C-reactive protein and risk of coronary heart disease, stroke, and mortality: individual participant meta-analysis

The Emerging Risk Factors Collaboration*

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Supplementary materials

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eTable 1. Descriptive summaries by study of baseline characteristics of participants, follow up time, and number of outcomes contributed.

Study design/ Study	Number of cohorts	Total No. with CRP measured	Males (%)	Age (yrs) mean (SD)	Follow up (yrs) median (5, 95) percentiles	Log_e CRP (log_e mg/l) mean(sd)	Non-fatal MI and CHD death	CHD deaths	Non-fatal MI	Fatal MI	All cerebrovascular events	Haemorrhagic stroke	Ischaemic stroke	Unclassified stroke	Other vascular deaths	All vascular deaths	Non-vascular deaths	Unclassified deaths	All-cause mortality
Cohort																			
ATTICA[1]	1	1442	744 (52%)	50.5 (11.0)	5.0 (5.0, 5.0)	0.13 (1.10)	0	0	0	0	0	0	0	0	25	25	17	0	42
BRUN[2]	1	817	398 (49%)	57.9 (11.4)	15.3 (3.9, 15.5)	0.48 (0.94)	54	31	23	19	40	15	24	0	7	56	123	1	180
BWHHS[3]	1	3156	0 (0%)	68.5 (5.5)	4.6 (2.0, 5.6)	0.52 (1.14)	55	23	32	12	46	4	20	14	13	54	148	2	204
CAPS[4]	1	848	848 (100%)	57.3 (4.6)	8.0 (4.1, 8.3)	0.51 (1.05)	56	19	37	12	2	0	0	2	6	27	60	0	87
CHS[5]	1	4333	1658 (38%)	72.3 (5.2)	11.1 (1.9, 12.9)	0.89 (1.02)	640	233	407	233	514	67	406	41	62	297	864	2	1163
COPEN[6]	1	7479	3172 (42%)	59.7 (13.5)	7.3 (1.8, 8.8)	0.73 (0.78)	248	32	216	0	301	35	166	85	90	138	520	68	726
EAS[7]	1	754	365 (48%)	64.2 (5.6)	15.1 (2.3, 15.7)	0.60 (1.10)	60	28	32	21	50	2	0	44	13	56	155	2	213
ESTHER[8]	1	7894	3304 (42%)	61.6 (6.6)	2.0 (1.9, 2.7)	0.74 (1.08)	58	10	48	8	86	1	3	81	4	21	68	11	100
FINRISK97[9]	1	1266	1266 (100%)	61.6 (8.6)	6.8 (1.8, 6.9)	0.61 (1.19)	72	24	48	14	57	11	46	0	12	39	90	1	130
FRAMOFF[10]	1	3296	1498 (45%)	55.3 (9.7)	11.6 (4.2, 14.3)	0.60 (1.46)	121	13	108	0	68	7	60	0	6	19	194	32	245
GOH[11]	1	567	277 (49%)	70.6 (6.6)	3.9 (0.3, 6.9)	0.90 (0.96)	0	0	0	0	0	0	0	0	0	0	0	16	16
GOTOW[12]	1	36	0 (0%)	48.9 (7.9)	20.4 (0.5, 32.6)	2.41 (0.74)	7	4	3	4	7	0	0	7	3	9	9	0	18
HELSINAG[13]	1	391	105 (27%)	79.5 (4.4)	7.9 (1.7, 11.0)	0.56 (1.21)	38	38	0	27	43	2	20	4	22	103	117	15	235
HISAYAMA[14]	1	2578	1088 (42%)	59.0 (11.5)	14.2 (3.4, 14.2)	-0.68 (1.28)	77	10	67	3	220	49	148	0	59	76	311	2	389
HOORN[15]	1	531	254 (48%)	63.9 (7.2)	8.7 (2.7, 9.9)	0.43 (1.24)	19	4	15	3	13	0	2	11	15	22	30	21	73
KIHD[16]	1	2040	2040 (100%)	52.5 (5.3)	19.2 (3.0, 23.1)	0.27 (0.96)	394	11	383	6	146	34	106	3	26	46	257	1	304
LASA[17]	1	1518	689 (45%)	69.7 (8.4)	9.7 (1.6, 10.4)	0.77 (1.18)	25	0	25	0	14	0	0	14	0	0	0	428	428
MESA[18]	1	6716	3170 (47%)	62.2 (10.2)	4.8 (2.5, 5.2)	0.65 (1.16)	83	14	69	0	84	13	68	2	6	21	120	1	142
MOGERAUG1[19]	1	874	874 (100%)	53.9 (5.8)	12.9 (3.6, 13.4)	0.47 (1.14)	79	32	47	26	5	2	0	2	24	61	65	0	126
MOGERAUG2	1	1265	1265 (100%)	58.7 (8.4)	7.8 (1.3, 8.4)	0.52 (1.14)	74	34	40	28	3	1	0	1	8	45	66	2	113
MOGERAUG3	1	3152	1596 (51%)	54.9 (10.4)	3.0 (2.0, 3.6)	0.42 (1.09)	16	5	11	5	4	1	2	1	9	18	27	0	45
MOSWEGOT[20]	1	745	362 (49%)	49.0 (9.5)	8.7 (7.6, 9.2)	0.69 (1.23)	8	1	7	1	16	4	8	2	1	5	21	0	26
NHANESIII[21]	1	3722	1434 (39%)	55.6 (15.6)	8.2 (3.0, 11.2)	1.99 (0.70)	137	137	0	49	58	0	0	58	67	262	391	2	655
NPHSII[22]	1	2637	2637 (100%)	57.2 (3.6)	7.6 (3.1, 9.9)	1.09 (1.18)	166	16	150	13	38	3	23	8	22	41	120	1	162
NSHS[23]	1	1448	695 (48%)	53.8 (15.0)	9.7 (2.4, 10.0)	0.52 (1.32)	5	5	0	0	30	0	0	30	0	5	9	0	14
QUEBEC[24]	1	1913	1913 (100%)	56.3 (6.9)	5.3 (4.6, 5.6)	0.56 (1.13)	40	5	35	4	9	0	0	9	12	17	45	2	64
RANCHO[25]	1	1381	578 (42%)	67.0 (11.1)	14.6 (2.0, 17.8)	0.51 (1.11)	161	1	160	1	131	1	0	127	71	76	274	1	351
ROTT[26]	1	4825	1824 (38%)	67.7 (8.2)	12.0 (2.9, 14.2)	0.53 (1.04)	249	35	214	30	146	23	39	64	275	456	796	181	1433
SHS[27]	1	3194	1157 (36%)	59.7 (7.9)	8.9 (1.7, 10.3)	1.38 (1.00)	286	90	196	38	133	5	4	120	76	189	503	8	700
SPEED[28]	1	1576	1576 (100%)	57.7 (4.4)	13.9 (2.8, 15.3)	0.42 (1.14)	154	90	64	78	56	2	46	5	12	115	194	0	309
TARFS[29]	1	2006	979 (49%)	51.6 (11.1)	4.5 (0.9, 8.2)	0.85 (1.23)	39	28	11	8	20	0	1	19	17	60	48	3	111
ULSAM[30]	1	1014	1014 (100%)	71.4 (1.7)	12.1 (2.1, 14.9)	0.66 (1.01)	145	47	98	19	111	16	83	7	38	88	199	2	289
WHITEI	1	3954	3954 (100%)	76.4 (4.6)	8.2 (2.0, 8.4)	0.52 (1.11)	209	209	0	92	137	14	20	71	111	457	743	14	1214
WHITEII[31]	1	7496	5201 (69%)	49.5 (6.0)	7.6 (3.8, 8.2)	-0.09 (1.18)	161	23	138	18	6	0	1	3	11	40	95	1	136
WHS[32]	1	27938	0 (0%)	54.7 (7.1)	10.2 (8.4, 10.8)	0.62 (1.21)	249	10	239	4	284	26	237	2	82	96	544	0	640
Subtotal	35	114802	47935 (42%)	60.3 (8.6)	8.2 (2.0, 14.2)	0.65 (1.12)	4185	1262	2923	776	2878	338	1533	837	1205	3040	7223	820	11083

Study design/ Study	Number of cohorts	Total No. with CRP measured	Males (%)	Age (yrs) mean (SD)	Follow up (yrs) median (5, 95) percentiles	Log_e CRP (log_e mg/l) mean(sd)	Non-fatal MI and CHD death	CHD deaths	Non-fatal MI	Fatal MI	All cerebrovascular events	Haemorrhagic stroke	Ischaemic stroke	Unclassified stroke	Other vascular deaths	All vascular deaths	Non-vascular deaths	Unclassified deaths	All-cause mortality
Case-cohort																			
ARIC[33]	1	1183	687 (58%)	58.6 (5.5)	10.8 (1.8, 12.7)	0.67 (1.11)	249	36	213	21	44	1	39	2	19	57	71	1	129
FINRISK92[34]	1	864	459 (53%)	51.8 (9.2)	11.8 (1.8, 11.9)	0.62 (1.15)	97	20	77	8	80	21	56	0	13	36	112	1	149
Subtotal	2	2047	1146 (56%)	55.2 (7.3)	11.2 (1.8, 12.6)	0.65 (1.13)	346	56	290	29	124	22	95	2	32	93	183	2	278
Nested case-control (frequency matched)																			
BRHS[35]	1	1298	1298 (100%)	51.9 (5.3)	20.5 (3.2, 23.6)	0.50 (1.22)	456	189	267	128	68	0	2	62	24	233	178	1	412
REYK[36]	1	5457	3880 (71%)	54.4 (8.3)	21.3 (4.1, 36.6)	0.31 (1.12)	2009	751	1258	552	334	64	102	92	212	1297	1503	31	2831
Subtotal	2	6755	5178 (77%)	53.2 (7.8)	21.2 (3.8, 35.3)	0.40 (1.14)	2465	940	1525	680	402	64	104	154	236	1530	1681	32	3243
Nested case-control (individually matched)																			
EPICNOR[37]	1	3316	2105 (63%)	65.3 (7.8)	7.5 (3.4, 9.3)	0.59 (1.18)	481	228	253	4	0	0	0	0	19	247	105	0	352
FIA[38]	1	1612	1176 (73%)	54.9 (7.6)	3.5 (0.4, 8.5)	0.44 (1.04)	583	123	460	123	0	0	0	0	0	123	0	0	123
FLETCHER[39]	1	620	478 (77%)	56.9 (14.4)	5.5 (2.1, 6.4)	0.20 (1.01)	128	0	0	0	0	0	0	0	0	0	0	0	0
GLOSTRUP[40]	1	382	281 (74%)	50.3 (8.5)	4.5 (0.5, 12.5)	0.58 (1.03)	75	17	58	17	0	0	0	0	0	17	0	0	17
HPFS[41]	1	730	730 (100%)	63.1 (8.3)	7.7 (3.0, 8.5)	0.28 (1.17)	221	37	184	11	7	3	2	1	34	78	20	0	98
MRFIT[42]	1	737	737 (100%)	46.5 (5.6)	7.1 (6.0, 7.8)	0.70 (0.79)	246	148	98	13	0	0	0	0	0	19	5	0	24
NHS[43]	1	720	0 (0%)	60.4 (6.5)	8.0 (1.3, 8.8)	0.89 (1.16)	238	30	208	30	0	0	0	0	3	33	11	1	45
PRIME[44]	1	916	916 (100%)	55.2 (2.8)	5.2 (1.9, 7.3)	0.40 (1.10)	143	17	126	12	6	2	4	0	14	31	3	0	34
USPHS[45]	1	938	938 (100%)	59.6 (9.1)	-	0.20 (0.94)	246	22	224	22	154	0	154	0	0	27	0	0	27
WHIHABPS[46]	1	1548	0 (0%)	68.5 (6.3)	6.8 (1.2, 9.3)	1.01 (1.13)	49	6	43	0	706	0	706	0	1	12	24	2	38
Subtotal	10	11519	7361 (64%)	58.1 (7.8)	6.6 (1.4, 9.0)	0.53 (1.09)	2410	628	1654	232	873	5	866	1	71	587	168	3	758
Clinical trials																			
AFTCAPS[47]	1	5398	4589 (85%)	58.3 (7.2)	5.1 (4.5, 6.7)	0.55 (1.03)	102	3	99	3	17	0	16	1	14	18	23	0	41
LEADER[48]	1	434	434 (100%)	67.1 (9.1)	3.8 (0.8, 4.9)	1.51 (0.93)	36	25	11	13	24	0	15	9	7	37	30	3	70
PROSPER[49]	1	3179	1320 (42%)	75.1 (3.3)	3.2 (1.1, 3.8)	1.12 (1.12)	261	64	197	0	112	0	0	112	13	86	150	0	236
USPHS2[50]	1	10724	10724 (100%)	63.7 (7.7)	10.9 (4.9, 11.5)	-0.11 (1.06)	311	28	283	2	259	40	217	2	75	105	690	0	795
WOSCOPS[51]	1	5451	5451 (100%)	55.1 (5.5)	4.8 (2.9, 6.0)	0.53 (1.07)	335	64	271	0	62	0	0	62	6	70	88	0	158
Subtotal	5	25186	22518 (89%)	63.9 (6.8)	5.6 (3.0, 11.4)	0.72 (1.06)	1045	184	861	18	474	40	248	186	115	316	981	3	1300
Total	54	160309	84138 (52%)	59.8 (8.2)	8.0 (2.0, 15.1)	0.62 (1.11)	10451	3070	7253	1735	4751	469	2846	1180	1659	5566	10236	860	16662

eTable 2. Study level characteristics and laboratory methods for measurement of CRP.

Study	Geographical location	Population source/sampling method	Fasting status at blood sampling/duration	Sample source	Time between collection and measurement	Sample state before analysis, storage temperature (°C) if frozen	Assay method (source)	Assay standard	Assay source
AFTCAPS†	USA	Popln. Screening/Complete	Fasted / > 8 hrs	Serum	< 1 week	NS	EIA (Behring)	Manufacturer	Commercial
ARIC	USA	Household listings/Random	Fasted / > 8 hrs	Plasma	> 10 yrs	Frozen, -70	ITA (Denka Seiken)	Manufacturer	Commercial
ATTICA	Greece	Popln. Register/Random	Fasted / >8hrs	Serum	< 1 week	Fresh	INA (Behring)	Manufacturer	Commercial
BRHS	UK	GP lists/Random	Non-fasted	Serum	> 10 yrs	Frozen, -20	MEIA (Abbott)	WHO 85/506	Commercial
BRUN†	Italy	Popln. Register/Random	Fasted / > 8 hrs	Plasma	> 10 yrs	Frozen, -70	ITA / INA, Behring	IFCC CRM 470	Commercial
BWHHS	UK	Popln. Register/Random	Fasted / >8 hrs	Serum	1-5 yrs	Frozen, -80	INA (Behring)	Manufacturer	Commercial
CAPS	UK	Electoral rolls/Random	Fasted / > 8 hrs	Plasma	NS	Frozen, -70	EIA (Behring)	WHO 85/506	Commercial
CHS†	USA	Medicare lists/Random	Fasted / > 8 hrs	Plasma	5-10 yrs	Frozen, -70	ELISA (In-house)	WHO 85/506	In-house
COPEN†	Denmark	Popln. Register/Random	Non-fasted	Serum	> 10 yrs	Frozen, -80	ITA (DAKO)	Manufacturer	Commercial
EAS	Scotland	GP list/Random	Fasted/ > 8 hrs	Serum	> 10 yrs	Frozen, -50	INA (Behring)	Manufacturer	Commercial
EPICNOR	UK	GP lists/Complete	Non-fasted	Serum	NS	Frozen, -80	ELISA (Sanquin Res)	Behringwerke	Commercial
ESTHER	Germany	GP list/Complete	Fasted/ NS	Serum	1 week-1 yr	Frozen, -80	ITA (ADIVA)	Manufacturer	Commercial
FIA†	Sweden	Popln. Register/Random	Fasted / 4 hrs	Plasma	5 – 18 yrs	Frozen, -80	CIA (Immulite)	WHO 85/506	Commercial
FINRISK92	Finland	Popln. Register/Random	Fasted / 4-8 hrs	Serum	> 10 yrs	Frozen, -20	CIA (Immulite)	Manufacturer	Commercial
FINRISK97	Finland	Popln. Register/Random	Fasted / 4-8 hrs	Serum	1 week - 1 yr	Frozen, -70	ELISA, Eucardio Lab	Manufacturer	Commercial
FLETCHER†	New Zealand	Occup. , electoral roll/Complete, random	Non-fasted	Plasma	> 10 yrs	Frozen, -70	INA (Behring)	Manufacturer	Commercial
FRAMOFF†	USA	Offspring & spouse to FHS/Complete	Fasted / > 8 hrs	Serum	3 - 7 yrs	Frozen, -70	ELISA (Hemagen)	WHO	Commercial
GLOSTRUP	Denmark	Popln. Register/Random	Fasted / > 8 hrs	Serum	7-15 yrs	Frozen, -20	ELISA (In-house)	Behring	In-house
GOH	Israel	Popln. Register/Random	Fasted / > 8 hrs	Plasma	< 1 week	Fresh	Olympus	Manufacturer	Commercial
GOTOW‡	Sweden	Popln. Register/Random	Fasted / > 8 hrs	Serum	NS	NS	NS	NS	NS
HELSINAG	Finland	Popln. Register/Random	Fasted / > 8 hrs	Serum	5-10 yrs	Frozen, -20	EIA (Medix Diacor)	WHO 85/506	Commercial
HISAYAMA	Japan	Popln. Register/Complete	Fasted / > 8 hrs	Serum	> 10 yrs	Frozen, -20	INA (Behring)	Manufacturer	Commercial
HOORN	Netherlands	Popln. Register/Random	Fasted / >8 hrs	Plasma	5-10 yrs	Frozen, -70	ELISA (DAKO)	Behring	Commercial
HPFS	USA	Occupational/Complete	2/3 Fasted / NS	Plasma	5-10 yrs	Frozen, -130	ITA (Denka Seiken)	Denka Seiken	Commercial
KIHD	Finland	Popln. Register/Random	Fasted / > 8 hrs	Serum	> 10 yrs	Frozen, -20	CIA (Immulite)	WHO 85/506	Commercial
LASA†	Netherlands	Popln. Register/Random	Non-fasted	Serum	5 - 10 yrs	Frozen, -80	ELISA (In-house)	In-house	In-house
LEADER†	UK	GP listings/Complete	Non-fasted	Serum	NS	Frozen, -70	CIA (Immulite)	NS	Commercial
MESA†	USA	Popln. Register/Random	Fasted / > 8 hrs	Plasma	1 week - 1 yr	Frozen, -70	INA (Behring)	CDC	Commercial
MOGERAUG1†	Germany	Popln. Register/Random	Non-fasted	Serum	> 10 yrs	Frozen, -80	IRMA, In-house	WHO 85/506	In-house
MOGERAUG2	Germany	Popln. Register/Random	Non-fasted	Serum	> 10 yrs	Frozen, -80	IRMA, In-house	WHO 85/506	In-house
MOGERAUG3	Germany	Popln. Register/Random	Non-fasted	Serum	1-5 yrs	Frozen, -80	IRMA, In-house	WHO 85/506	In-house
MOSWEGOT	Sweden	Popln. Register/Random	Fasted / > 8 hrs	Serum	NS	NS	NS	NS	NS
MRFIT	USA	Popln. Screening/Complete	Fasted / > 8 hrs	Plasma	10 yrs	Frozen, -50	ELISA (Calbiochem)	WHO 85/506	Commercial
NHANESIII‡	USA	Census list/Cluster	Fasted / > 6 hrs	Serum	1 week – 1 yr	Frozen, -70	INA, Behring	Manufacturer	Commercial
NHS	USA	Occupational/Complete	Fasted / Variable	Plasma	5-10 yrs	Frozen, -130	ITA (Denka Seiken)	Denka Seiken	Commercial
NPHSII	UK	GP list/Complete	Non-fasted	Serum	7-14 years	Frozen, -40	? (Cordia)	NS	Commercial

Study	Geographical location	Population source/sampling method	Fasting status at blood sampling/duration	Sample source	Time between collection and measurement	Sample state before analysis, storage temperature (°C) if frozen	Assay method (source)	Assay standard	Assay source
NSHS	Canada	Medicare lists/Random	Fasted / > 8 hrs	Plasma	> 10 yrs	Frozen, -80	INA (Behring)	NS	Commercial
PRIME	France / Northern Ireland	General Popln./Quota	Fasted / > 8 hrs	Plasma	5-10 yrs	Frozen, -130	INA (Behring)	NS	Commercial
PROSPER	Scotland/Ireland/Netherlands	Primary Care screening/Complete	Fasted / >8 hrs	Plasma	1-5 yrs	Frozen, -80	ITA (Roche)	cFas calibrator	Commercial
QUEBEC	Canada	Popln. Register/Random	Fasted / > 8 hrs	Plasma	5-10 yrs	Frozen, -70	INA (Behring)	Manufacturer	Commercial
RANCHO	USA	Household listings/Complete	Fasted / > 8 hrs	Plasma	> 10 yrs	Frozen, -70	INA (Behring)	NS	Commercial
REYK	Iceland	Popln. Register/Complete	Fasted / > 8 hrs	Serum	NS	Frozen, -20	ITA (Roche)	WHO 85/506	Commercial
ROTT†	Netherlands	Popln. Register/Complete	Non-fasted	Serum	> 10 yrs	Frozen, -20	INA (Immage)	Manufacturer	Commercial
SHS	USA	Tribal rolls/Complete	Fasted / > 8 hrs	Plasma	NS	Frozen, -80	ELISA (In-house)	In-house	In-house
SPEED	UK	GP list/Complete	Fasted / >8hrs	Plasma	NS	Frozen, -20	EIA (Behring)	WHO 85/506	Commercial
TARFS†	Turkey	Household listings/Random	Fasted / > 8 hrs	Plasma	< 1 week	Frozen, -80	INA (Behring)	Manufacturer	Commercial
ULSAM†	Sweden	Popln. Register/Complete	Fasted/ > 8 hrs	Serum	>10 yrs	Frozen, -150	INA (Behring)	NS	Commercial
USPHS	USA	Occupational/Complete	Non-fasted	Plasma	> 10 yrs	Frozen, -80	ELISA (In-house)	WHO 85/506	In-house
USPHS2	USA	Occupational/Complete	Fasted / >8hrs	Plasma	NS	NS	ELISA (In-house)	WHO 85/506	In-house
WHIHABPS	USA	Popln. Register/Complete	Fastes/NS	Plasma	7-12 yrs	Frozen, -70	ITA (Denka Seiken)	NS	Commercial
WHITEI	UK	Occupational/Complete	Fasted / > 8 hrs	Plasma	NS	Frozen, -150	INA (Behring)	Manufacturer	Commercial
WHITEII	UK	Civil servant/Complete	Fasted /NS	Serum	NS	Frozen, -80	INA (Behring)	NS	Commercial
WHS	USA	Health professionals/Complete	3/4 Fasted / >8 hrs	Plasma	5-10 yrs	Frozen, -130	ITA (Denka Seiken)	NS	Commercial
WOSCOPS	UK	Heart screening clinic/Complete	Fasted / > 8 hrs	Plasma	10 yrs	Frozen, -70	ELISA (In-house)	IFCC CRM470	In-house

‡These studies used a non-high sensitivity CRP assay, measuring only CRP values > 2 mg/l

†These studies have contributed data on baseline and re-survey measurements

Popln. = Population; Occup./Occupational = Occupation based cohort; GP = General Practitioner; FHS = Framingham Heart Study; NS = Not Stated

eTable 3. Characterisation of baseline and incident vascular disease outcomes in the contributing studies.

	Coronary heat disease assessed at baseline				Definition of incident endpoints						Classification of incident endpoints						
					Death	Nonfatal MI			Nonfatal Stroke		MI			Stroke			
Study	MI	Angina	Coronary revascularization	Heart failure		Clinical feature	ECG	Cardiac markers	Clinical feature	CT/MRI imaging	Definite	Probable	Silent	Ischemic	Hemorrhagic	SAH	Unclassified
AFTCAPS	++	++	-	-	**	✓	✓	✓	✓	✓	✓	-	✓NC	✓NC	NS	NS	✓NC
ARIC	++ NC	++ NC	++ NC	-	**	✓	✓	✓	✓	✓	✓	✓ NC	✓ NC	✓	✓	✓	✓
ATTICA	+	+	+	+	*	-	-	-	-	-	-	-	-	-	-	-	-
BRHS	++	++	-	++	*	✓	✓	✓	NS	NS	✓	o	o	✓	✓	✓	✓
BRUN	++	++	++ NC	++ NC	**	✓	✓	✓	✓	✓	✓	o	o	✓	✓	o	o
BWHHS	++	++	++	-	**	✓	✓	✓	✓	✓	✓	o	o	✓	✓	✓	✓
CAPS	++	++ NC	-	-	**	✓	✓	o	✓	✓	✓	✓ NC	o	✓	✓	✓	✓
CHS	++	++	++	++	**	✓	✓	✓	✓	✓	✓	✓ NC	✓ NC	✓	✓	o	✓
COPEN	++	++	-	-	**	✓	✓	✓	✓	✓	✓	o	o	✓	✓	✓	✓
EAS	++	++	-	-	**	✓	✓	✓	✓	✓	✓	✓	✓ NC	✓	✓	✓	✓
EPICNOR	+	-	-	-	*	✓	✓	✓	✓	✓	✓	o	o	✓ NC	✓ NC	✓ NC	✓ NC
ESTHER	++	++	++	+	**	✓	✓	✓	✓	✓	✓	o	o	o	o	o	✓
FIA	++	-	-	-	**	✓	✓	✓	NA	NA	✓	o	o	✓ NC	✓ NC	✓ NC	✓ NC
FINRISK92	++	++	++ NC	-	**	✓	✓	✓	✓	✓	✓	o	o	✓	✓	✓	✓
FINRISK97	++	++	++ NC	-	**	✓	✓	✓	✓	✓	✓	o	o	✓	✓	✓	✓
FLETCHER	+ NC	+	+ NC	-	*	✓	✓	✓	✓	✓	✓	o	o	✓NC	✓NC	✓NC	✓NC
FRAMOFF	++	++	-	++NC	**	✓	✓	✓	✓	✓	✓	o	✓	✓	✓	✓	✓
GLOSTRUP	++	++	++ NC	-	**	✓	✓	✓	NA	NA	✓	o	o	o	o	o	✓ NC
GOH	++	-	-	-	**	NA	NA	NA	NA	NA	✓	✓ NC	o	✓	✓	✓	✓
GOTOW	++	NS	NS	NS	*	✓	✓	✓	✓	✓	✓	o	o	NS	NS	NS	✓
HELSINAG	++ NC	++ NC	++ NC	++ NC	**	NA	NA	NA	NA	NA	✓	o	o	✓	✓	✓	✓
HISAYAMA	++	++	++	++	**	✓	✓	✓	✓	✓	✓	0	✓	✓	✓	✓	✓
HOORN	++ NC	++ NC	++ NC	NS	*	✓	✓	✓	✓	o	✓	o	o	✓	✓	✓	✓
HPFS	+	+	+	-	**	✓	✓	✓	NA	NA	✓	✓ NC	o	o	o	o	o
KIHD	++	++	++	++	**	✓	✓	✓	✓	✓	✓	✓ NC	o	✓	✓	✓	✓
LASA	++	++	-	++	*	NA	NA	NA	✓	✓	o	O	o	o	o	o	✓
LEADER	++	++	-	-	**	✓	✓	✓	✓	✓	✓	O	o	✓	✓	✓	✓
MESA	+	+	+	+	**	✓	✓	✓	✓	✓	✓	NS	✓	✓	✓	✓	✓
MOGERAUG1	+	+ NC	-	-	**	✓	✓	✓	NA	NA	✓	✓ NC	o	✓	✓	✓	✓
MOGERAUG2	+	+ NC	-	-	**	✓	✓	✓	NA	NA	✓	✓ NC	o	✓	✓	✓	✓
MOGERAUG3	+	+ NC	-	-	**	✓	✓	✓	NA	NA	✓	✓ NC	o	✓	✓	✓	✓
MOSWEGOT	+	+	-	-	**	✓	✓	✓	✓	✓	✓	O	o	✓	✓	✓	✓
MRFIT	++	++	-	-	**	✓	✓	✓	✓	✓	✓	O	✓	✓	✓	✓	✓
NHANESIII	+	-	-	+	*	✓	✓	✓	✓	✓	✓ NC	O	o	✓ NC	✓ NC	✓ NC	✓ NC
NHS	+	+	+	-	**	✓	✓	✓	NA	NA	✓	✓ NC	o	o	o	o	o
NPHSII	++	++	++ NC	+NC	**	✓	✓	✓	✓	✓	✓	✓ NC	✓ NC	✓	✓	✓	✓

	Coronary heat disease assessed at baseline				Definition of incident endpoints					Classification of incident endpoints						
					Death	Nonfatal MI			Nonfatal Stroke		MI			Stroke		
Study	MI	Angina	Coronary revascularization	Heart failure		Clinical feature	ECG	Cardiac markers	Clinical feature	CT/MRI imaging	Definite	Probable	Silent	Ischemic	Hemorrhagic	SAH	Unclassified
NSHS	++	++	++	++	**	✓	✓	✓	✓	✓	✓	o	o	✓	✓	✓	✓
PRIME	++	++	+	-	**	✓	✓	✓	✓	✓	✓	o	o	✓	✓	✓	✓
PROSPER	++	++	++	++	**	✓	✓	✓	✓	✓	✓	o	o	NS	NS	NS	✓
QUEBEC	++	++	-	-	**	✓	✓	✓	✓	✓	✓	o	✓	o	o	o	✓
RANCHO	++	++	++	+	*	✓	✓	✓	✓	✓	✓	o	o	✓	✓	✓	✓
REYK	++	++	++	-	**	✓	✓	✓	✓	✓	✓	✓	o	✓	✓	✓	✓
ROTT	++	++ NC	++	++	**	✓	✓	✓	NA	NA	✓	✓ NC	o	✓	✓	✓	✓
SHS	++ NC	++ NC	++ NC	++ NC	**	✓	✓	✓	✓	✓	✓	✓ NC	o	✓	✓	✓	✓
SPEED	++	++NC	-	-	**	✓	✓	✓	✓	✓	✓	o	✓NC	✓	✓	✓	✓
TARFS	++	++	++ NC	-	*	✓	✓	o	✓	o	✓	o	✓	✓	o	o	✓
ULSAM	++	++	++	++	**	✓	✓	✓	✓	✓	✓	o	o	✓	✓	✓	✓
USPHS	+	-	-	-	**	✓	✓	✓	NA	NA	✓	o	o	✓ NC	✓ NC	✓ NC	✓ NC
USPHS2	+	-	-	-	*	✓	✓	✓	✓	✓	✓	o	o	✓	✓	✓	✓
WHIHABPS	+	+	+	NS	**	✓	✓	✓	✓	✓	✓	o	o	✓	✓	✓	✓
WHITEI	+	+ NC	+ NC	+	*	-	-	-	-	-	-	-	-	-	-	-	-
WHITEII	++	++ NC	++ NC	++ NC	*	✓	✓	✓	✓	✓	✓	o	o	✓	✓	✓	✓
WHS	+	+	+	-	**	✓	✓	✓	✓	✓	✓	o	o	✓	✓	✓	✓
WOSCOPS	++	++	++ NC	++ NC	**	✓	✓	✓	✓	✓	✓	✓	✓ NC	o	o	o	✓

–: Not recorded; +: Self-report only; ++: Self-report supplemented by objective criteria (e.g., Electrocardiogram, Physical examination)

* Death certificate only; ** Death certificate supplemented by medical record

0: Feature not included in criteria; ✓: Feature included in criteria

SAH: Subarachnoid haemorrhage; NS: Not stated

NC = reportedly measured but data not contributed to the ERFC; NA = not applicable, where cohorts contributed data on fatal endpoints only

eTable 4. Summary of data available and associations with CRP levels.

	Summary of available data			Association with log_e CRP value
	No. of studies	No. of participants	Mean (SD) or %	Percent difference (95% CI) in CRP levels per 1 SD increase or compared to reference category [§]
Log_e CRP (mg/l)	54	160309	0.62 (1.11)	-
Age at survey (years)	54	160309	59.8 (8.2)	15% (12%, 17%)
Non-lipid markers				
Systolic blood pressure (mmHg)	52	152145	137 (18)	13% (11%, 16%)
Diastolic blood pressure (mmHg)	52	153810	81 (10)	10% (7%, 12%)
Body mass index (kg/m^2)	53	155391	26.6 (4.4)	37% (33%, 40%)
Lipid markers				
Total cholesterol (mmol/l)	53	157758	5.90 (1.07)	3% (2%, 5%)
LDL cholesterol (mmol/l)	12	50157	3.51 (0.85)	9% (2%, 16%)
Non-HDL cholesterol (mmol/l)	51	144752	4.60 (1.07)	10% (8%, 12%)
HDL cholesterol (mmol/l)	51	144792	1.30 (0.38)	-18% (-20%, -16%)
Log_e triglycerides (mmol/l)	46	130201	0.38 (0.51)	21% (17%, 25%)
Inflammatory and metabolic markers				
Fibrinogen level (µmol/l)	32	97146	9.91 (2.27)	72% (64%, 81%)
Albumin (g/l)	22	61148	43.1 (4.4)	-20% (-25%, -15%)
Log_e leukocyte count ($x10^9/l$)	19	40094	1.85 (0.27)	36% (30%, 42%)
Log_e interleukin 6 (ng/l)	11	26465	0.55 (0.66)	74% (55%, 96%)
Log_e fibrin D-dimer (µg/l)	7	14018	4.57 (0.84)	35% (16%, 57%)
Fasting glucose (mmol/l)	24	49487	5.83 (1.83)	14% (10%, 18%)
Categorical variables				
Sex				
Male	49	84138	52%	Ref
Female	36	76171	48%	8% (1%, 16%)
Ethnicity				
White	42	129017	94%	Ref
Asian	7	3862	3%	-16% (-40%, 19%)
Black	14	5101	4%	26% (15%, 38%)
Smoking status				
Not current	53	125132	79%	Ref
Current	51	32286	21%	37% (31%, 44%)
Alcohol consumption				
Not current	43	49552	35%	Ref
Current	42	90130	65%	-5% (-9%, -1%)
History of diabetes				
No	51	143257	94%	Ref
Yes	48	9650	6%	32% (24%, 41%)
Physical activity				
Inactive	27	30331	64%	Ref
Active	14	16950	36%	-24% (-32%, -14%)

[§] Percent change in CRP per 1-SD higher value of the row variable (or, for categorical variables, the percentage difference in mean CRP levels compared to reference category) adjusted for sex and age, pooled across studies using random effects meta-analysis.

eTable 5. Risk ratios for vascular disease and non-vascular mortality per 3-fold higher baseline and usual CRP levels and between study heterogeneity statistics.

				Risk ratio (95% CI) per 3-fold higher CRP levels[†]			Between study heterogeneity in models involving usual $\log_e$ CRP levels		
Outcome	No. of studies	No. of participants	No. of outcomes	Baseline $\log_e$ CRP levels	Usual $\log_e$ CRP levels	Wald χ^2_1	Q statistic χ^2 (df)	p-value	I^2 (95% CI)
Fatal/ non-fatal CHD and stroke outcomes									
Coronary heart disease	48	151972	10341	1.36 (1.32, 1.40)	1.68 (1.59, 1.78)	317	90 (47)	<0.0001	48 (27, 63)
Non-fatal MI[‡]	25	47113	4610	1.31 (1.24, 1.38)	1.59 (1.45, 1.75)	93	53 (24)	0.001	54 (28, 71)
Fatal MI[‡]	25	44835	1501	1.43 (1.31, 1.56)	1.84 (1.59, 2.14)	65	39 (24)	0.025	39 (1, 62)
Ischaemic stroke	23	94761	2611	1.25 (1.18, 1.32)	1.46 (1.32, 1.61)	57	34 (22)	0.049	35 (0, 61)
Haemorrhagic stroke	13	74548	364	1.04 (0.91, 1.19)	1.07 (0.86, 1.32)	0.3	18 (12)	0.125	32 (0, 65)
Unclassified stroke	16	54825	953	1.24 (1.13, 1.34)	1.41 (1.22, 1.63)	21	23 (15)	0.084	35 (0, 64)
Fatal outcomes									
All vascular deaths	37	136912	3430	1.43 (1.35, 1.51)	1.82 (1.66, 2.00)	160	73 (36)	<0.0001	51 (28, 66)
All nonvascular deaths	38	138063	8369	1.29 (1.24, 1.34)	1.55 (1.46, 1.66)	177	86 (37)	<0.0001	57 (38, 70)
Cancer deaths									
Respiratory / intrathorasic cancer deaths	24	61356	666	1.66 (1.50, 1.83)	2.32 (1.96, 2.74)	95	32 (23)	0.094	29 (0, 57)
Breast cancer deaths	8	18276	130	1.46 (1.21, 1.76)	1.88 (1.39, 2.55)	17	6 (7)	0.568	0 (0, 68)
Blood related cancer deaths	14	45806	220	1.34 (1.16, 1.54)	1.57 (1.24, 1.99)	14	11 (13)	0.618	0 (0, 55)
Digestive cancer deaths	25	64508	906	1.23 (1.12, 1.35)	1.44 (1.23, 1.70)	20	39 (24)	0.028	38 (0, 62)
Genitourinary related cancer deaths	17	48646	502	1.26 (1.11, 1.43)	1.45 (1.18, 1.78)	12	23 (16)	0.114	30 (0, 61)
Non-cancer nonvascular deaths									
Respiratory disease deaths	22	73342	915	1.35 (1.24, 1.48)	1.67 (1.44, 1.92)	49	29 (21)	0.126	26 (0, 56)
Digestive system (except liver) disease deaths	13	32943	173	1.36 (1.13, 1.64)	1.72 (1.24, 2.39)	11	17 (12)	0.138	31 (0, 64)
Endocrine, nutritional & metabolic disease deaths	8	24505	180	1.37 (0.99, 1.88)	1.64 (0.97, 2.77)	3.5	18 (7)	0.012	61 (16, 82)
Nervous system disorder deaths	11	37397	280	0.92 (0.74, 1.16)	0.90 (0.64, 1.28)	0.3	19 (10)	0.045	46 (0, 73)
External causes (violence/suicide/trauma)	19	74631	356	1.14 (1.02, 1.27)	1.26 (1.05, 1.52)	6	12 (18)	0.840	0 (0, 49)
Unclassified deaths	9	30455	786	1.32 (1.17, 1.49)	1.57 (1.37, 1.81)	41	9 (8)	0.354	10 (0, 68)

[†] Risk ratios are adjusted only for age, and stratified where appropriate, by sex and trial arm. Studies with fewer than 10 cases of CHD, stroke, and the composite all vascular and all non vascular deaths outcomes or 5 cases of the specific nonvascular outcomes were excluded from the analysis of that outcome. The risk ratios are presented per 1.11 higher $\log_e$ CRP (i.e. 1-SD of observed levels at baseline), corresponding to a 3-fold higher CRP levels.

[‡] Direct comparison of risk ratios for non-fatal MI vs. fatal MI using data from 25 studies that recorded both types of outcomes to avoid confounding by study when making comparisons.

eTable 6. Risk ratios for vascular and nonvascular mortality per 3-fold higher usual CRP levels with progressive adjustment for usual levels of potential confounders.

	Basic adjustment[¶]			Further adjustment[¶]		
	RR (95% CI) usual $\log_e$ CRP levels, usual confounders	Wald χ^2_1	I^2 (95% CI)	RR (95% CI) usual $\log_e$ CRP levels, usual confounders	Wald χ^2_1	I^2 (95% CI)
All vascular deaths	**27 studies, 95583 participants, 1810 events**			**23 studies, 80905 participants, 1544 events**		
Adjusted for age, sex, and study	1.77 (1.59, 1.99)	99	41 (6, 63)	1.71 (1.53, 1.91)	86	33 (0, 60)
plus systolic blood pressure	1.70 (1.52, 1.90)	87	36 (0, 60)	1.64 (1.46, 1.83)	73	30 (0, 58)
plus smoking	1.62 (1.46, 1.80)	84	22 (0, 52)	1.58 (1.41, 1.77)	61	28 (0, 57)
plus history of diabetes	1.56 (1.40, 1.73)	67	23 (0, 52)	1.49 (1.33, 1.67)	49	22 (0, 53)
plus BMI	1.65 (1.47, 1.85)	74	24 (0, 53)	1.59 (1.40, 1.81)	51	30 (0, 58)
plus $\log_e$ triglycerides	1.62 (1.45, 1.81)	73	18 (0, 49)	1.55 (1.38, 1.75)	51	21 (0, 53)
plus total cholesterol	1.65 (1.46, 1.86)	66	30 (0, 56)	1.59 (1.39, 1.81)	45	35 (0, 61)
plus non-HDL cholesterol[§]	-	-	-	1.55 (1.37, 1.76)	49	23 (0, 54)
plus HDL cholesterol[§]	-	-	-	1.56 (1.38, 1.76)	50	23 (0, 54)
plus alcohol[§]	-	-	-	1.55 (1.37, 1.76)	49	23 (0, 54)
Non-vascular deaths	**30 studies, 99863 participants, 5109 events**			**26 studies, 88399 participants, 4599 events**		
Adjusted for age, sex, and study	1.54 (1.42, 1.67)	105	56 (34, 71)	1.55 (1.41, 1.69)	93	58 (34, 73)
plus systolic blood pressure	1.55 (1.43, 1.68)	108	54 (30, 70)	1.56 (1.43, 1.70)	96	56 (32, 72)
plus smoking	1.47 (1.36, 1.59)	93	45 (15, 64)	1.47 (1.35, 1.60)	82	47 (16, 66)
plus history of diabetes	1.45 (1.33, 1.57)	76	50 (24, 67)	1.45 (1.33, 1.59)	67	53 (26, 70)
plus BMI	1.56 (1.42, 1.71)	86	54 (31, 70)	1.57 (1.42, 1.73)	79	55 (30, 71)
plus $\log_e$ triglycerides	1.56 (1.43, 1.71)	91	52 (27, 68)	1.57 (1.43, 1.73)	84	52 (25, 70)
plus total cholesterol	1.54 (1.41, 1.68)	90	50 (24, 67)	1.55 (1.41, 1.71)	83	51 (23, 69)
plus non-HDL cholesterol[§]	-	-	-	1.56 (1.42, 1.72)	85	50 (22, 68)
plus HDL cholesterol[§]	-	-	-	1.55 (1.42, 1.70)	90	46 (15, 66)
plus alcohol[§]	-	-	-	1.54 (1.40, 1.68)	88	45 (12, 65)

[†] Risk ratios are presented per 1.11 higher $\log_e$ CRP (i.e. 1-SD of observed levels at baseline), corresponding to a 3-fold higher CRP levels, progressively adjusted as shown and stratified where appropriate, by sex and trial arm.
[¶] Analyses were restricted to participants with complete information on sex, trial arm, and all confounding variables. Studies with fewer than 10 cases were excluded from the analysis of each outcome.
[§] Non-HDL cholesterol has been substituted for total cholesterol in these adjusted models
I^2 is a measure of consistency across studies: the percentage of variance in estimated log RRs that is attributable to between study variation as opposed to sampling variation. Values of I^2 close to 0 correspond to lack of heterogeneity.

eTable 7. Risk ratios for vascular and non-vascular mortality per 3-fold higher usual CRP levels with adjustment for usual levels of conventional risk factors plus inflammatory markers.

Outcome / adjusted variables[¶]	No. of studies	No. of participants	No. of outcomes	RR (95% CI) usual $\log_e$ CRP levels, usual confounders	Wald χ^2_1	I^2 (95% CI)
All vascular deaths						
Adjusted for age, sex, and study	17	64740	1138	1.65 (1.49, 1.83)	89	4 (0, 53)
plus conventional risk factors	17	64740	1138	1.53 (1.33, 1.75)	36	14 (0, 50)
plus fibrinogen	17	64740	1138	1.34 (1.18, 1.52)	22	0 (0, 51)
Adjusted for age, sex, and study	9	27005	824	1.67 (1.40, 1.99)	33	49 (0, 76)
plus conventional risk factors	9	27005	824	1.57 (1.32, 1.87)	26	32 (0, 69)
plus albumin	9	27005	824	1.46 (1.27, 1.68)	27	13 (0, 55)
Adjusted for age, sex, and study	9	20078	678	1.67 (1.38, 2.01)	29	40 (0, 72)
plus conventional risk factors	9	20078	678	1.52 (1.30, 1.78)	27	6 (0, 67)
plus $\log_e$ leukocyte count	9	20078	678	1.47 (1.24, 1.76)	19	22 (0, 63)
Adjusted for age, sex, and study	5	18054	392	1.48 (1.26, 1.75)	23	0 (0, 79)
plus conventional risk factors	5	18054	392	1.30 (1.08, 1.56)	8	0 (0, 79)
plus $\log_e$ interleukin 6	5	18054	392	1.02 (0.79, 1.32)	0	12 (0, 82)
Non-vascular deaths						
Adjusted for age, sex, and study	18	65311	3472	1.55 (1.39, 1.71)	69	57 (28, 75)
plus conventional risk factors	18	65311	3472	1.52 (1.37, 1.69)	62	44 (3, 68)
plus fibrinogen	18	65311	3472	1.34 (1.20, 1.50)	25	49 (12, 70)
Adjusted for age, sex, and study	10	30972	2579	1.64 (1.42, 1.90)	44	75 (53, 87)
plus conventional risk factors	10	30972	2579	1.53 (1.36, 1.73)	48	51 (0, 76)
plus albumin	10	30972	2579	1.45 (1.29, 1.62)	41	47 (0, 74)
Adjusted for age, sex, and study	9	20078	1819	1.52 (1.27, 1.83)	21	73 (48, 86)
plus conventional risk factors	9	20078	1819	1.45 (1.24, 1.70)	22	52 (0, 77)
plus $\log_e$ leukocyte count	9	20078	1819	1.36 (1.19, 1.56)	20	43 (0, 74)
Adjusted for age, sex, and study	5	18054	1082	1.51 (1.27, 1.81)	21	66 (12, 87)
plus conventional risk factors	5	18054	1082	1.49 (1.31, 1.70)	37	50 (0, 82)
plus $\log_e$ interleukin 6	5	18054	1082	1.16 (1.03, 1.30)	6	0 (0, 79)

[†] Risk ratios are presented per 1.11 higher $\log_e$ CRP (i.e. 1-SD of observed levels at baseline), corresponding to a 3-fold higher CRP levels, progressively adjusted as shown and stratified where appropriate, by sex and trial arm.

[¶] The conventional risk factors included age, sex, systolic blood pressure, smoking, history of diabetes, BMI, $\log_e$ triglycerides, non-HDL cholesterol, HDL cholesterol, and alcohol consumption. Analyses were restricted to participants with complete information on sex, trial arm, and all the conventional risk factors plus each inflammatory marker in turn. Studies with fewer than 10 cases were excluded from the analysis of each outcome.

I^2 is a measure of consistency across studies: the percentage of variance in estimated log RRs that is attributable to between study variation as opposed to sampling variation. Values of I^2 close to 0 correspond to lack of heterogeneity.

eTable 8. Risk ratios for major vascular and nonvascular outcomes per 3-fold higher baseline CRP levels with progressive adjustment for baseline levels of potential confounders.

	Basic adjustment[¶]			Further adjustment[¶]		
	RR (95% CI) baseline $\log_e$ CRP levels, baseline confounders	Wald χ^2_1	I^2 (95% CI)	RR (95% CI) baseline $\log_e$ CRP levels, baseline confounders	Wald χ^2_1	I^2 (95% CI)
Coronary heart disease	**37 studies, 109742 participants, 8056 events**			**31 studies, 91990 participants, 5373 events**		
Adjusted for age, sex, and study	1.34 (1.30, 1.39)	258	38 (7, 58)	1.34 (1.28, 1.40)	168	45 (16, 64)
plus systolic blood pressure	1.32 (1.27, 1.36)	229	35 (3, 56)	1.31 (1.25, 1.37)	148	42 (11, 62)
plus smoking[‡]	1.28 (1.24, 1.32)	214	24 (0, 50)	1.27 (1.22, 1.32)	138	32 (0, 56)
plus history of diabetes	1.26 (1.22, 1.31)	164	34 (1, 56)	1.25 (1.20, 1.31)	103	41 (10, 62)
plus BMI	1.25 (1.21, 1.29)	171	21 (0, 47)	1.24 (1.19, 1.29)	105	31 (0, 56)
plus $\log_e$ triglycerides	1.23 (1.19, 1.28)	138	25 (0, 50)	1.23 (1.17, 1.28)	86	34 (0, 57)
plus total cholesterol	1.24 (1.20, 1.28)	150	21 (0, 48)	1.23 (1.18, 1.29)	92	31 (0, 56)
plus non-HDL cholesterol[§]	-	-	-	1.23 (1.18, 1.28)	100	24 (0, 52)
plus HDL cholesterol[§]	-	-	-	1.22 (1.17, 1.27)	92	24 (0, 51)
plus alcohol[§]	-	-	-	1.22 (1.17, 1.27)	84	28 (0, 54)
Ischaemic stroke	**17 studies, 65825 participants, 2006 events**			**15 studies, 60763 participants, 1931 events**		
Adjusted for age, sex, and study	1.24 (1.19, 1.31)	77	0 (0, 51)	1.24 (1.18, 1.31)	74	0 (0, 54)
plus systolic blood pressure	1.21 (1.15, 1.27)	56	0 (0, 51)	1.21 (1.15, 1.27)	54	0 (0, 54)
plus smoking[‡]	1.19 (1.14, 1.25)	48	0 (0, 51)	1.20 (1.14, 1.26)	47	0 (0, 54)
plus history of diabetes	1.17 (1.11, 1.23)	37	0 (0, 51)	1.17 (1.11, 1.23)	36	0 (0, 54)
plus BMI	1.17 (1.11, 1.23)	35	0 (0, 51)	1.17 (1.11, 1.24)	34	0 (0, 54)
plus $\log_e$ triglycerides	1.16 (1.10, 1.23)	31	0 (0, 51)	1.16 (1.10, 1.23)	29	0 (0, 54)
plus total cholesterol	1.17 (1.10, 1.23)	32	0 (0, 51)	1.16 (1.10, 1.23)	30	0 (0, 54)
plus non-HDL cholesterol[§]	-	-	-	1.17 (1.10, 1.23)	30	0 (0, 54)
plus HDL cholesterol[§]	-	-	-	1.16 (1.10, 1.23)	29	0 (0, 54)
plus alcohol[§]	-	-	-	1.16 (1.10, 1.23)	30	0 (0, 54)
All vascular deaths	**27 studies, 95583 participants, 1810 events**			**23 studies, 80905 participants, 1544 events**		
Adjusted for age, sex, and study	1.41 (1.32, 1.51)	96	42 (9, 64)	1.39 (1.30, 1.49)	83	37 (0, 62)
plus systolic blood pressure	1.39 (1.30, 1.49)	89	40 (4, 62)	1.37 (1.27, 1.47)	75	35 (0, 61)
plus smoking[‡]	1.35 (1.27, 1.44)	84	32 (0, 57)	1.33 (1.24, 1.43)	66	30 (0, 58)
plus history of diabetes	1.34 (1.25, 1.43)	69	37 (0, 61)	1.32 (1.22, 1.41)	54	37 (0, 62)
plus BMI	1.34 (1.26, 1.44)	79	30 (0, 56)	1.32 (1.23, 1.42)	60	32 (0, 59)
plus $\log_e$ triglycerides	1.35 (1.26, 1.44)	75	33 (0, 58)	1.33 (1.23, 1.43)	56	35 (0, 61)
plus total cholesterol	1.34 (1.26, 1.44)	73	33 (0, 58)	1.32 (1.23, 1.43)	54	36 (0, 61)
plus non-HDL cholesterol[§]	-	-	-	1.33 (1.23, 1.43)	54	37 (0, 62)
plus HDL cholesterol[§]	-	-	-	1.32 (1.23, 1.43)	54	35 (0, 61)
plus alcohol[§]	-	-	-	1.32 (1.23, 1.43)	54	36 (0, 61)
Non-vascular deaths	**30 studies, 99863 participants, 5109 events**			**26 studies, 88399 participants, 4599 events**		
Adjusted for age, sex, and study	1.29 (1.22, 1.35)	97	57 (36, 72)	1.29 (1.22, 1.36)	85	60 (38, 74)
plus systolic blood pressure	1.29 (1.22, 1.35)	98	57 (35, 71)	1.29 (1.22, 1.36)	84	60 (38, 74)
plus smoking[‡]	1.25 (1.19, 1.31)	91	48 (21, 66)	1.25 (1.19, 1.32)	78	52 (24, 69)
plus history of diabetes	1.24 (1.19, 1.30)	81	51 (25, 68)	1.25 (1.18, 1.31)	69	54 (28, 71)
plus BMI	1.27 (1.21, 1.34)	87	55 (32, 70)	1.28 (1.21, 1.35)	79	57 (33, 72)
plus $\log_e$ triglycerides	1.27 (1.21, 1.34)	92	52 (27, 68)	1.28 (1.21, 1.35)	83	53 (27, 70)
plus total cholesterol	1.26 (1.20, 1.32)	90	50 (23, 67)	1.27 (1.20, 1.33)	79	52 (25, 69)
plus non-HDL cholesterol[§]	-	-	-	1.27 (1.21, 1.34)	81	52 (25, 70)
plus HDL cholesterol[§]	-	-	-	1.27 (1.21, 1.33)	86	48 (18, 67)
plus alcohol[§]	-	-	-	1.27 (1.20, 1.33)	87	47 (17, 67)

[†] Risk ratios are presented per 1.11 higher $\log_e$ CRP (i.e. 1-SD of observed levels at baseline), corresponding to a 3-fold higher CRP levels, progressively adjusted as shown and stratified where appropriate, by sex and trial arm.

[¶] Analyses were restricted to participants with complete information on sex, trial arm, and all confounding variables. Studies with fewer than 10 cases were excluded from the analysis of each outcome.

[§] Non-HDL cholesterol has been substituted for total cholesterol in these adjusted models

I^2 is a measure of consistency across studies: the percentage of variance in estimated log RRs that is attributable to between study variation as opposed to sampling variation. Values of I^2 close to 0 correspond to lack of heterogeneity.

[‡]Subsidiary analyses were done in the 37,802 participants who had complete data on all the risk factors in this table plus information on pack-years of smoking. In this subset, the RR for CHD, adjusted for the factors listed in the left-hand column above, was 1.14 (1.08-1.20) and it was almost exactly the same when adjustment also included information on pack-years of smoking. The pattern of findings was similar in such subsidiary analyses of other disease endpoints.

eTable 9. Risk ratios for major vascular and nonvascular outcomes per 3-fold higher usual CRP levels with progressive adjustment for usual levels of potential confounders, pooled by fixed effects meta-analysis.

	Basic adjustment[¶]			Further adjustment[¶]		
	RR (95% CI) usual $\log_e$ CRP levels, usual confounders	Wald χ^2_1	I^2 (95% CI)	RR (95% CI) usual $\log_e$ CRP levels, usual confounders	Wald χ^2_1	I^2 (95% CI)
Coronary heart disease	**37 studies, 109742 participants, 8056 events**			**31 studies, 91990 participants, 5373 events**		
Adjusted for age, sex, and study	1.61 (1.54, 1.68)	483	44 (17, 62)	1.61 (1.53, 1.69)	353	51 (26, 68)
plus systolic blood pressure	1.54 (1.47, 1.61)	377	37 (7, 58)	1.54 (1.46, 1.62)	273	42 (12, 62)
plus smoking	1.47 (1.40, 1.53)	276	26 (0, 51)	1.47 (1.39, 1.55)	203	30 (0, 55)
plus history of diabetes	1.42 (1.36, 1.49)	224	38 (7, 58)	1.41 (1.34, 1.49)	156	42 (10, 62)
plus BMI	1.43 (1.36, 1.50)	197	22 (0, 48)	1.43 (1.35, 1.52)	143	31 (0, 56)
plus $\log_e$ triglycerides	1.38 (1.32, 1.46)	159	26 (0, 51)	1.39 (1.31, 1.47)	117	35 (0, 58)
plus total cholesterol	1.39 (1.32, 1.47)	163	24 (0, 50)	1.40 (1.32, 1.48)	121	33 (0, 57)
plus non-HDL cholesterol[§]	-	-	-	1.39 (1.31, 1.47)	115	26 (0, 53)
plus HDL cholesterol[§]	-	-	-	1.37 (1.29, 1.46)	108	25 (0, 52)
plus alcohol[§]	-	-	-	1.36 (1.29, 1.45)	103	26 (0, 53)
Ischaemic stroke	**17 studies, 65825 participants, 2006 events**			**15 studies, 60763 participants, 1931 events**		
Adjusted for age, sex, and study	1.43 (1.32, 1.55)	80	0 (0, 51)	1.43 (1.32, 1.55)	76	7 (0, 57)
plus systolic blood pressure	1.34 (1.23, 1.45)	50	0 (0, 51)	1.33 (1.23, 1.45)	46	0 (0, 54)
plus smoking	1.31 (1.20, 1.42)	40	0 (0, 51)	1.31 (1.20, 1.42)	38	0 (0, 54)
plus history of diabetes	1.25 (1.14, 1.35)	26	0 (0, 51)	1.24 (1.14, 1.36)	25	0 (0, 54)
plus BMI	1.29 (1.18, 1.41)	29	0 (0, 51)	1.29 (1.18, 1.42)	28	0 (0, 54)
plus $\log_e$ triglycerides	1.27 (1.16, 1.40)	26	0 (0, 51)	1.27 (1.15, 1.40)	24	0 (0, 54)
plus total cholesterol	1.28 (1.17, 1.41)	27	0 (0, 51)	1.28 (1.16, 1.40)	25	0 (0, 54)
plus non-HDL cholesterol[§]	-	-	-	1.28 (1.16, 1.40)	25	0 (0, 54)
plus HDL cholesterol[§]	-	-	-	1.27 (1.16, 1.40)	25	0 (0, 54)
plus alcohol[§]	-	-	-	1.27 (1.15, 1.40)	24	0 (0, 54)
All vascular deaths	**27 studies, 95583 participants, 1810 events**			**23 studies, 80905 participants, 1544 events**		
Adjusted for age, sex, and study	1.71 (1.58, 1.85)	175	41 (6, 63)	1.66 (1.53, 1.80)	140	33 (0, 60)
plus systolic blood pressure	1.65 (1.52, 1.79)	145	36 (0, 60)	1.60 (1.47, 1.74)	114	30 (0, 58)
plus smoking	1.59 (1.46, 1.73)	118	22 (0, 52)	1.55 (1.42, 1.69)	95	28 (0, 57)
plus history of diabetes	1.52 (1.40, 1.66)	94	23 (0, 52)	1.47 (1.34, 1.61)	71	22 (0, 53)
plus BMI	1.61 (1.47, 1.76)	105	24 (0, 53)	1.57 (1.42, 1.73)	85	38 (0, 63)
plus $\log_e$ triglycerides	1.59 (1.45, 1.74)	97	18 (0, 49)	1.53 (1.39, 1.69)	74	21 (0, 53)
plus total cholesterol	1.60 (1.46, 1.75)	102	30 (0, 56)	1.57 (1.43, 1.73)	85	58 (34, 74)
plus non-HDL cholesterol[§]	-	-	-	1.53 (1.39, 1.69)	73	23 (0, 54)
plus HDL cholesterol[§]	-	-	-	1.56 (1.42, 1.72)	80	60 (37, 75)
plus alcohol[§]	-	-	-	1.56 (1.42, 1.72)	80	64 (44, 77)
Non-vascular deaths	**30 studies, 99863 participants, 5109 events**			**26 studies, 88399 participants, 4599 events**		
Adjusted for age, sex, and study	1.46 (1.39, 1.53)	247	56 (34, 71)	1.45 (1.38, 1.52)	219	58 (34, 73)
plus systolic blood pressure	1.47 (1.40, 1.54)	247	54 (30, 70)	1.46 (1.39, 1.54)	221	56 (32, 72)
plus smoking	1.41 (1.34, 1.48)	187	45 (15, 64)	1.40 (1.33, 1.48)	166	47 (16, 66)
plus history of diabetes	1.38 (1.31, 1.45)	160	50 (24, 67)	1.37 (1.30, 1.44)	142	53 (26, 70)
plus BMI	1.48 (1.40, 1.56)	206	54 (31, 70)	1.47 (1.39, 1.55)	183	55 (30, 71)
plus $\log_e$ triglycerides	1.49 (1.41, 1.57)	209	52 (27, 68)	1.48 (1.40, 1.56)	186	52 (25, 70)
plus total cholesterol	1.47 (1.39, 1.55)	199	50 (24, 67)	1.46 (1.38, 1.54)	177	51 (23, 69)
plus non-HDL cholesterol[§]	-	-	-	1.47 (1.39, 1.55)	181	50 (22, 68)
plus HDL cholesterol[§]	-	-	-	1.47 (1.39, 1.55)	181	46 (15, 66)
plus alcohol[§]	-	-	-	1.46 (1.38, 1.54)	175	45 (12, 65)

[†] Risk ratios are presented per 1.11 higher $\log_e$ CRP (i.e. 1-SD of observed levels at baseline), corresponding to a 3-fold higher CRP levels, progressively adjusted as shown and stratified where appropriate, by sex and trial arm.

[¶] Analyses were restricted to participants with complete information on sex, trial arm, and all confounding variables. Studies with fewer than 10 cases were excluded from the analysis of each outcome.

[§] Non-HDL cholesterol has been substituted for total cholesterol in these adjusted models

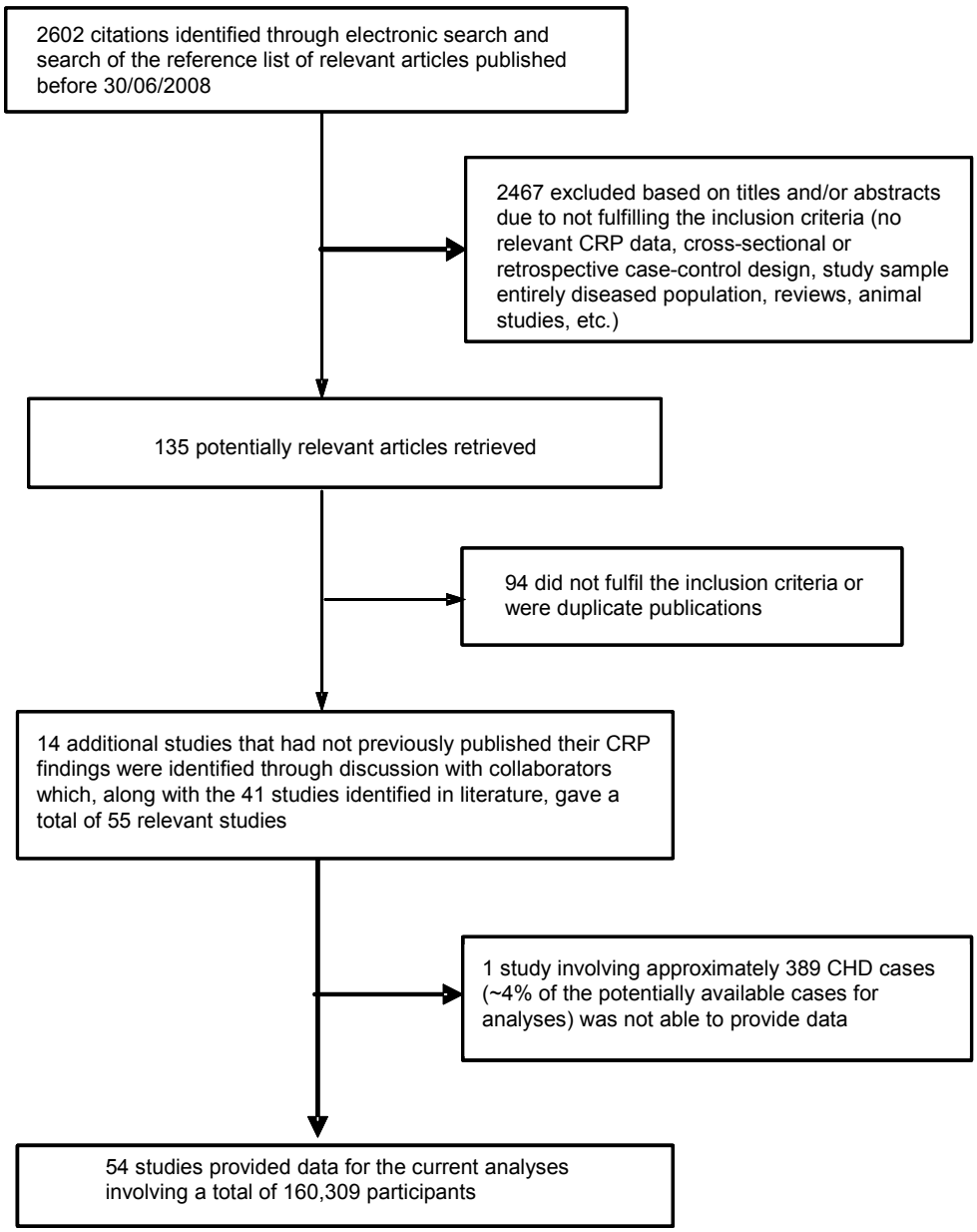
I^2 is a measure of consistency across studies: the percentage of variance in estimated log RRs that is attributable to between study variation as opposed to sampling variation. Values of I^2 close to 0 correspond to lack of heterogeneity.

eTable 10. Risk ratios for vascular and nonvascular mortality without censoring for non-fatal events per 3-fold higher usual CRP levels with progres9sive adjustment for usual levels of potential confounders.

	Basic adjustment[¶]			Further adjustment[¶]		
	RR (95% CI) usual $\log_e$ CRP levels, usual confounders	Wald χ^2_1	I^2 (95% CI)	RR (95% CI) usual $\log_e$ CRP levels, usual confounders	Wald χ^2_1	I^2 (95% CI)
All vascular deaths	**28 studies, 96025 participants, 3196 events**			**23 studies, 81311 participants, 2795 events**		
Adjusted for age, sex, and study	1.79 (1.64, 1.95)	173	39 (4, 61)	1.76 (1.60, 1.93)	134	43 (7, 65)
plus systolic blood pressure	1.70 (1.56, 1.85)	153	33 (0, 58)	1.67 (1.52, 1.83)	120	36 (0, 61)
plus smoking	1.62 (1.50, 1.74)	165	14 (0, 46)	1.60 (1.47, 1.74)	117	24 (0, 54)
plus history of diabetes	1.56 (1.44, 1.69)	114	24 (0, 52)	1.52 (1.39, 1.66)	87	26 (0, 55)
plus BMI	1.65 (1.51, 1.80)	132	21 (0, 50)	1.62 (1.47, 1.78)	96	27 (0, 56)
plus $\log_e$ triglycerides	1.59 (1.48, 1.71)	151	6 (0, 37)	1.57 (1.44, 1.71)	104	15 (0, 48)
plus total cholesterol	1.63 (1.50, 1.78)	124	21 (0, 50)	1.61 (1.45, 1.78)	86	31 (0, 58)
plus non-HDL cholesterol[§]	-	-	-	1.57 (1.44, 1.72)	102	16 (0, 49)
plus HDL cholesterol[§]	-	-	-	1.57 (1.44, 1.71)	105	14 (0, 48)
plus alcohol[§]	-	-	-	1.57 (1.44, 1.71)	102	15 (0, 48)
Non-vascular deaths	**31 studies, 100302 participants, 6255 events**			**26 studies, 88802 participants, 5518 events**		
Adjusted for age, sex, and study	1.53 (1.41, 1.65)	111	60 (40, 73)	1.55 (1.42, 1.69)	100	62 (43, 75)
plus systolic blood pressure	1.54 (1.42, 1.66)	110	59 (40, 73)	1.56 (1.43, 1.70)	99	62 (42, 75)
plus smoking	1.45 (1.34, 1.56)	94	51 (25, 67)	1.46 (1.35, 1.59)	83	53 (27, 70)
plus history of diabetes	1.42 (1.32, 1.54)	77	54 (31, 69)	1.44 (1.32, 1.57)	68	57 (34, 72)
plus BMI	1.53 (1.40, 1.67)	88	58 (38, 72)	1.56 (1.42, 1.72)	83	59 (37, 73)
plus $\log_e$ triglycerides	1.54 (1.41, 1.68)	93	57 (36, 71)	1.56 (1.42, 1.72)	89	57 (33, 72)
plus total cholesterol	1.52 (1.40, 1.66)	91	56 (34, 70)	1.55 (1.41, 1.69)	86	56 (31, 71)
plus non-HDL cholesterol[§]	-	-	-	1.55 (1.42, 1.70)	89	55 (30, 71)
plus HDL cholesterol[§]	-	-	-	1.55 (1.41, 1.69)	93	52 (25, 69)
plus alcohol[§]	-	-	-	1.53 (1.40, 1.67)	90	51 (22, 69)

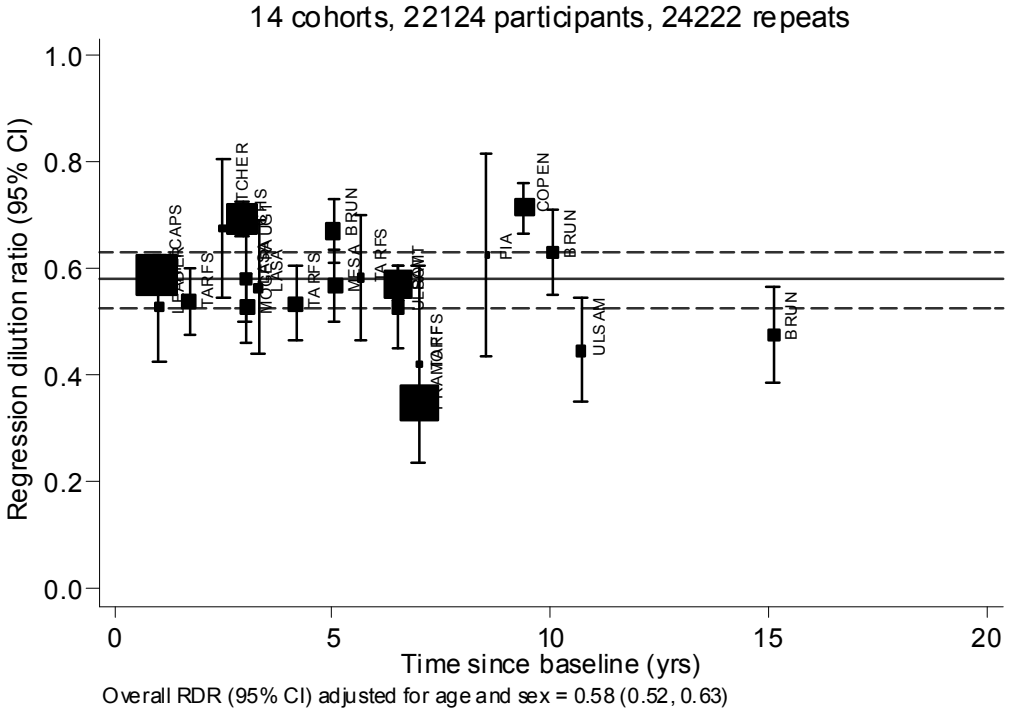
[†] Risk ratios are presented per 1.11 higher $\log_e$ CRP (i.e. 1-SD of observed levels at baseline), corresponding to a 3-fold higher CRP levels, progressively adjusted as shown and stratified where appropriate, by sex and trial arm.
[¶] Analyses were restricted to participants with complete information on sex, trial arm, and all confounding variables. Studies with fewer than 10 cases were excluded from the analysis of each outcome.
[§] Non-HDL cholesterol has been substituted for total cholesterol in these adjusted models
I^2 is a measure of consistency across studies: the percentage of variance in estimated log RRs that is attributable to between study variation as opposed to sampling variation. Values of I^2 close to 0 correspond to lack of heterogeneity.

eFigure 1. Study flow diagram



Studies were identified through electronic search of databases, scanning of the reference list of relevant articles (including previously published reviews) and discussion with investigators. Electronic searches, not limited to the English language, were performed in MEDLINE and EMBASE for studies published between January 1970 and June 2008 using terms related to CRP (e.g. "C-reactive protein", "CRP") and cardiovascular disease outcomes (e.g. "cardiovascular disease", "coronary heart disease", "myocardial infarction", "stroke"). Studies were considered for inclusion if they had baseline information on age, sex, CRP and conventional vascular risk factors; if they did not select participants on the basis of having previous cardiovascular disease; used well-described assay methods; recorded cause-specific mortality and/or vascular morbidity using accepted criteria; and had accrued >1-year of follow-up. The reported findings on CHD from the non-contributing study were broadly similar to those in the current study.

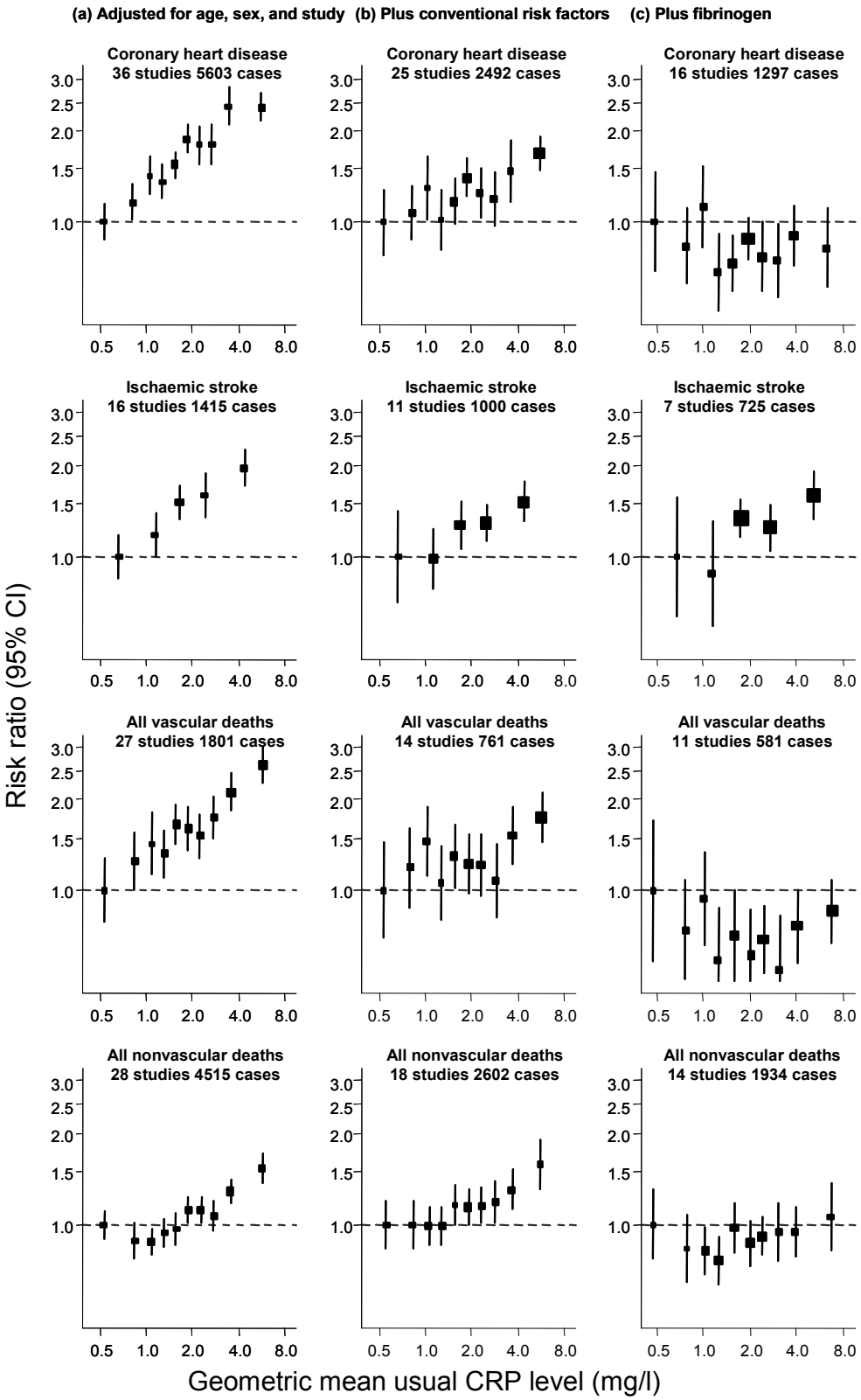
eFigure 2. Regression dilution ratios for log$_e$ CRP concentration plotted against time since baseline measurement by study.



The size of the markers are inversely proportional to the variance of the regression dilution ratio. CI indicates confidence interval.

Comparisons were done to assess the comparability of baseline characteristics of the 22,124 participants who provided repeat CRP measurements with others in the same studies. Compared with individuals who did not provide repeat CRP measurements, participants who did so tended to be younger (p=0.002), less likely to be smokers(p=0.02) or to be diagnosed with diabetes (p=0.002), and had lower systolic blood pressure (p=0.009). These two groups did not, however, differ significantly in relation to sex composition, CRP concentration, body mass index, and concentration of total cholesterol, and HDL-C (p>0.05 for each).

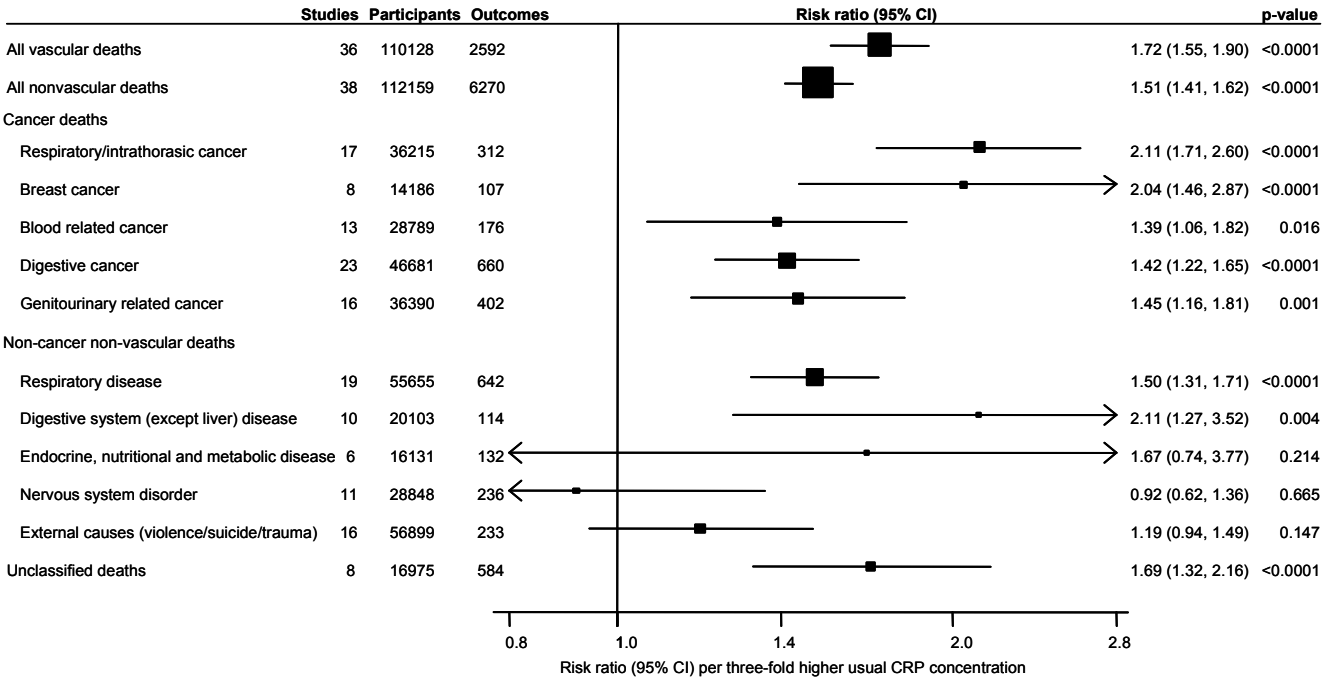
eFigure 3. Risk ratios for major vascular and nonvascular outcomes by quantiles of CRP levels, with different degree of adjustment for potential confounders, after excluding data from first 5 years of follow up.



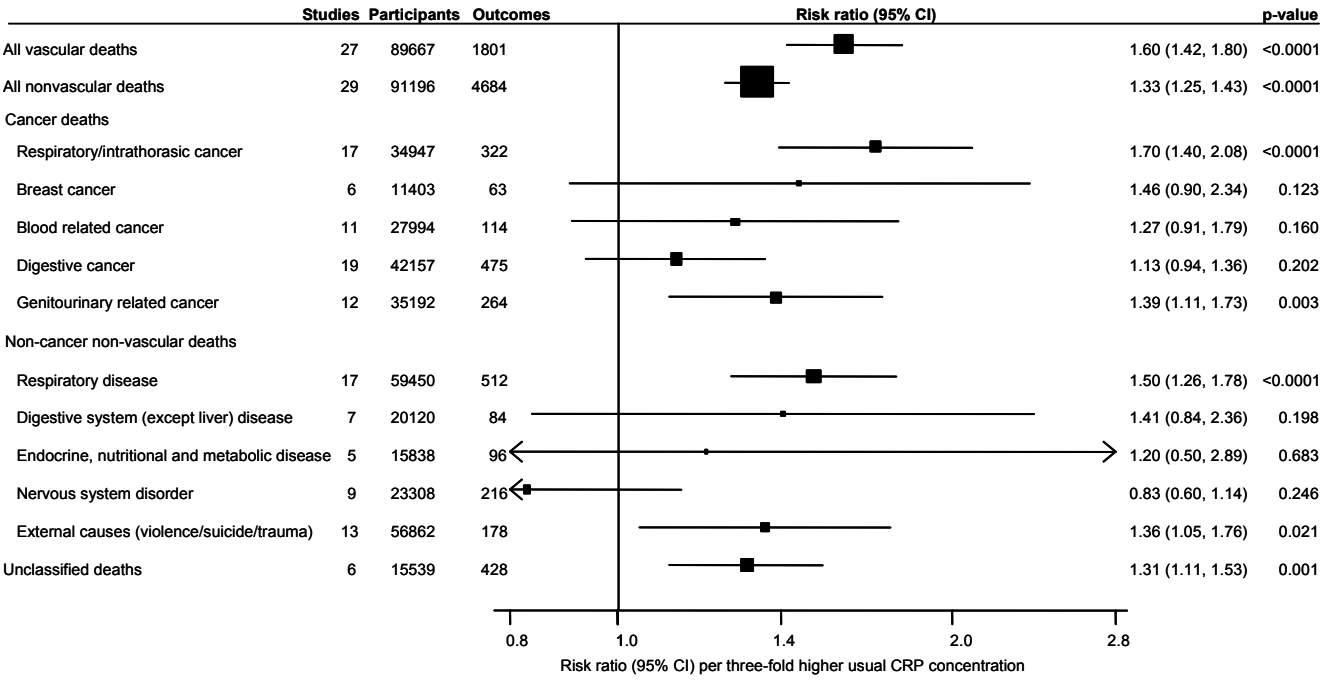
Adjusted study-specific log risk ratios were combined by multivariate random effects meta-analysis. The adjustments included age, sex, and study only in column (a); age, sex, study, systolic blood pressure, smoking, history of diabetes, BMI, $\log_e$ triglycerides, non-HDL cholesterol, HDL cholesterol, and alcohol consumption, in column (b); and the preceding plus fibrinogen in column (c). Studies with fewer than 10 cases of any outcome were excluded from the analysis of that outcome. CI indicates confidence interval, calculated using floating absolute risk technique. The sizes of data markers are proportional to the inverse of the variance of the risk ratios.

eFigure 4. Age- and sex- adjusted only risk ratios for vascular and non-vascular mortality per 3-fold higher usual CRP levels after (a) excluding current smokers and (b) excluding data from first 5 years of follow up.

(a) Excluding current smokers



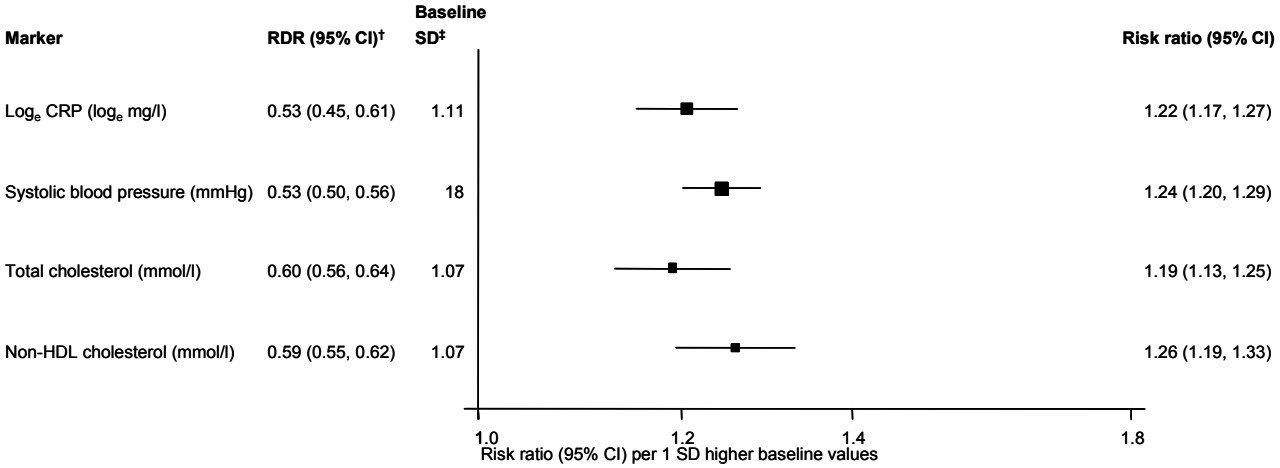
(b) Excluding data from first 5 years of follow up



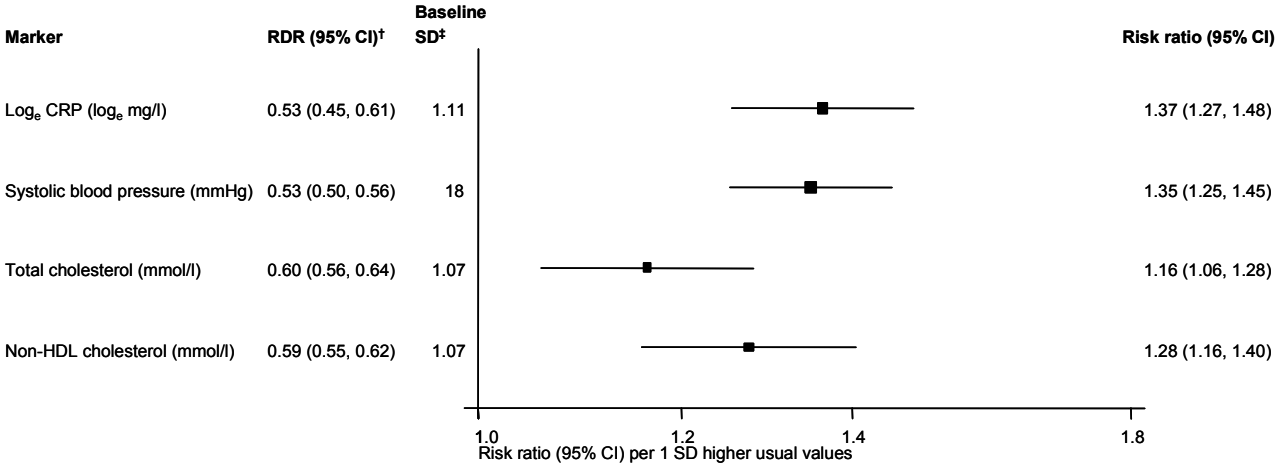
Risk ratios are adjusted only for age, and stratified where appropriate, by sex and trial arm. Studies with fewer than 10 cases of the composite all vascular and all non vascular deaths outcomes or 5 cases of the specific nonvascular outcomes were excluded from the analysis of that outcome. The risk ratios are presented per 1.11 higher $\log_e$ CRP (i.e. 1-SD of observed levels at baseline), corresponding to a 3-fold higher CRP levels. Respiratory diseases included Chronic Obstructive Pulmonary Disease (COPD) and related conditions including ICD10 codes J40 – J47 (Bronchitis, Emphysema, Asthma, Other COPD, etc). CI indicates confidence interval. The sizes of data markers are proportional to the inverse of the variance of the risk ratios.

eFigure 5. Direct comparison of risk ratios for coronary heart disease per 1-SD higher log_e CRP with those of systolic blood pressure and lipids mutually adjusted for each other plus other conventional risk factors.

(a) Baseline levels of risk factors adjusted for baseline levels of confounders



(b) Usual levels of risk factors adjusted for usual levels of confounders

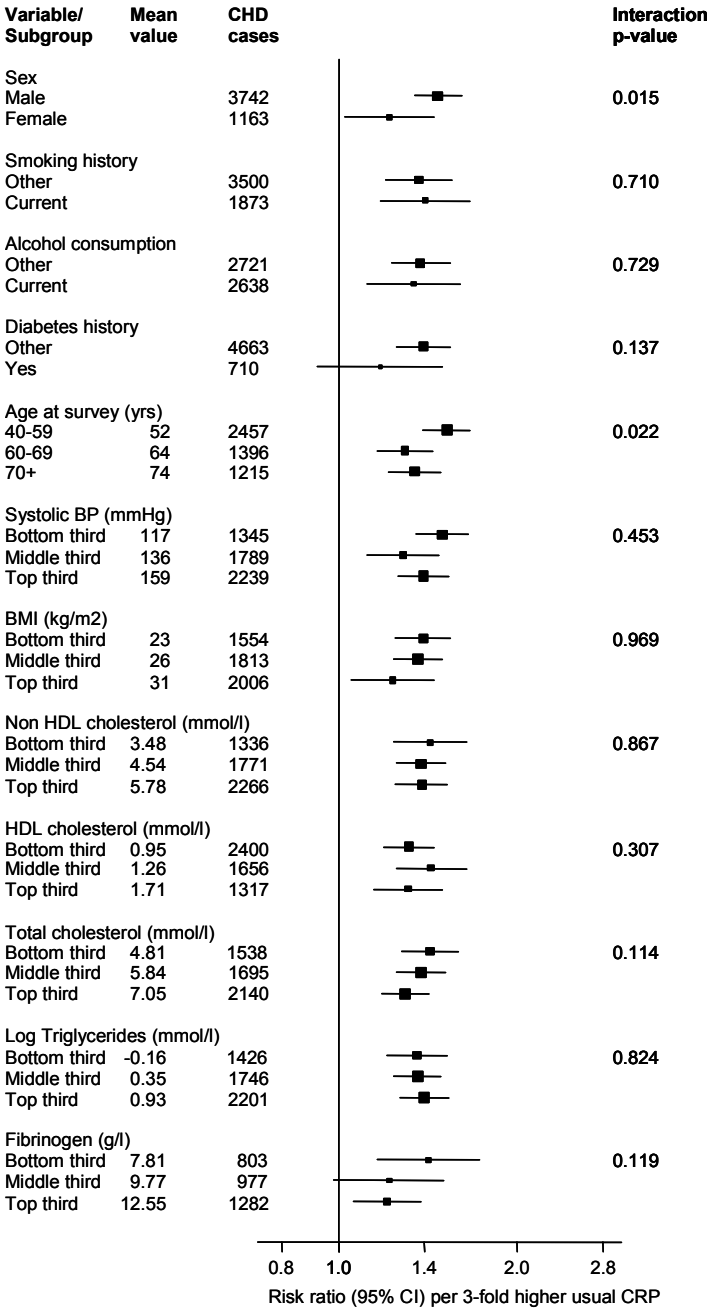


* The direct comparisons used data from 91990 participants (5373 CHD events) from 31 studies with concomitant information on these risk factors plus age, sex, smoking status, history of diabetes, BMI, log_e triglycerides, and alcohol consumption that were adjusted for. The model for non-HDL cholesterol substituted HDL cholesterol in place of total cholesterol in the adjustment.

† The regression dilution ratio (RDR) is an indicator of the long-term within person consistency of the values for each risk marker. RDR values range between 0 and 1, with values closer to 1 indicating high within person consistency of measured values. The RDRs were adjusted for baseline values of the risk factors included in the CHD risk model.

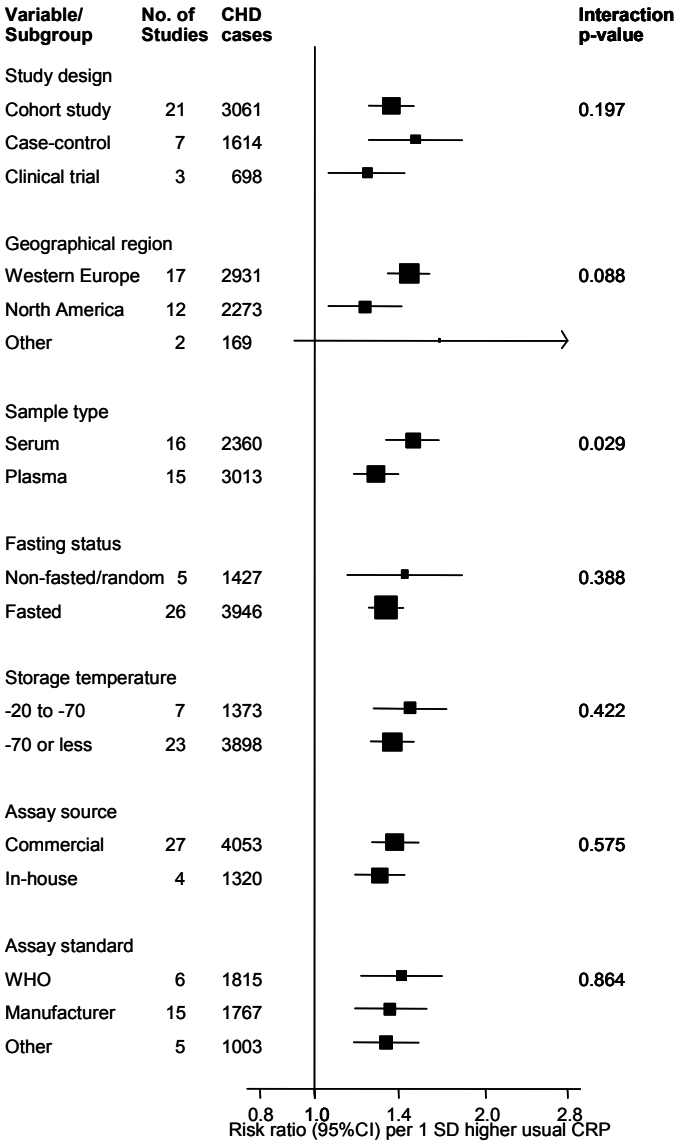
‡ Baseline SD refers to the standard deviation of observed values at baseline. CI indicates confidence interval. The sizes of data markers are proportional to the inverse of the variance of the risk ratios.

eFigure 6. Risk ratios for coronary heart disease per 3-fold higher usual CRP according to several individual level characteristics.



Study-specific risk ratios were adjusted for age, sex, systolic BP, smoking, history of diabetes, BMI, $\log_e$ triglycerides, non-HDL cholesterol, HDL cholesterol, and alcohol consumption, stratified where appropriate, by sex and trial arm. Studies with fewer than 10 cases were excluded from the analysis. CI indicates confidence interval. The sizes of data markers are proportional to the inverse of the variance of the risk ratios.

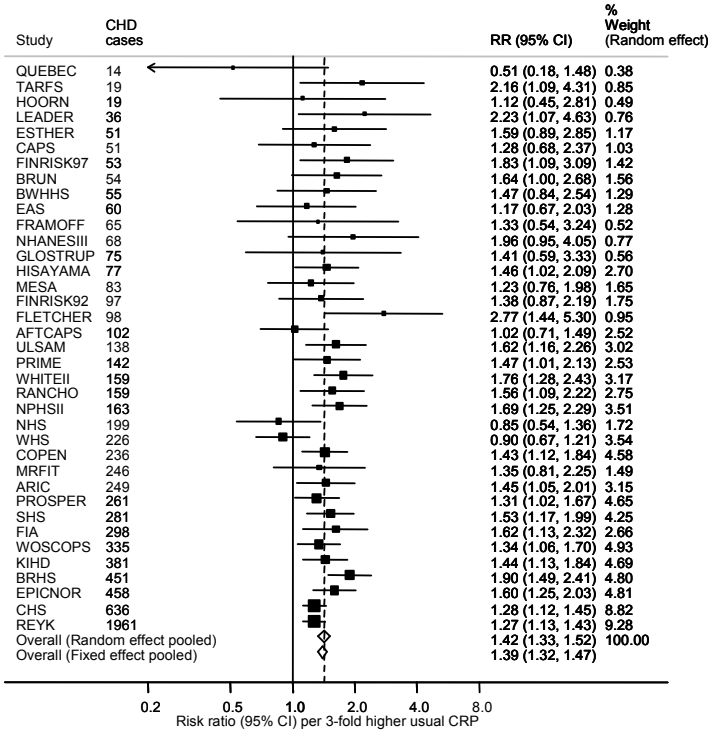
eFigure 7. Risk ratios for coronary heart disease per 3-fold higher usual CRP according to several individual level characteristics.



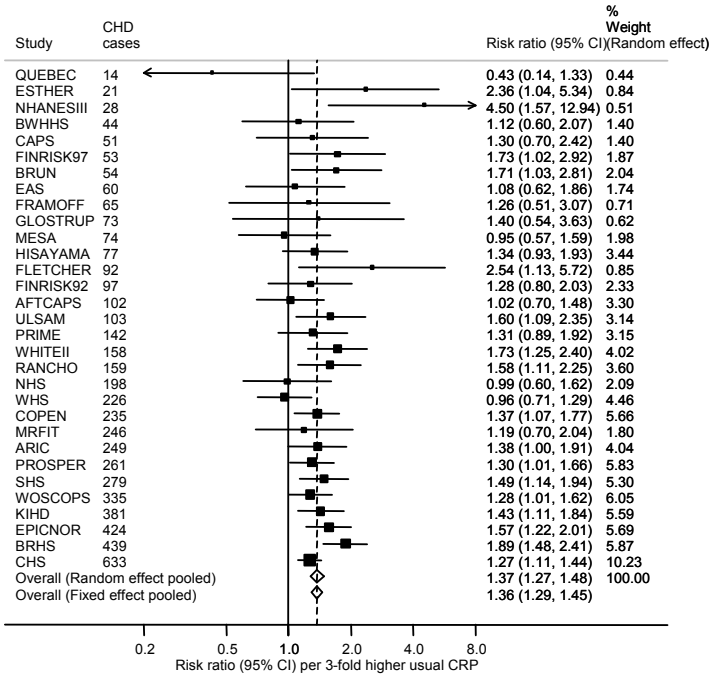
Study-specific risk ratios were adjusted for age, sex, systolic BP, smoking, history of diabetes, BMI, $\log_e$ triglycerides, non-HDL cholesterol, HDL cholesterol, and alcohol consumption, stratified where appropriate, by sex and trial arm. Studies with fewer than 10 cases were excluded from the analysis. CI indicates confidence interval. The sizes of data markers are proportional to the inverse of the variance of the risk ratios.

eFigure 8. Study-specific risk ratios for CHD per 3-fold higher usual CRP levels adjusted for all the factors in the final model in Table 2.

(a) Adjusted for age, sex, systolic blood pressure, smoking, history of diabetes, BMI, $\log_e$ triglycerides, total cholesterol, and stratified where appropriate, by sex and trial arm.

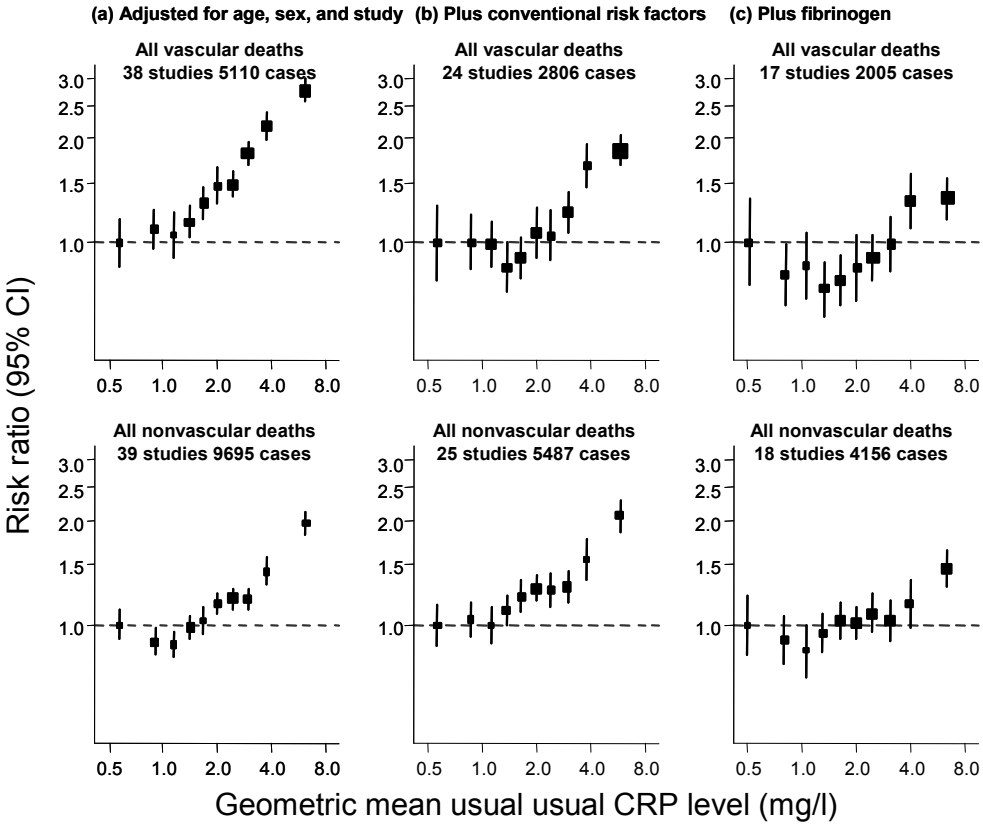


(b) Adjusted for age, sex, systolic blood pressure, smoking, history of diabetes, BMI, $\log_e$ triglycerides, non-HDL cholesterol, HDL cholesterol, alcohol consumption, and stratified where appropriate, by sex and trial arm.



CI indicates confidence interval. The sizes of data markers are proportional to the inverse of the variance of the risk ratios. Test for heterogeneity were: I^2 (95% CI) = 24% (0%, 50%), p=0.096 in (a) and 26% (0%, 53%), p=0.095 n (b), but the small residual heterogeneity was not significantly explained by study size as measured by the number of CHD cases recorded (p>0.27 for meta-regression of log RR on the number of CHD cases).

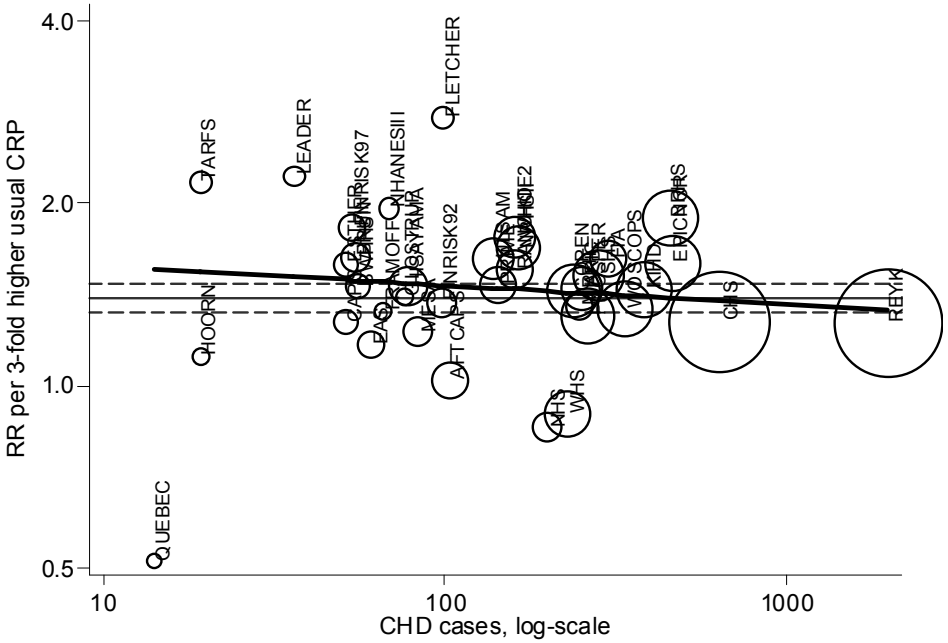
eFigure 9. Risk ratios for vascular and nonvascular mortality without censoring for non-fatal outcomes by quantiles of CRP levels with different degree of adjustment for potential confounders.



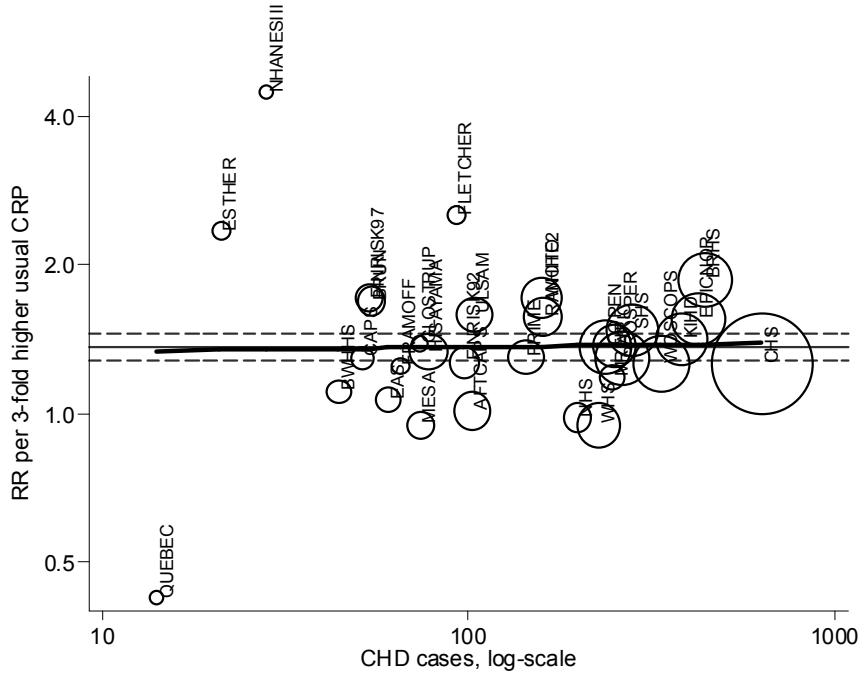
Adjusted study-specific log risk ratios were combined by multivariate random effects meta-analysis. The adjustments included age, sex, and study only in column (a); age, sex, study, systolic blood pressure, smoking, history of diabetes, BMI, $\log_e$ triglycerides, non-HDL cholesterol, HDL cholesterol, and alcohol consumption, in column (b); and the preceding plus fibrinogen in column (c). Studies with fewer than 10 cases of any outcome were excluded from the analysis of that outcome. CI indicates confidence interval, calculated using floating absolute risk technique. The sizes of data markers are proportional to the inverse of the variance of the risk ratios.

eFigure 10. Meta-regression plots assessing potential bias from small study effects in the meta-analysis of association of CRP levels and CHD risk.

(a) Adjusted for age, sex, systolic blood pressure, smoking, history of diabetes, BMI, $\log_e$ triglycerides, total cholesterol, and stratified where appropriate, by sex and trial arm.



(b) Adjusted for age, sex, systolic blood pressure, smoking, history of diabetes, BMI, $\log_e$ triglycerides, non-HDL cholesterol, HDL cholesterol, alcohol consumption, and stratified where appropriate, by sex and trial arm.



The horizontal solid line shows the overall random effect pooled estimate with 95% CI indicated by the dashed lines. The thick solid line corresponds to the meta-regression of log RR on number of CHD cases. The sizes of the markers are inversely proportional to the variance of the log RR in each study. There was no evidence of bias from small-studies (meta-regression p=0.27 in (a) and p=0.80 in (b)).

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