CRP in the model (i.e. change in HR from Model 1 to Model 1 + CRP). CRP was log-transformed. [‖] Adjusted for age, CRP (log-transformed), smoking, total cholesterol, high-density lipoprotein cholesterol, diabetes mellitus, systolic blood pressure, body mass index, lipid-lowering medication, antihypertensive medication ([#] and sex).

Table S13. Incidence rates (IRs) and hazard ratios (HRs) with 95% confidence intervals (CIs) of first-ever ischemic stroke (IS) and myocardial infarction (MI) from time-fixed[*] Cox models across constellations of C-reactive protein (CRP) and categories of total plaque area (TPA). The Tromsø Study.

			Ischemic stroke				Myocardial infraction	
	n[**]	Incident IS	IR[†] (95% CI)	HR[‡] (95% CI)	n[**]	Incident MI	IR[†] (95% CI)	HR[‡] (95% CI)
Both sexes [‖]								
No plaque & CRP <1 mg/L	2565	88	2.8 (2.3, 3.5)	Ref.	2565	134	4.4 (3.7, 5.2)	Ref.
No plaque & CRP 1-3mg/L	2149	84	3.5 (2.8, 4.3)	1.07 (0.79, 1.44)	2149	159	6.7 (5.8, 7.9)	1.36 (1.08, 1.71)
No plaque & CRP >3 mg/L	997	61	5.8 (4.5, 7.4)	1.90 (1.37, 2.64)	997	92	8.8 (7.2, 10.8)	1.89 (1.45, 2.47)
TPA<median & CRP <1 mg/L	912	55	4.7 (3.6, 6.2)	1.11 (0.79, 1.56)	912	106	9.4 (7.8, 11.3)	1.52 (1.17, 1.96)
TPA<median & CRP 1-3 mg/L	825	73	7.7 (6.1, 9.6)	1.78 (1.30, 2.44)	825	117	12.4 (10.4, 14.9)	1.96 (1.53, 2.52)
TPA<median & CRP >3 mg/L	461	47	9.6 (7.2, 12.8)	2.20 (1.54, 3.15)	461	77	16.1 (12.9, 20.1)	2.52 (1.89, 3.34)
TPA>median & CRP <1 mg/L	681	68	9.1 (6.3, 10.1)	1.87 (1.35, 2.58)	681	99	13.5 (11.1, 16.4)	2.00 (1.54, 2.61)
TPA>median & CRP 1-3 mg/L	924	101	10.3 (8.4, 12.5)	2.10 (1.57, 2.82)	924	176	18.6 (16.0, 21.5)	2.69 (2.14, 3.39)
TPA>median & CRP >3 mg/L	594	94	17.2 (14.0, 21.0)	3.58 (2.66, 4.83)	595	119	21.6 (18.0, 25.8)	3.06 (2.37, 3.94)
Men								
No plaque & CRP <1 mg/L	990	41	3.4 (2.5, 4.6)	Ref.	990	77	6.4 (5.2, 8.1)	Ref.
No plaque & CRP 1-3mg/L	912	44	4.4 (3.3, 5.9)	1.12(0.73, 1.72)	912	97	10.0 (8.2, 12.2)	1.29 (1.01, 1.88)
No plaque & CRP >3 mg/L	382	29	7.1 (4.9, 10.2)	1.96 (1.22, 3.17)	383	55	14.1 (10.8, 18.4)	2.05 (1.45, 2.90)
TPA<median & CRP <1 mg/L	437	28	4.8 (3.3, 5.9)	0.98 (0.60, 1.59)	437	60	10.8 (8.4, 13.9)	1.28 (0.91, 1.80)
TPA<median & CRP 1-3 mg/L	408	44	9.6 (7.2, 12.9)	1.95 (1.27, 3.00)	408	72	16.0 (12.7, 20.2)	1.85 (1.34, 2.56)
TPA<median & CRP >3 mg/L	215	24	10.6 (7.1, 15.8)	2.11 (1.27, 3.51)	215	40	18.1 (13.3, 24.7)	2.09 (1.42, 3.07)
TPA>median & CRP <1 mg/L	311	34	10.7 (7.6, 15.0)	1.92 (1.21, 3.51)	311	57	18.3 (14.1, 23.8)	1.95 (1.38, 2.77)
TPA>median & CRP 1-3 mg/L	449	50	10.6 (8.1, 14.0)	1.94 (1.28, 2.96)	449	103	23.2 19.1, 28.1)	2.49 (1.84, 3.38)
TPA>median & CRP >3 mg/L	301	51	19.0 (14.4, 25.0)	3.43 (2.24, 5.23)	301	72	26.3 (20.9, 33.1)	2.76 (1.98, 3.84)
Women								
No plaque & CRP <1 mg/L	1575	47	2.5 (1.8, 3.3)	Ref.	1575	57	3.0 (2.4, 3.6)	Ref.
No plaque & CRP 1-3mg/L	1237	40	2.9 (2.1, 3.9)	1.02 (0.67, 1.55)	1237	62	4.5 (3.5, 5.7)	1.31 (0.91, 1.87)
No plaque & CRP >3 mg/L	615	32	4.9 (3.5, 6.9)	1.86 (1.19, 2.92)	615	37	5.7 (4.1, 7.8)	1.72 (1.14, 2.60)
TPA<median & CRP <1 mg/L	475	27	4.6 (3.2, 6.7)	1.30 (0.81, 2.09)	475	46	8.0 (6.0, 10.7)	1.94 (1.31, 2.86)
TPA<median & CRP 1-3 mg/L	417	29	5.8 (4.1, 8.4)	1.57 (0.98, 2.50)	417	45	9.2 (6.9, 12.3)	2.11 (1.42, 3.12)
TPA<median & CRP >3 mg/L	246	23	8.8 (5.8, 13-1)	2.30 (1.39, 3.81)	245	37	14.3 (10.4, 19.8)	3.17 (2.09, 4.82)
TPA>median & CRP <1 mg/L	370	34	7.8 (5.6, 11.0)	1.81 (1.16, 2.84)	370	42	9.9 (7.3, 13.4)	2.05 (1.37, 3.07)
TPA>median & CRP 1-3 mg/L	475	51	9.9 (7.5, 13.1)	2.27 (1.52, 3.41)	475	73	14.5 (11.5, 18.2)	2.94 (2.06, 4.19)
TPA>median & CRP >3 mg/L	294	43	15.4 (11.4, 20.8)	3.78 (2.45, 5.77)	294	47	16.9 (12.7, 22.5)	3.58 (2.41, 5.30)

*Values of exposure variables at time of study entrance. **Participants. † Crude incidence rates per 1000 person-years. ‡ Adjusted for age (∥ and sex).

Table S14. Performance of time-fixed[*] Cox regression models for ischemic stroke (IS) with addition of total plaque area (TPA), C-reactive protein (CRP) and both (TPA+CRP) compared to Framingham risk factor based model. The Tromsø Study.

Performance measure		Framingham risk factor model	+TPA[†]	+CRP[†]	+Both[†]	+TPA[‡]	+CRP[‡]	+Both[‡]
Harrels C-index		0.7523	0.7594	0.7552	0.7613	0.7586	0.7574	0.7630
(95% CI)		(0.7358, 0.7613)	(0.7355, 0.7736)	(0.7348, 0.7722)	(0.7350, 0.7730)	(0.7338, 0.7663)	(0.7339, 0.7687)	(0.7342, 0.7714)
	p-value		**0.040**	0.394	**0.010**	**0.045**	0.104	**0.002**
NRI								
Estimated incident IS at 10 years follow-up (n=490) [§]								
% cases moved up[‖]			12.3	10.8	19.3	11.7	13.5	17.8
% cases moved down[‖]			10.0	8.1	12.6	9.5	5.4	13.2
NRI for IS cases, % (95% CI)			2.3 (-2.5, 7.1)	2.8 (-1.9, 7.)	6.6 (1.9, 11.3)	2.2 (-1.7, 6.1)	3.8 (-0.5, 8.0)	4.6 (0.3, 8.9)
	p-value		0.226	0.214	**0.005**	0.280	0.069	**0.036**
Estimated non-events (controls) at 10 years follow-up (n=9619) [§]								
% non-events moved up[‖]			5.6	4.5	7.1	6.5	5.7	7.7
% non-events moved down[‖]			6.4	3.9	7.1	6.3	5.4	7.6
NRI for controls, % (95% CI)			0.6 (-0.8, 2.0)	-0.5 (1.9, 1.4)	-0.03 (-1.5, 1.2)	-0.2 (-0.1, 1.6)	-0.03 (-1.8 , 1.2)	-0.1 (-1.5, 1.3)
	p-value		0.369	0.400	0.956	0.773	0.675	0.849
Overall categorical NRI[‖]**, % (95% CI)**			2.8 (-2.0, 7.6)	2.2 (-2.7, 6.9)	6.6 (1.8, 11.4)	2.1 (-2.1, 6.3)	3.6 (-0.8, 8.0)	4.5 (-0.1, 9.1)
	p-value		0.226	0.338	**0.007**	0.35	0.110	0.051
Continuous NRI, % (95% CI)			19.8 (5.5, 34.1)	20.1 (5.0, 35.2)	22.2 (8.7, 35.7)	22.8 (11.2, 34.4)	19.5 (8.6, 31.3)	31.1 (16.6, 45.8)
	p-value		**0.002**	**0.002**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Relative IDI, % (95% CI)			0.16 (0.03, 0.29)	0.09 (-0.03, 0.21)	0.24 (0.09, 0.38)	0.09 (0.02, 0.17)	0.13 (0.06, 0.20)	0.22 (0.09, 0.35)
	p-value		**0.0023**	0.075	**<0.001**	**0.03**	**<0.001**	**<0.001**
HL-X²		9.96	10.33	10.63	8.67	8.25	8.21	11.8
	p-value	0.268	0.240	0.220	0.498	0.410	0.413	0.159

NRI, net reclassification improvement; IDI, integrated discrimination improvement; HL-X², Hosmer-Lemeshow chi² test; CI, confidence interval. Framingham risk factor model includes sex, age, systolic blood pressure, high-density lipoprotein cholesterol, total cholesterol, smoking and antihypertensive medication. [*]Values of exposure variables at time of study entrance. [†] Included as continuous variables TPA (square root transformed), CRP (log transformed). [‡] Included as categorical variables; TPA (no plaque, < median and > median, with no plaque as reference category); CRP (<1 mg/L, 1-3 mg/L and >3 mg /L, with CRP <1 mg/L as reference category). [§]All observed risks have been interpolated to 10-year event rates by Kaplan Meier risk estimates using the actual observed events over a median follow up of 11 years. [‖]Considering risk-categories; <5%, 5-10%, 10-20% and >20%. *p*-values are for comparison with Framingham risk factor model. Bold; *p*<0.05.

Table S15. Performance of time-fixed[*] Cox regression models for myocardial infarction (MI) with addition total plaque area (TPA), C-reactive protein (CRP) and both (TPA+CRP) compared to Framingham risk factor-based model. The Tromsø Study.

Performance measure		Framingham risk factor model	+TPA[†]	+CRP[†]	+Both[†]	+TPA[‡]	+CRP[‡]	+Both[‡]
Harrels C-index		0.7435	0.7501	0.7452	0.7514	0.7499	0.7458	0.7519
(95% CI)		(0.7251, 0.7606)	(0.7321, 0.7655)	(0.7318, 0.7648)	(0.7369, 0.7672)	(0.7318, 0.7648)	(0.7317, 0.7644)	(0.7344, 0.7643)
	p-value		**0.013**	0.535	**<0.001**	**0.016**	0.386	**0.003**
NRI								
Estimated incident MI at 10 years follow-up (n=895) [§]								
% cases moved up[‖]			11.4	8.0	11.9	12.1	9.2	13.4
% cases moved down[‖]			8.8	4.3	9.3	8.9	5.5	9.1
NRI for MI cases, % (95% CI)			2.5 (-0.5, 5.5)	3.7 (0.3-7.1)	2.6 (- 1.0, 6.2)	3.2 (-0.01, 6.6)	3.7 (0.1, 7.3)	4.3 (0.5, 8.0)
	p-value		0.052	**0.038**	0.16	0.06	**0.049**	**0.025**
Estimated non-events (controls) at 10 years follow-up (n=9214) [§]								
% non-events moved up[‖]			6.2	3.3	6.6	7.0	4.6	7.8
% non-events moved down[‖]			7.4	3.3	7.6	8.0	4.6	8.5
NRI for controls, % (95% CI)			1.2 (0.2, 2.2)	0.02 (-1.3, 1.7)	1.0 (-0.3, 2.3)	1.0 (0.2, 1.8)	-0.02 (-0.5 , 0.5)	0.7 (-0.6, 1.7)
	p-value		**0.049**	0.973	0.10	**0.015**	0.974	0.240
Overall categorical NRI[‖], % (95% CI)			3.8 (0.6, 7.0)	3.7 (-0.1, 7.5)	3.6 (-0.01, 7.3)	4.2 (0.5, 7.3)	3.7 (-0.01, 7.1)	5.0 (1.2, 8.7)
	p-value		**0.03**	0.051	0.062	**0.029**	0.055	**0.011**
Continuous NRI, % (95% CI)			19.4 (12.6, 27.0)	22.0 (13.6, 30.4)	13.8 (3.3, 24.3)	26.7 (19.5, 33.9)	13.0 (-0.02, 28.2)	20.6 (9.7, 31.5)
	p-value		**<0.001**	**<0.001**	**0.007**	**<0.001**	0.098	**<0.001**
Relative IDI, % (95% CI)			0.07 (0.05, 0.10)	0.03 (-0.01, 0.07)	0.09 (0.04, 0.15)	0.04 (0.02, 0.06)	0.04 (0.02, 0.05)	0.07 (0.02, 0.11)
	p-value		**<0.001**	0.174	**0.002**	**0.030**	**0.041**	**0.012**
HL-X²		40.7	29.4	44.6	29.0	29.9	40.65	29.6
	p-value	**<0.0001**	**<0.0001**	**<0.0001**	**0.0003**	**<0.0001**	**<0.0001**	**<0.0001**

NRI, net reclassification improvement; IDI, integrated discrimination improvement; HL-X², Hosmer-Lemeshow chi² test; CI, confidence interval. Framingham risk factor model includes sex, age, systolic blood pressure, high-density lipoprotein cholesterol, total cholesterol, smoking and antihypertensive medication. [*]Values of variables at time of study entrance. [†] Included as continuous variables TPA (square root transformed), CRP (log transformed). [‡] Included as categorical variables; TPA (no plaque, < median and > median, with no plaque as reference category); CRP (<1 mg/L, 1-3 mg/L and >3 mg /L, with CRP <1 mg/L as reference category). [§] All observed risks have been interpolated to 10-year event rates by Kaplan Meier risk estimates using the actual observed events over a median follow up of 11 years. [‖] Considering risk-categories; <5%, 5-10%, 10-20% and >20%. *p*-values are for comparison with Framingham risk factor model. Bold; *p*<0.05.

Table S16. Performance of time-fixed* Cox regression models for ischemic stroke (IS) in subjects at intermediate risk (5-20%, n=2994) with addition of total plaque area (TPA), C-reactive protein (CRP) and both (TPA+CRP) compared to Framingham risk factor-based model. The Tromsø Study.

Performance measure	+TPA[†]	+CRP[†]	+Both[†]	+TPA[‡]	+CRP[‡]	+Both[‡]
NRI						
Estimated incident IS at 10 years follow-up (n=299) [§]						
% cases moved up[‖]	14.7	13.3	24.4	15.2	16.6	22.1
% cases moved down[‖]	13.5	9.9	16.5	12.9	12.8	18.3
NRI for IS cases, % (95% CI)	1.2 (-6.0, 8.4)	3.5 (-3.6, 10.6)	7.8 (-0.4, 16.0)	2.2 (-4.5, 8.9)	3.8 (-3.3, 10.9)	3.8 (-3.3, 10.9)
p-value	0.74	0.33	0.06	0.52	0.29	0.29
Estimated non-events (controls) at 10 years follow-up (n=2695) [§]						
% non-events moved up[‖]	8.8	6.4	10.4	9.5	9.1	11.3
% non-events moved down[‖]	21.9	13.1	24.2	21.6	17.9	25.8
NRI for controls, % (95% CI)	13.3 (9.0, 17.6)	6.7 (1.0, 12.4)	13.8 (8.1, 19.5)	12.1 (9.9, 14.3)	8.8 (5.1, 12.5)	14.5 (10.2, 18.8)
p-value	**<0.001**	**0.02**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Overall categorical NRI[‖]**, % (95% CI)**	14.4 (6.6, 22.2)	10.1 (2.3, 17.9)	21.6 (11.0, 32.2)	14.3 (7.1, 21.4)	12.6 (5.2, 20.1)	18.3 (10.3, 26.3)
p-value	**<0.001**	**0.016**	**<0.001**	**<0.001**	**0.001**	**<0.001**
Continuous NRI, % (95% CI)	21.0 (6.7, 35.3)	24.7 (10.4, 39.0)	30.8 (15.3, 46.3)	24.8 (11.1, 38.5)	20.8 (6.9, 34.7)	30.5 (16.0, 45.0)
p-value	**0.004**	**<0.001**	**<0.001**	**<0.001**	**0.004**	**<0.001**
Relative IDI, % (95% CI)	0.46 (0.23, 0.69)	0.32 (0.09, 0.56)	0.78 (0.43, 1.13)	0.38 (0.33, 0.43)	0.48 (0.36, 0.60)	0.86 (0.59, 1.13)
p-value	**<0.001**	**0.007**	**<0.001**	**0.01**	**<0.001**	**<0.001**

NRI, net reclassification improvement; IDI, integrated discrimination improvement; CI, confidence interval. Framingham risk factor model includes sex, age, systolic blood pressure, high-density lipoprotein cholesterol, total cholesterol, smoking and antihypertensive medication. *Values of variables at time of study entrance. [†] Included as continuous variables, TPA (square root transformed), CRP (log transformed). [‡] Included as categorical variables; TPA (no plaque, < median and > median, with no plaque as reference category); CRP (<1 mg/L, 1-3 mg/L and >3 mg /L, with CRP <1 mg/L as reference category). [§] All observed risks have been interpolated to 10-year event rates by Kaplan Meier risk estimates using the actual observed events over a median follow up of 11 years. [‖] Considering risk-categories; <5%, 5-10%, 10-20% and >20%. *p*-values are for comparison with Framingham risk factor model. Bold; *p*<0.05.

Table S17. Performance of time-fixed[*] Cox regression models for myocardial infarction (MI) in subjects at intermediate risk (5-20%, n=5250) with addition of total plaque area (TPA), C-reactive protein (CRP) and both (TPA+CRP) compared to Framingham risk factor-based model. The Tromsø Study.

Performance measure	+TPA[†]	+CRP[†]	+Both[†]	+TPA[‡]	+CRP[‡]	+Both[‡]
NRI						
Estimated incident MI at 10 years follow-up (n=562) [§]						
% cases moved up[∥]	15.4	10.3	15.0	16.4	11.5	17.3
% cases moved down[∥]	9.6	4.6	10.5	10.5	6.7	10.6
NRI for MI cases, % (95% CI)	5.7 (-1.6, 13.0)	5.7 (-1.4, 12.8)	4.5 (-2.4, 11.4)	5.9 (-1.9, 13.7)	4.8 (-2.6, 12.2)	6.7 (-0.7, 14.1)
p-value	0.12	0.11	0.20	0.14	0.21	**0.08**
Estimated non-events (controls) at 10 years follow-up (n=4688) [§]						
% non-events moved up[∥]	7.7	3.4	8.0	8.3	4.8	9.4
% non-events moved down[∥]	12.5	5.9	12.9	13.9	8.1	14.6
NRI for controls, % (95% CI)	4.8 (-2.8, 12.4)	2.5 (-5.5, 10.5)	4.8 (-3.0, 11.8)	5.6 (-0.8, 12.0)	3.3 (-4.3, 10.9)	5.3 (2.3, 12.9)
p-value	0.22	0.55	0.23	0.06	0.40	0.18
Overall categorical NRI[∥]**, % (95% CI)**	10.5 (1.3, 19.7)	8.2 (-1.6, 18.0)	9.3 (-0.3, 18.9)	11.6 (1.4, 21.8)	8.1 (-2.3, 18.5)	12.0 (2.0, 22.0)
p-value	**0.04**	0.10	0.06	**0.03**	0.13	**0.02**
Continuous NRI, % (95% CI)	18.2 (0.4, 20.3)	18.2 (1.0, 35.4)	14.9 (-2.2, 32.0)	15.1 (-1.2, 31.4)	7.1 (-11.9, 26.1)	17.0 (-1.4, 35.4)
p-value	**0.05**	**0.04**	0.09	0.07	0.463	0.07
Relative IDI, % (95% CI)	0.24 (-0.15, 0.64)	0.06 (-0.35, 0.47)	0.28 (-0.11, 0.67)	0.22 (-0.15, 0.59)	0.09 (-0.34, 0.52)	0.30 (-0.11, 0.71)
p-value	0.24	0.78	0.18	0.25	0.67	0.14

NRI, net reclassification improvement; IDI, integrated discrimination improvement; CI, confidence interval. Framingham risk factor model includes sex, age, systolic blood pressure, high-density lipoprotein cholesterol, total cholesterol, smoking and antihypertensive medication. [*]Values of variables at time of study entrance. [†] Included as continuous variables, TPA (square root transformed), CRP (log transformed). [‡] Included as categorical variables; TPA (no plaque, < median and > median, with no plaque as reference category); CRP (<1 mg/L, 1-3 mg/L and >3 mg /L, with CRP <1 mg/L as reference category). [§] All observed risks have been interpolated to 10-year event rates by Kaplan Meier risk estimates using the actual observed events over a median follow up of 11 years. [∥] Considering risk-categories; <5%, 5-10%, 10-20% and >20%. *p*-values are for comparison with Framingham risk factor model. Bold; *p*<0.05.