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Supplementary appendix

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Supplement to: IL6R Genetics Consortium and Emerging Risk Factors Collaboration. Interleukin-6 receptor pathways in coronary heart disease: a collaborative meta-analysis of 82 studies. *Lancet* 2012; published online March 14. DOI:10.1016/S0140-6736(11)61931-4.

Interleukin-6 receptor pathways in coronary heart disease: collaborative meta-analysis of 82 studies

Web Appendix

Supplementary Methods, 7 Supplementary Tables, 8 Supplementary Figures and a Supplementary Appendix

Correspondence: Dr Nadeem Sarwar or Dr Adam Butterworth
Department of Public Health and Primary Care
University of Cambridge
Strangeways Research Laboratory
Cambridge, CB1 8RN
UK
Email: erfc@phpc.cam.ac.uk
Tel: +44 1223 741302
Fax: +44 1223 741339

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Supplementary Methods

Associations of IL6R *genotypes with* IL6R *gene expression*

Expression quantitative trait loci (eQTL) analyses were carried out in transcriptomes from 395 healthy blood donors (recruited from one centre) and 363 patients with premature myocardial infarction (recruited from 4 centres) assembled by the Cardiogenics consortium (http://www.cardiogenics.eu). All subjects were of white European continental ancestry. RNA was extracted from monocytes and macrophages isolated from whole blood with CD14 micro beads (AutoMacs Pro, Miltenyi). Genomic DNA was extracted from peripheral blood by standard procedures. Gene expression profiling was performed using Illumina Human Ref-8 arrays (Illumina Inc., San Diego, CA). mRNA was amplified and labelled using the Illumina Total Prep RNA Amplification Kit (Ambion, Inc., Austin, TX). After hybridization, array images were scanned using the 7 Illumina BeadArray Reader and probe intensities were extracted using the Gene expression module of the Illumina's Bead Studio software. Variance Stabilization Transformation (VST) was applied to the raw intensities and quantile normalization was performed in the R statistical environment using the Lumi and beadarray packages. Whole-genome genotyping was carried out using either the Human Custom 1.2M or the Human Quad Custom 670 arrays from Illumina. The associations of 2 *IL6R* SNPs (rs4537545 and rs4129267) with transcript levels of *IL6R* were assessed using additive regression models adjusted for age, gender and centre.

Data on associations of *IL6R* genotypes with *IL6R* mRNA levels in 1,490 healthy individuals from the Gutenberg Heart Study were accessed online. Details of the methods used in this study have been described previously.[24] Briefly, the participants were healthy population subjects aged between 35 and 74 living in Mainz, Germany. Following separation of monocytes and purification of cells, genome-wide expression analysis was conducted using the Illumina HT-12 v3 BeadChip and the Affymetrix Human SNP array 6.0. The associations of 2 *IL6R* SNPs (rs4537545 and rs4129267) with *IL6R* transcript levels were assessed using additive regression models adjusted for age and gender.

To test whether the change in IL-6 levels in response to an inflammatory stimulus is affected by carriage of 358Ala, monocytes from 205 healthy blood donors were stimulated with LPS 0ng/ml, LPS 1ng/ml and LPS 5ng/ml. IL-6 concentration was assessed at baseline and 4 hours post-stimulation. The relationship between IL-6 production and *IL6R* rs4537545 genotype was calculated relative to LPS 0ng/ml using linear regression.

Data on associations with *IL6R* genotypes with *IL6R* mRNA levels were also looked up in in liver cells from 427 European individuals,[27] lymphoblastoid cell lines from multiple European adult populations,[28] T-cell or lymphoblastoid cell lines from umbilical cords of 75 individuals,[26] or lymphoblastoid cell lines from 166 healthy female twins.[25]

Supplementary Table 1: Studies contributing to analyses of *IL6R* genotypes

Study	Genotyping				Conventional risk factors									Inflammation biomarkers				Coronary disease	
Acronym*	SNP assessed			MAF	No. of participants with available information									No. of participants with available information					
	rs4537545	rs4129267	rs2228145		LDL-C	HDL-C	TG	FBG	SBP	BMI	WC	Smoking	Diabetes	s-IL-6R	IL-6	CRP	Fib	No. of cases	No. of controls
ADVANCE	✓			0.43	282	288	288	282	311	310	308	312	312			301		278	312
AGES	✓			0.43	3214	3216	3216	3216	3215	3213	3211	3216	3212			3215		775	2574
BHF-FHS	✓			0.42														2101	2426
BLOODOMICS-1	✓			0.39														1462	1222
BLOODOMICS-2	✓			0.39														1910	1932
CIHD	✓			0.42														5111	6626
COPEN	✓			0.42	8851	9114	9100		9122	9098	9075	9080	9083			8281	8867	1968	7162
COROGENE	✓			0.32								1856	1870						
CUDAS/CUPID	✓			0.40	1001	1001	1001	995	1001	1001	1001	1001	1001		933	968	984	548	1001
DECODE	✓			0.43	1685	11998	11952	6719	10852	27877	6123	21382				6215		7370	27059
DILGOM		✓		0.28	3975	3975	3975	3986	3980	3996	3975	3976	3996		3941	3975		128	3868
EPIC-NL	✓			0.39	2427	2427	2427		2427	2427	2427	1638	2009			2427		1221	1833
FHS-G3	✓			0.41		3531	3532	3532	3532	3528	3517	3531	3526		3494	3515			
FHS-offspring	✓			0.40	2648	2678	2683	2622	2792	2685	2662	2793	2692		2667	2672	2671		
Framingham	✓			0.41														489	7338
FUSION_1	✓			0.31	1560	1587	1587	1594	1619	1620	1613	578	1651					309	2022
FUSION_2			✓	0.39														165	2633
GerMIFS_1	✓			0.39						1531								970	1604
GerMIFS_2	✓			0.39	489	499	499		499	485								1222	1284
GLACIER		✓		0.35	3144	3168	3492	5970	5930	5991	108	5951	5951						
Guangzhou‡			✓	0.34	1904	1905	1905	1905	1899	1905	1905				1235	1871			
HealthABC‡			✓	0.15						1168				577	1116	1172			
HPS	✓			0.39														2703	2884
HUNT		✓		0.37	1222	1318	1319		1308	1284	1290	1325	1325					159	1299
HVHS	✓			0.42	744	1046	813		1070	1069		1070	1070					221	849
INCHIANTI	✓			0.40	1064	1064	1064	1064	1054	1012	1011	1093	967	1068	1067	1058	1058	106	1163
InterHeart-1†‡§	✓																	1137	1215
InterHeart-2†§	✓																	796	895
ISIS†§	✓																	2073	1493
LOLIPOP‡	✓			0.31	5430	5589	5589	5589	5590	5586	5589	5590	5589			4797		2979	3556
LURIC	✓			0.40	647	647	647	647	647	647	641				645	647	646	2493	693
METSIM		✓		0.27	1727	1728	1728	1729	1729	1728	1728	1729	1729			1679		117	1823
MOGERAUG	✓			0.40	1210	1662	478	478	1662	1655	1208	1662	1662		1662	1660	1206	272	1390
MrOS	✓			0.40					2004	2030		2030	2029			1980		587	2195
NHS	✓			0.40						3192	2213	2035	3219		972	988		301	976
ORCADES		✓		0.36	766	766	766	766	760	760	760	766	766			761	761	107	766
PennCATH	✓			0.42														1027	489
PIVUS		✓		0.38	881	883	883	883	882	886	877	885	886		871	880		94	885
PROCARDIS	✓			0.42	2957	2957	2957		2904	2908		2955	2969			2954	2954	2121	2969
PROMIS‡	✓			0.30														4741	4575
ROTT	✓			0.40		378			377	377	329				379	362	257	1317	3730
SARDINIA		✓		0.26	5424	5424	5424	5424	5418	5425	5425	5705	5432		5325	5138	5420	44	5705
SCARF		✓		0.37	383	383	385	381	380	385	383	383			374	378	380	336	386
SHEEP	✓			0.40	2563	2590	2613	2356	2601	2595	2601	2558	2614		1615	1935	2442	1135	1481
ULSAM		✓		0.39	967	970	972	971	971	968	954	972	971		889	941	445	233	942
WGHS	✓			0.41	23178	23178	23178		23041	22880	20558	23268	23286			23178	22262	315	22971
Total				**0.39**	**80343**	**95970**	**94473**	**51109**	**99577**	**122222**	**81492**	**109340**	**89817**	**1645**	**27185**	**83948**	**50353**	**51441**	**136226**

MAF, minor allele frequency; LDL-C, low-density lipoprotein cholesterol; HDL-C high-density lipoprotein cholesterol; TG, triglyceride; FBG, fasting blood glucose; SBP, systolic blood pressure; BMI, body mass index; WC waist circumference; s-IL-6R, soluble interleukin-6 receptor; IL-6, interleukin-6; CRP, C-reactive protein; Fib, fibrinogen.

* Study acronyms are listed in the Supplementary Appendix; † For these studies, data were extracted from publications; ‡ These studies were based in populations not of predominantly white European descent; § Calculated in people without cardiovascular disease.

Data on conventional risk factors or inflammation biomarkers were from people with no known history of cardiovascular disease.

Supplementary Table 2: Study level characteristics of studies contributing to analyses of the *IL6*R genotypes

	Study			Genotyping	Coronary disease		
Acronym*	**Design**	**Location**	**Population source**	**Platform used**	**Coronary disease assessed**	**MI definition†**	**CAD definition**
ADVANCE	Case-control	USA	Healthcare register	Illumina 550K array	MI & CAD	●●	>50% stenosis or Revascularisation§
AGES	Cohort	Iceland	Population register	Illumina 370CNV BeadChip array	MI & CAD	●●●	Revascularisation§
BHF-FHS	Case-control	England	Population register	Affymetrix 500K array	CAD		>50% stenosis or Revascularisation§
BLOODOMICS-1	Case-control	Netherlands	Hospital admissions/blood donors	Illumina IBC 50K array	MI	●●●	
BLOODOMICS-2	Case-control	Germany	Hospital admissions/general population	Illumina IBC 50K array	CAD		>50% stenosis or Revascularisation§
CIHDS	Case-control	Denmark	Hospital admissions/general population	TaqMan	MI & CAD	●●	Stenosis‡
COPEN	Cohort	Denmark	Population register	TaqMan	MI & CAD	●●	
COROGENE		Finland	Hospital admissions				
CUDAS/CUPID	Case-control	Australia	Electoral rolls/Hospital admissions	TaqMan	MI & CAD	●	>50% stenosis
DECODE	Cohort	Iceland	Population register	Illumina 370CNV BeadChip array	MI & CAD	●●●	Revascularisation§
DILGOM	Cohort	Finland	Population register	Illumina 610-Quad array	MI & CAD	●●●	Revascularisation§
EPIC-NL	Nested case-control	Netherlands	Population register	Illumina IBC 50K array	MI	●	
FHS-G3	Cohort	USA	Household listings	Affymetrix 500K array			
FHS-offspring	Cohort	USA	Household listings	Multiplex			
Framingham	Cohort	USA	Population register	Multiplex	MI	●●●	
FUSION_1	Cohort	Finland	Hospital admissions/general population	Illumina HumanHap300 BeadChip	MI	●	
FUSION_2	Cohort	Finland	Hospital admissions/general population	Illumina Cardio-Metabochip			
GerMIFS_1	Case-control	Germany	Cardiac rehabilitation/general population	Affymetrix 500K array	MI	●●●	
GerMIFS_2	Case-control	Germany	Cardiac rehabilitation/general population	Affymetrix 500K array	MI	●●●	
GLACIER	Cohort	Sweden	Population register	OpenArray SNP Genotyping System			
Guangzhou	Cohort	China	Population register	TaqMan			
HealthABC	Cohort	USA	Population register	Sequenom Mass array			
HPS	Clinical trial	UK	Hospital admissions/general population	Illumina 610-Quad array	MI & CAD	●	
HUNT	Cohort	Norway	Population register	Illumina Cardio-Metabochip	MI	●	
HVHS	Case-control	USA	GP lists	Illumina GoldenGate	MI	●●●	
INCHIANTI	Cohort	Italy	Population register	TaqMan	MI	●	
InterHeart-1	Case-control	India	Hospital admissions/general population	Illumina GoldenGate	MI	●●●	
InterHeart-2	Case-control	Europe	Hospital admissions/general population	Illumina GoldenGate	MI	●●●	
ISIS	Case-control	UK	Hospital admissions/general population	TaqMan	MI	●●	
LOLIPOP	Case-control	UK	General population	Illumina IBC 50K array	MI & CAD	●●●	
LURIC	Cross-sectional	Germany	Elective angiography patients	Illumina IBC 50K array	MI & CAD	●●●	>50% stenosis
METSIM	Cohort	Finland	Population register	Illumina Cardio-Metabochip	MI	●	
MOGERAUG	Case-cohort	Germany	Population register	Illumina IBC 50K array	MI	●●●	
MrOS	Cohort	Sweden	Population register	KASPar/TaqMan	MI	●●	
NHS	Nested case-control	USA	Occupational	TaqMan	MI	●●●	
ORCADES	Cohort	Scotland	Population register	Illumina HumanHap300 BeadChip	MI		
PennCATH	Case-control	USA	Hospital admissions	Illumina IBC 50K array	CAD		>50% stenosis
PIVUS	Cohort	Sweden	Population register	Illumina GoldenGate	MI	●●●	
PROCARDIS	Case-control	Europe	Hospital admissions/general population	Illumina IBC 50K array	MI & CAD	●●●	Stenosis‡
PROMIS	Case-control	Pakistan	Hospital admissions	Illumina IBC 50K / 660-Quad arrays	MI	●●●	
ROTT	Cohort	Netherlands	Population register	Illumina 550K array	MI & CAD	●●●	
SARDINIA	Cohort	Italy	Population register	Affymetrix 500K array	MI		
SCARF	Case-control	Sweden	Hospital admissions/general population		MI	●●	
SHEEP	Case-control	Sweden	GP lists, electoral roles	TaqMan	MI	●●●	
ULSAM	Cohort	Sweden	Population register	Illumina GoldenGate	MI	●●	
WGHS	Cohort	USA	Occupational	Illumina Infinium II	MI	●●●	

CAD, angiographically defined coronary stenosis; GP, general practitioner; MI, myocardial infarction.

* Study acronyms are listed in the Supplementary Appendix; † Diagnosis of myocardial infarction was based on: ● patient self report, ●● hospital discharge records, ●●● at least 2 of: clinical features, cardiac markers, and ECG; ‡ Angiographically confirmed coronary stenosis from hospital discharge records. § Coronary revascularisation defined as coronary artery bypass graft or percutaneous transluminal coronary angioplasty.

Supplementary Table 3: Assay methods of studies contributing data to analysis of *IL6R* genotypes and inflammation biomarkers

Study	Soluble-IL-6R				IL-6				CRP				Fibrinogen			
Acronym*	**n**	**Sample source**	**Assay type**	**Manufacturer**	**n**	**Sample source**	**Assay type**	**Manufacturer**	**n**	**Sample source**	**Assay type**	**Manufacturer**	**n**	**Sample source**	**Assay type**	**Manufacturer**
ADVANCE									301	Serum	ITA / ELISA	Denka Seiken				
AGES									3215	Serum	ITA	RochDiag				
COPEN									8281	Plasma	ITA / INA	Dade Behring	8867	Plasma	ITA	BoehrMann
CUDAS/CUPID					933	Serum	ELISA	R&D Systems	968	Serum	ITA	RochDiag	984	Plasma	Clauss	
DECODE									6215							
DILGOM					3941	Serum	CIA	ImmuliteDiag	3975							
EPIC-NL									2427	Plasma	ITA	BeckCoult				
FHS-G3					3494				3515							
FHS-offspring					2667	Serum	ELISA	R&D Systems	2672	Plasma	ELISA	Dade Behring	2671	Plasma	Clauss	DiagStago
Guangzhou					1235				1871		ITA	BioSystems SA				
HealthABC	577	Serum	ELISA	R&D Systems	1116	Serum	ELISA	R&D Systems	1172	Serum	ELISA	Calbiochem				
INCHIANTI	1068	Serum	ELISA	BioSource	1067	Serum	ELISA	BioSourceInt	1058	Serum	INA	Dade Behring	1058	Plasma	Clauss	DiagStago
LOLIPOP									4797	Serum	ITA	RochDiag				
LURIC					645	Plasma	ELISA	R&D Systems	647	Plasma	INA	Dade Behring	646		Clauss	Dade Behring
METSIM									1679	Plasma	ITA	RochDiag				
MOGERAUG					1662	Serum	ELISA	R&D Systems	1660	Plasma	IRMA / INA	Dade Behring	1206	Plasma	INA	Dade Behring
MrOS									1980		Quick	OrionDiag				
NHS					972	Plasma	ELISA	R&D Systems	988	Plasma	ITA	Denka Seiken				
ORCADES									761	Plasma	ELISA		761			
PIVUS					871	Serum	Biochip	RandoxLab	880							
PROCARDIS									2954	Plasma	INA	Dade Behring	2954	Plasma	Clauss	InstrLab
ROTT					379	Plasma	ELISA	R&D Systems	362	Serum	INA	Immage	257	Plasma	PT-based	InstrLab
SARDINIA					5325	Serum	ELISA	R&D Systems	5138	Serum	ELISA	UniVermont	5420			
SCARF					374		ELISA	R&D Systems	378				380	Plasma	TCA	InstrLab
SHEEP					1615	Serum	ELISA	DiacloneRes	1935	Plasma	INA	Dade Behring	2442	Plasma	FPT	In-house
ULSAM					889	Serum	ELISA	R&D Systems	941	Serum	INA	Dade Behring	445		INA	BeckCoult
WGHS									23178	Blood	ITA	Denka Seiken	22262	Plasma	ITA	RochDiag
Total	**1645**				**27185**				**83948**				**50353**			

BeckCoult, Beckman Coulter; BioSourceInt, BioSource International; BoehrMann, Boehringer Mannheim; CIA, chemiluminescence immunoassay; DiacloneRes, Diaclone Research; DiagStago, Diagnostica Stago; ELISA, enzyme-linked immunosorbent assay; FPT, fibrin polymerization time; ImmuliteDiag, Immulite Diagnostic; INA, immunonephelometric assay; InstrLab, Instrumentation Laboratory; IRMA, immunoradiometric assay; ITA, immunoturbidimetry assay; OrionDiag, Orion Diagnostica; PT, prothrombin time; RandoxLab, Randox Laboratories; RochDiag, Roche Diagnostics; TCA, thrombin clotting assay; UniVermont, University of Vermont.

* Study acronyms are listed in the Supplementary Appendix.

Supplementary Table 4: Observational studies from the Emerging Risk Factors Collaboration contributing to correlation analyses of inflammatory biomarkers

Study				IL-6				CRP				Fibrinogen			
Acronym*	Total n	Mean age (SD)	Male (%)	n	Sample source	Assay type	Manufacturer	n	Sample source	Assay type	Manufacturer	n	Sample source	Assay type	Manufacturer
ATTICA	1442	50.50 (11.00)	744 (51.6%)	1442	Serum	ELISA	R&D Systems	1442	Serum	INA	Behring	1180	Plasma	ITA	Dade Behring
BRHS	1199	51.92 (5.38)	1199 (100.0%)	1199	Serum	ELISA	R&D Systems	1199	Serum	MEIA	Abbott				
BRUN	817	57.86 (11.39)	398 (48.7%)					817	Plasma	ITA/INA	Behring	817	Plasma	Clauss	
CAPS	832	57.25 (4.58)	832 (100.0%)					832	Plasma	EIA	Behring	832	Plasma	INA/Clauss	
CHS1	3865	72.33 (5.22)	1479 (38.3%)	3572	Plasma	ELISA	R&D Systems	3865	Plasma	ELISA	In-house	3841	Plasma	Clauss	
CHS2	462	72.31 (5.22)	176 (38.1%)	437	Plasma	ELISA	R&D Systems	462	Plasma	ELISA	In-house	462	Plasma	Clauss	
COPEN	7161	59.58 (13.46)	3070 (42.9%)					7161	Serum	ITA	DAKO	7161	Plasma	ITA	BoehrMann
FIA	1495	54.99 (7.61)	1074 (71.8%)	1495				1495	Plasma	CIA	Immulite				
FINRISK92	446	55.49 (5.94)	235 (52.7%)					446	Serum	CIA	Immulite	446	Plasma	INA	InstrLab
FINRISK97	1156	60.92 (8.52)	1156 (100.0%)					1156	Serum	ELISA	Eucardio Lab	1156	Plasma	Clauss	InstrLab
FLETCHER	620	56.85 (14.43)	478 (77.1%)	572	Plasma	ELISA	R&D Systems	620	Plasma	INA	Behring	618	Plasma	INA	Behring
HPFS	730	63.11 (8.31)	730 (100.0%)	729	Plasma	ELISA	R&D Systems	730	Plasma	ITA	Denka Seiken	730	Plasma	ITA	Kamiya Biomedical
KIHD	1879	52.37 (5.36)	1879 (100.0%)					1879	Serum	CIA	Immulite	1879	Plasma	Clauss	
LEADER	434	67.09 (9.11)	434 (100.0%)					434	Serum	CIA	Immulite	434		Clauss	
MESA	6715	62.15 (10.24)	3170 (47.2%)	6568	Serum	ELISA	R&D Systems	6715	Plasma	INA	Behring	6700	Serum	INA	Dade Behring
MOGERAUG2	1221	58.67 (8.42)	1221 (100.0%)					1221	Serum	IRMA	In-house	1221	Plasma	INA	Behringwerke
MOGERAUG3	3150	54.89 (10.43)	1595 (50.6%)					3150	Serum	IRMA	In-house	3150	Plasma	INA	Dade Behring
MOSWEGOT	675	49.04 (9.51)	334 (49.5%)					675				675	Plasma	Clauss	
NHANES3	2894	60.70 (13.05)	1153 (39.8%)					2894	Serum	INA	Behring	2894	Plasma	Clauss	Organon Teknika
NHS	712	60.33 (6.52)	0 (0.0%)	679	Plasma	ELISA	R&D Systems	712	Plasma	ITA	Denka Seiken	712	Plasma	ITA	Kamiya Biomedical
NSHS	1421	53.93 (14.91)	681 (47.9%)	1421	Plasma	ELISA	R&D Systems	1421	Plasma	INA	Behring				
PRIME	891	55.22 (2.79)	891 (100.0%)					891	Plasma	INA	Behring	891	Plasma	Clauss	DiagStago
QUEBEC	1913	56.29 (6.94)	1913 (100.0%)					1913	Plasma	INA	Behring	1913		Clauss	
ROTT	1816	69.13 (7.99)	614 (33.8%)					1816	Serum	INA	Immage	1816	Plasma	PT-based	InstrLab
SHS	3166	59.73 (7.86)	1148 (36.3%)					3166	Plasma	ELISA	In-house	3166	Plasma	Clauss (m)	DiagStago
SPEED	1565	57.68 (4.37)	1565 (100.0%)					1565	Plasma	EIA	Behring	1565	Plasma	INA / Clauss	
TARFS	481	51.60 (12.28)	241 (50.1%)					481	Serum	INA	Behring	481	Plasma	Clauss (m)	Dade Behring
ULSAM	992	71.42 (1.74)	992 (100.0%)	939	Serum	ELISA	R&D Systems	992	Serum	INA	Behring	435		INA	BeckCoult
WHI-HaBPS	1369	68.42 (6.35)	0 (0.0%)					1369	Plasma	ITA	Denka Seiken	1369	Plasma	Clauss	DiagStago
WHS	27754	54.68 (7.08)	0 (0.0%)					27754	Plasma	ITA	Denka Seiken	27754	Plasma	ITA	Kamiya Biomedical
Total	**79273**	**59.22 (8.84)**	**29402 (37.1%)**	**19053**				**79273**				**74298**			

BeckCoult, Beckman Coulter; BoehrMann, Boehringer Mannheim; CIA, chemiluminescence immunoassay; DiagStago, Diagnostica Stago; ELISA, enzyme-linked immunosorbent assay; INA, immunonephelometric assay; InstrLab, Instrumentation Laboratory; IRMA, immunoradiometric assay; ITA, immunoturbidimetry assay; m, modified Clauss method.
IL-6, interleukin-6; CRP, C-reactive protein.
* Study acronyms are listed in the Supplementary Appendix.
Data on inflammation biomarkers were from people without cardiovascular disease.

Supplementary Table 5: Association of *IL6R* genotype with levels of inflammation markers and risk of coronary heart disease, in analyses restricted to studies based in populations of predominantly white European continental ancestry

	Total no. of participants with available data	Percentage mean difference, or odds ratio, (95% CI) per minor allele	P-value for association
Interleukin-6	24,834	13.5% (9.3 to 17.6%)	1.5×10^{-10}
C-reactive protein	76,108	-7.4% (-9.2 to -5.8%)	6.9×10^{-18}
Fibrinogen	50,353	-1.0% (-1.3 to -0.7%)	4.8×10^{-12}
Coronary heart disease cases vs. controls	42,925 vs. 127,200	0.963 (0.942 to 0.981)	9.9×10^{-5}

Odds ratio is presented for coronary heart disease risk. Percentage mean difference was calculated in reference to the overall mean for each marker among common homozygotes.

Supplementary Table 6: *IL6R* expression in circulating monocytes and macrophages

	rs4129267		rs4537545	
Gene	**Beta**	**P-value**	**Beta**	**P-value**
Monocytes				
MI cases (n=363)	-0.0272	0.26	-0.0247	0.30
Healthy blood donors (n=395)	0.0337	0.19	0.0324	0.20
Macrophages				
MI cases (n=363)	-0.0103	0.45	-0.0088	0.51
Healthy blood donors (n=395)	0.0309	0.13	0.0276	0.17

Data above from participants in the Cardiogenics Consortium (see Appendix for members).

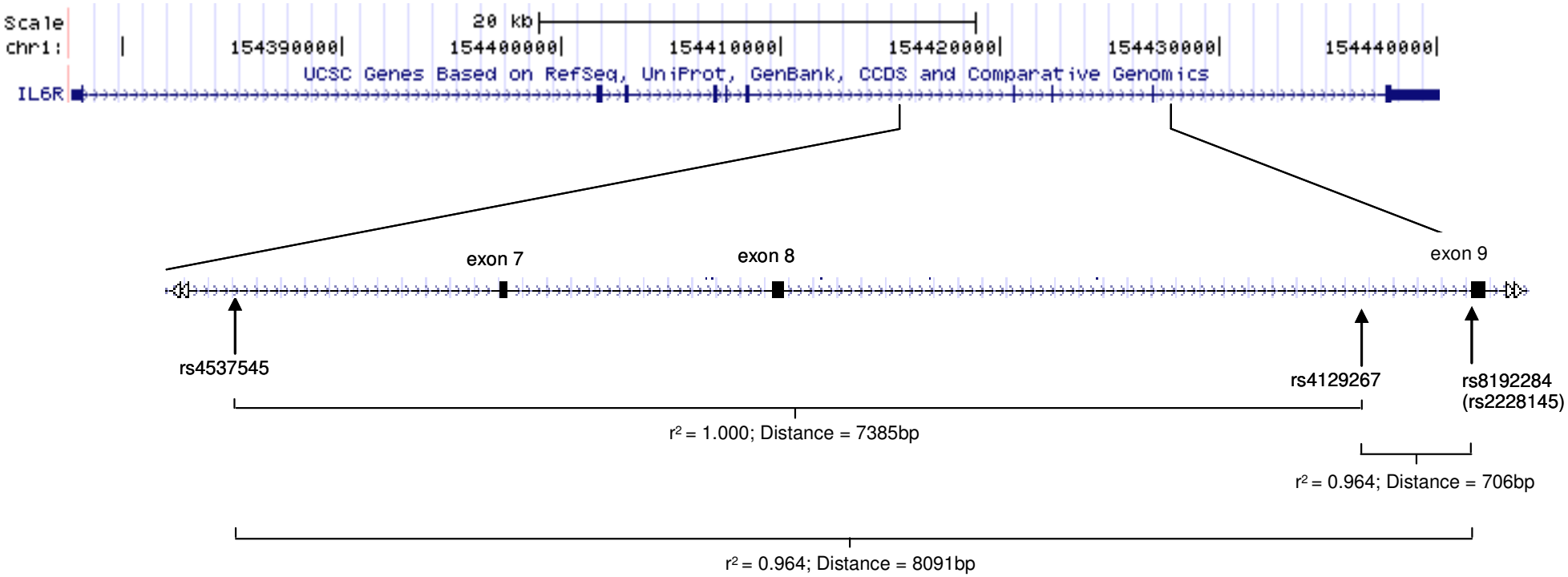
Similarly, no statistically significant associations were seen between either SNP and *IL6R* expression in monocytes from 1,409 healthy individuals from the Gutenberg Heart Study (Genome-wide $P>1x10^{-6}$; threshold for statistical significance=$5.87x10^{-12}$),[24] in liver cells from 427 European individuals,[27] lymphoblastoid cell lines from multiple European populations,[28] T-cell or lymphoblastoid cell lines from umbilical cords of 75 individuals,[26] or lymphoblastoid cell lines from 166 healthy female twins.[25]

Supplementary Table 7: Randomized trials contributing to analyses of tocilizumab (TCZ)

Study	Data source	Patient population	Duration of intervention (weeks)	Intervention (monthly)	No. of participants contributing data								
					Total	Soluble IL-6R	IL-6	CRP	Fibrinogen	HDL-C	LDL-C	Total cholesterol	Triglycerides
AMBITION [S1]	Tabular	RA	24	TCZ 8 mg/kg	286	206	171	254	-	240	224	248	252
				Placebo + MTX†	284	209	138	248	-	239	233	243	246
Ito *et al* [S4]	Published	CrD	12	TCZ 8 mg/kg‡	10	10	10	10	10	-	-	-	-
				TCZ/Placebo 8 mg/kg‡,§	13	-	-	-	-	-	-	-	-
				Placebo‡	13	13	13	13	13	-	-	-	-
LITHE [S5]	Tabular	RA	52	TCZ 8 mg/kg + MTX	398	-	-	285	-	271	265	280	282
				TCZ 4 mg/kg + MTX	399	-	-	247	-	239	236	251	252
				Placebo + MTX	393	-	-	157	-	156	156	157	158
Nishimoto *et al* [S9]	Published	RA	12	TCZ 8 mg/kg	55	-	-	-	55	-	-	-	-
				TCZ 4 mg/kg	54	-	-	-	54	-	-	-	-
				Placebo	53	-	-	-	53	-	-	-	-
OPTION [S11]	Tabular	RA	24	TCZ 8 mg/kg + MTX	205	158	116	167	-	158	155	169	169
				TCZ 4 mg/kg + MTX	213	143	94	151	-	151	151	160	160
				Placebo + MTX	204	119	82	121	-	111	110	122	122
RADIATE [S13]	Tabular	RA	24	TCZ 8 mg/kg + MTX	170	87	65	117	-	113	108	115	117
				TCZ 4 mg/kg + MTX	161	88	65	101	-	100	97	103	105
				Placebo + MTX	158	47	37	61	-	65	64	67	67
SAMURAI [S15]	Published	RA	12	TCZ 8 mg/kg	9	-	9	9	-	-	-	-	-
				DMARDs	10	-	10	10	-	-	-	-	-
SATORI [S17]	Published	RA	24	TCZ 8 mg/kg	53	-	-	53	-	-	-	-	-
				MTX	37	-	-	37	-	-	-	-	-
TOWARD [S21]	Tabular	RA	24	TCZ 8 mg/kg + DMARDs	803	516	413	686	-	645	617	672	682
				Placebo + DMARDs	413	269	194	301	-	285	280	298	302
Total					**4394**	**1865**	**1417**	**3028**	**185**	**2773**	**2696**	**2885**	**2914**

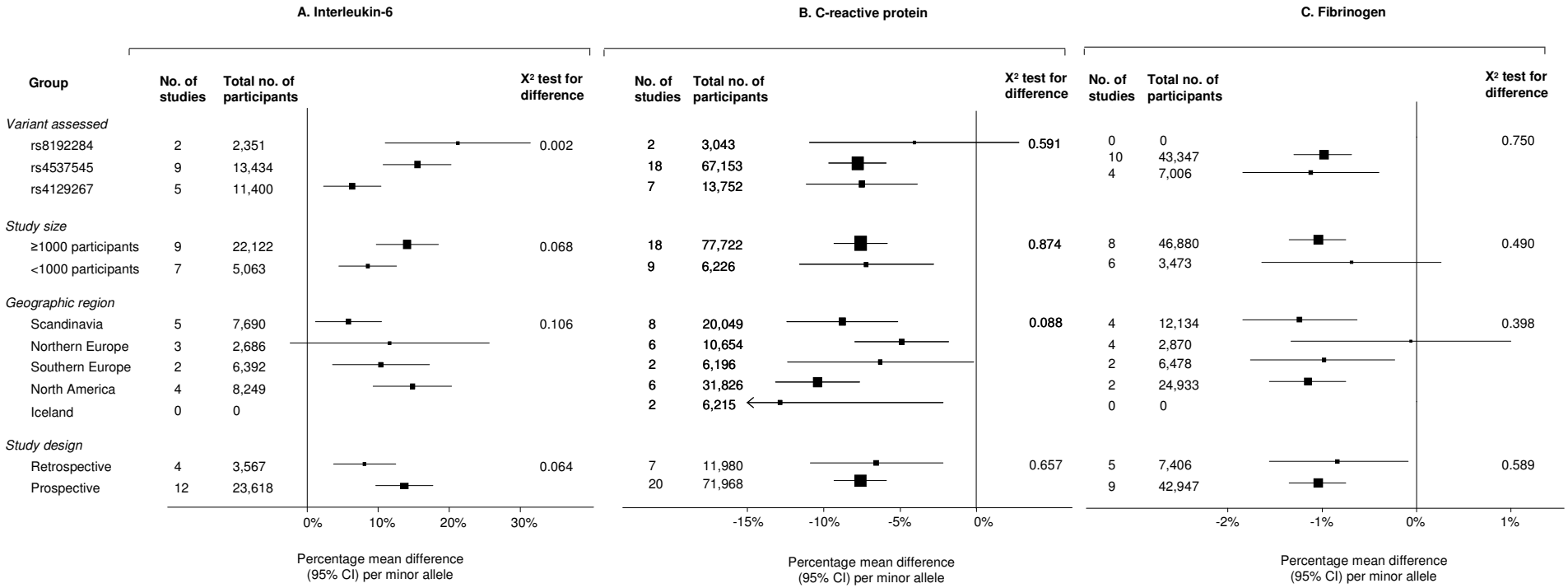
CrD, Crohn's disease; CRP, C-reactive protein; DMARDs, disease-modifying antirheumatic drugs; IL, interleukin; JIA, juvenile idiopathic arthritis; MTX, methotrexate; RA, rheumatoid arthritis.
† Received rescue therapy (TCZ 8mg/kg) on worsening of symptoms at the investigator's discretion; ‡ Intervention was administered biweekly; § Intervention was alternating injections of tocilizumab and placebo; - did not provide sufficient information to be included in analysis.
References for each of the studies listed in this table are provided in the Supplementary Appendix.

Supplementary Figure 1: Genomic location and linkage disequilibrium among the *IL6R* variants assessed



r^2 values are based on the CEU HapMap2 population. rs4537545 represents a C>T exchange; rs8192284 represents Asp358Ala; rs4129267 represents a C>T exchange. rs8192284 has recently been merged into rs2228145. In all genetic analyses, "1/1" is used to denote common homozygotes, "1/2" for heterozygotes and "2/2" for rare homozygotes.

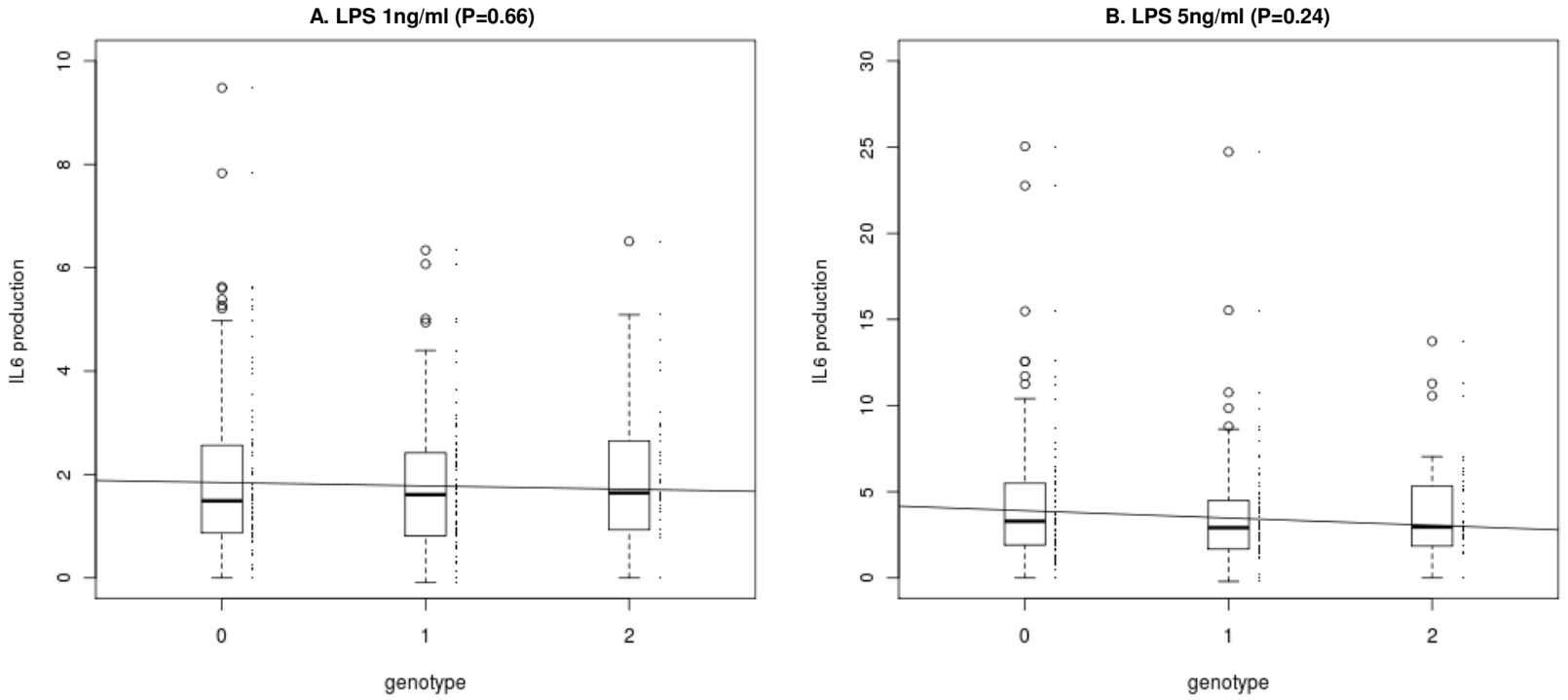
Supplementary Figure 2: Association of *IL6R* genotype with inflammation markers, by study characteristics



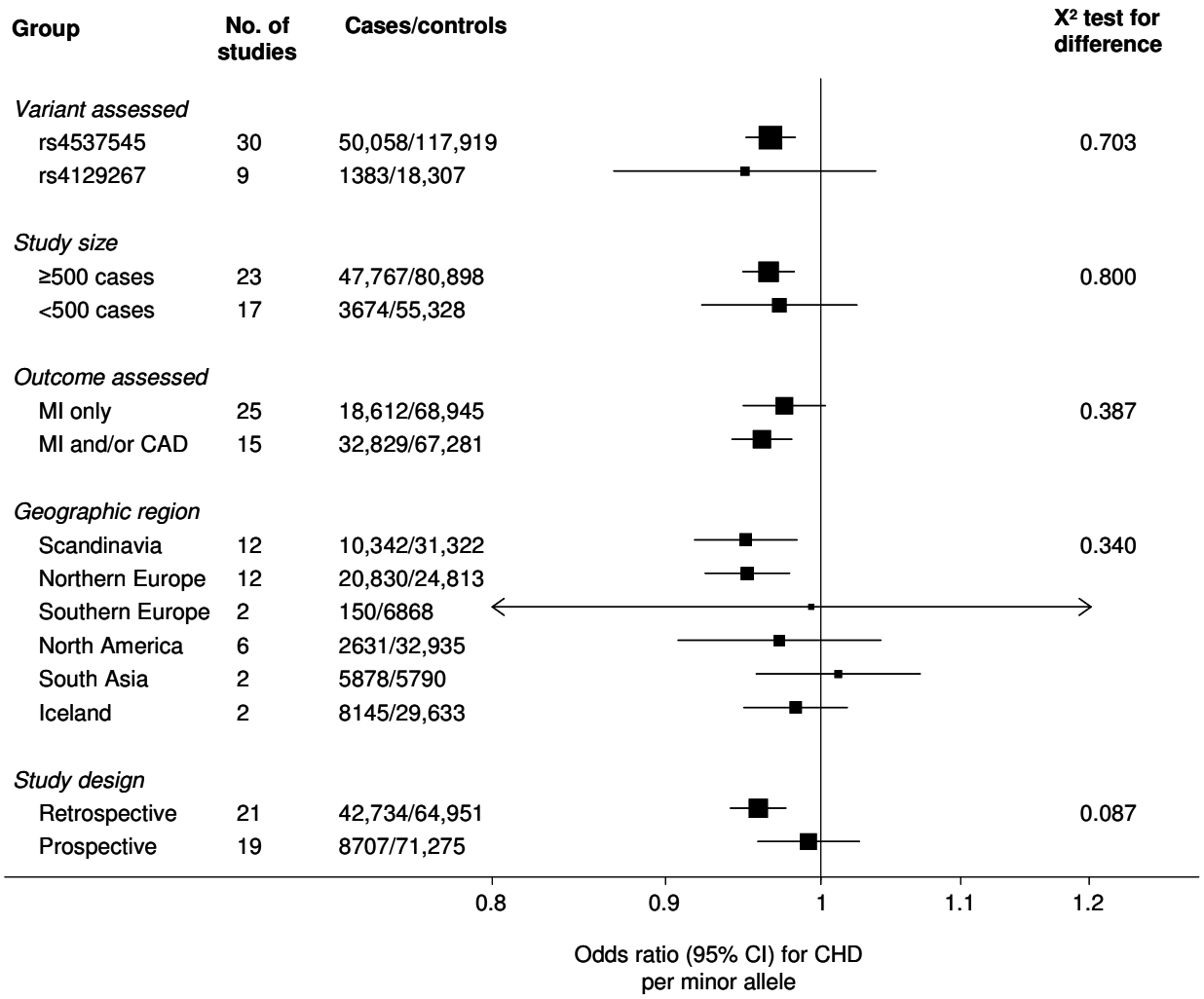
Percentage mean difference was calculated in reference to the overall mean for each markers among common homozygotes

Assessments of overall heterogeneity: A. $\chi^2_{14} = 17.5$ (P = 0.233); $I^2 = 20\%$ (0% to 56%). B. $\chi^2_{24} = 38.8$ (P = 0.03); $I^2 = 38\%$ (0% to 62%). C. $\chi^2_{13} = 15.3$ (P = 0.29); $I^2 = 15\%$ (0% to 53%)
Single outlying studies were excluded for IL-6 (Guangzhou Chinese study: 40% mean difference per minor allele) and CRP (Rotterdam study: -36% mean difference per minor allele).

Supplementary Figure 3: IL-6 production by monocytes following lipopolysaccharide (LPS) stimulation, by *IL6R* rs4537545 genotype

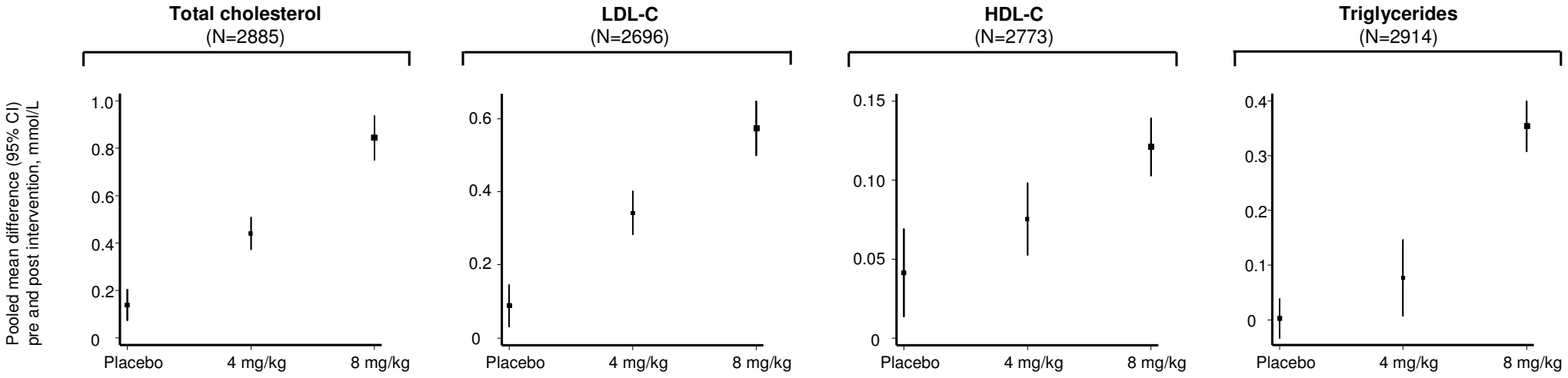


Supplementary Figure 4: Association of *IL6R* genotype with coronary heart disease risk, by study characteristics



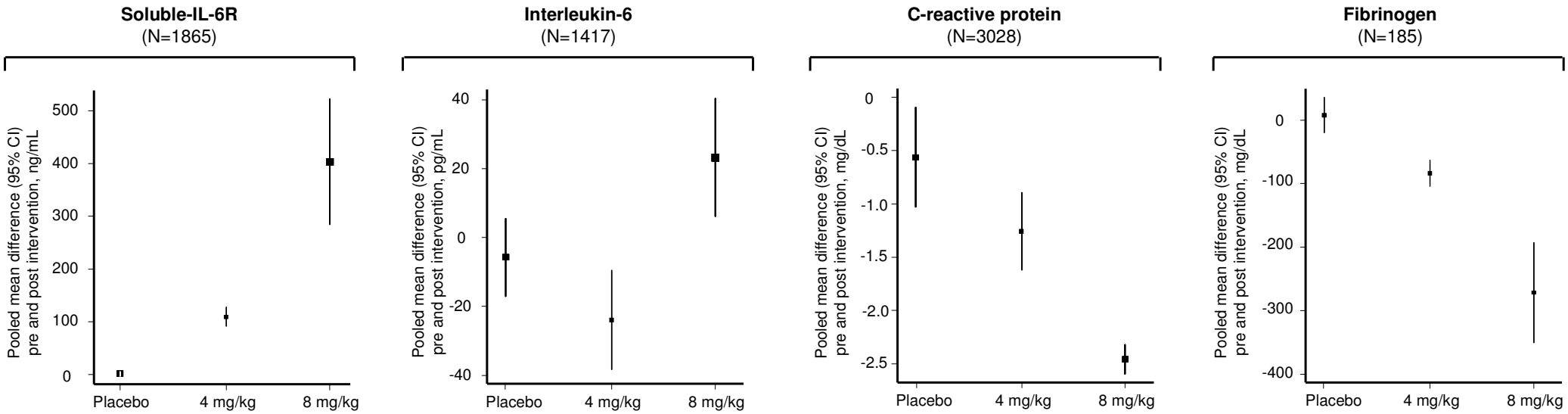
Assessment of overall heterogeneity: X^2_{38} = 44.84 (P=0.21); I^2 = 15% (0% to 43%).
Excludes categories containing only 1 study (geographic region = Australia) and studies that cross multiple categories (eg, studies based across multiple parts of Europe).

Supplementary Figure 5: Tociluzimab intervention in randomized trials and circulating lipid concentrations



Vertical lines represent 95% confidence intervals. Details of trials contributing to these analyses are provided in Supplementary Table 7.

Supplementary Figure 6: Tocilizumab intervention in randomized trials and circulating concentrations of inflammation markers

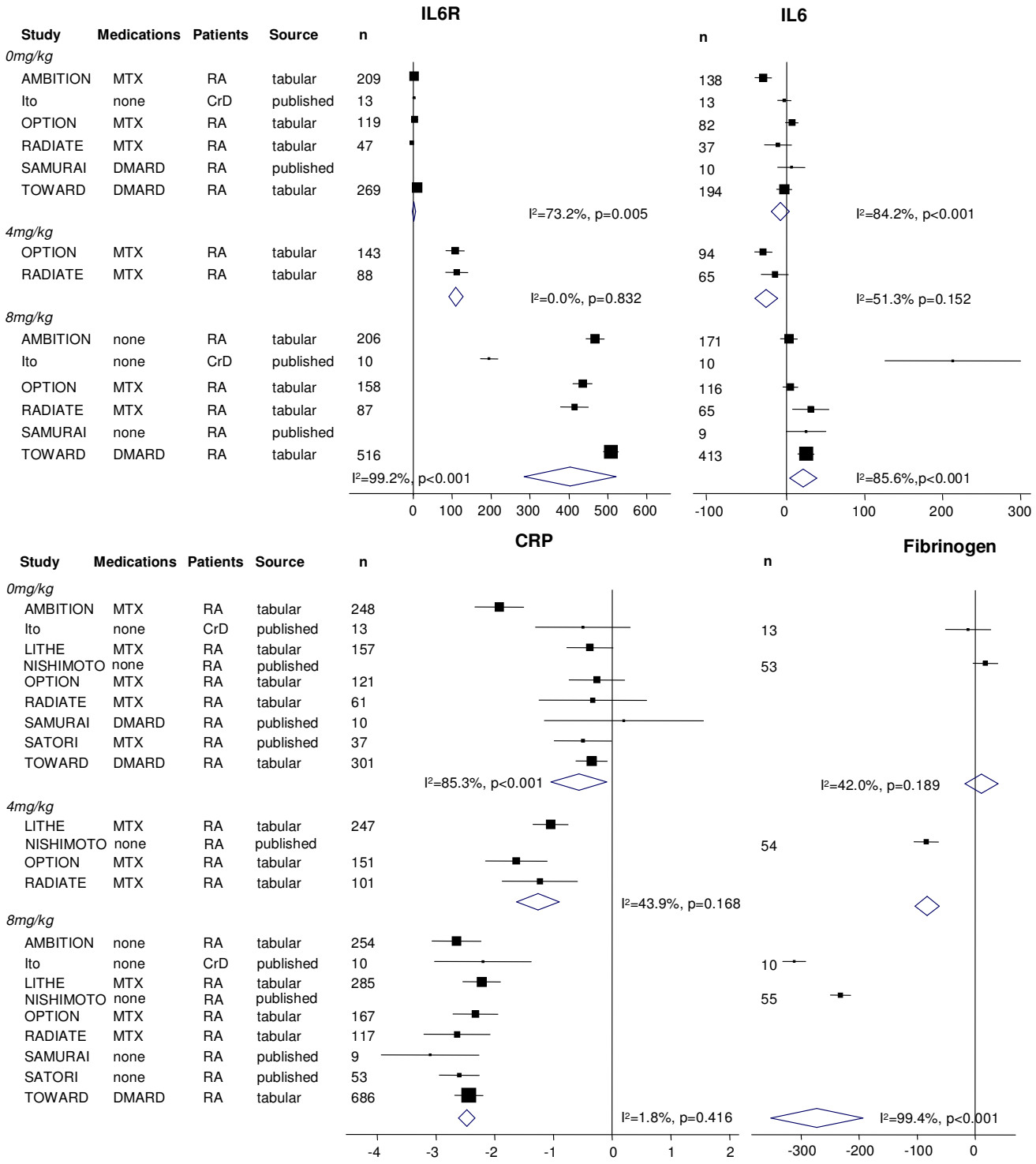


Vertical lines represent 95% confidence intervals. Details of trials contributing to these analyses are provided in Supplementary Table 7.

By comparison, the absolute mean differences (95% CI) seen by *IL6R* genotype displayed in Figure 1 are:

sIL6-R (ng/ml):	*1/2*: +10.4 (+8.9, +11.9)	*2/2*: +22.5 (+18.7, 26.3)
IL6 (ng/L):	*1/2*: +0.16 (+0.09, +0.24)	*2/2*: +0.56 (+0.40, +0.71)
CRP (mg/L):	*1/2*: -0.1 (-0.2, -0.05)	*2/2*: -0.4 (-0.5,-0.3)
Fibrinogen (umol/L):	*1/2*: -0.06 (-0.10, -0.01)	*2/2*: -0.23 (-0.29, -0.16)

Supplementary Figure 7: Heterogeneity in randomized trials of tocilizumab and inflammatory biomarkers



Box sizes are proportional to the number of participants in each trial.

After exclusion of 2 outlying trials - (1) the AMBITION trial, the only trial to use methotrexate in a "methotrexate-naïve" population in its placebo arm, (2) the Ito trial, the only trial set in Crohn's disease patients, pooled mean differences (95% CI) and heterogeneity statistics were:

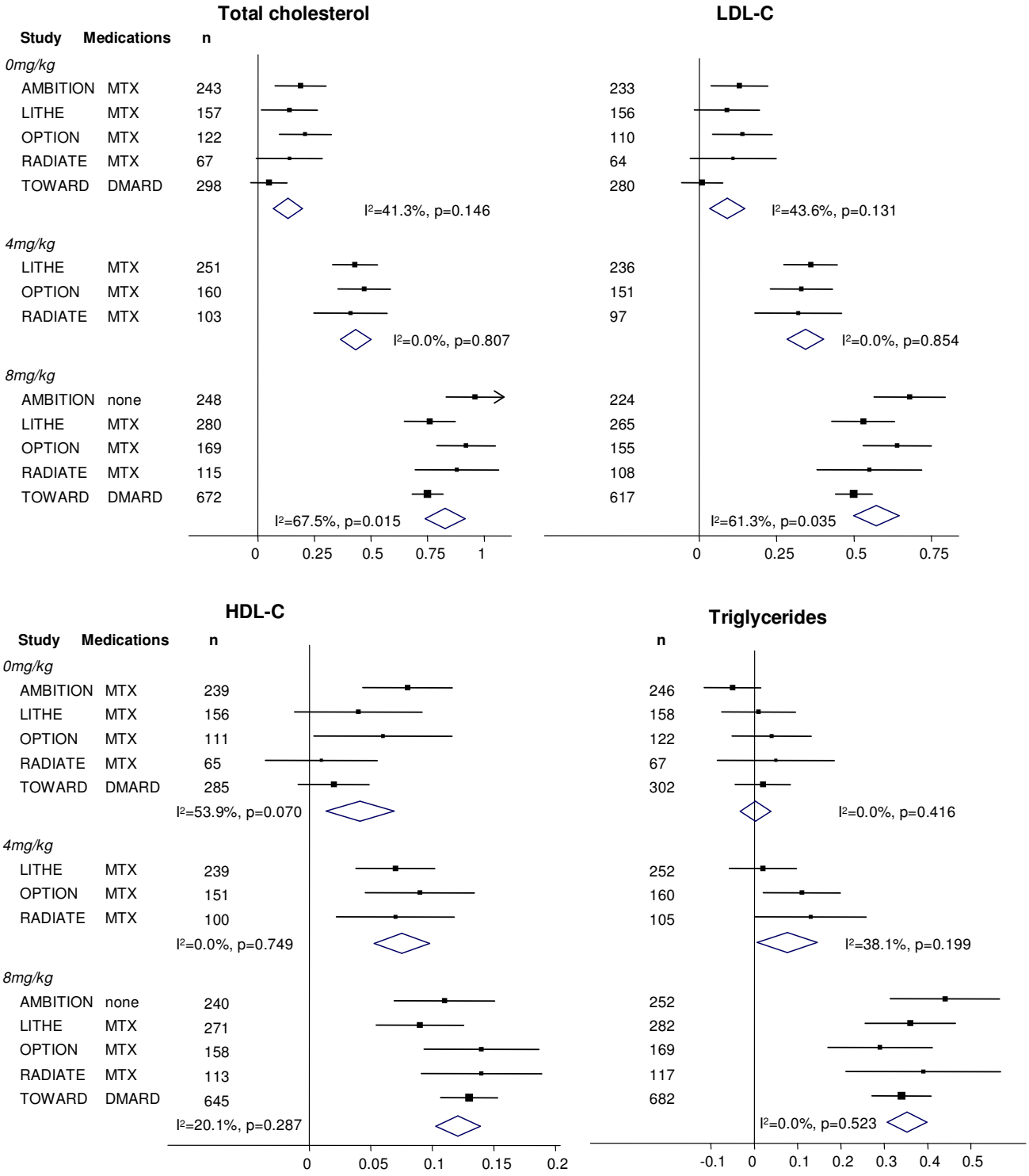
IL-6R: *0mg/kg* 3 (-6,11), I^2=77%,p=0.01. *4mg/kg* 110 (91,128), I^2=0%,p=0.83. *8mg/kg* 453 (394,513), I^2=94%,p<0.001.

IL-6: *0mg/kg* 0.9 (-6.8,8.5), I^2=38%,p=0.18. *4mg/kg* -24.0 (-38.4,-9.6), I^2=51%,p=0.15. *8mg/kg* 19.5 (5.8,33.2), I^2=70%,p=0.02.

CRP: *0mg/kg* -0.35 (-0.53,-0.17), I^2=0%,p=0.95. *4mg/kg* -1.26 (-1.62,-0.90), I^2=44%,p=0.17. *8mg/kg* -2.45 (-2.61,-2.28), I^2=15%,p=0.32.

Fibrinogen: *0mg/kg* 18 (-3,39). *4mg/kg* -84 (-105,-63). *8mg/kg* -232 (-249,-214).

Supplementary Figure 8: Heterogeneity in randomized trials of tocilizumab and lipids



Box sizes are proportional to the number of participants in each trial.

After exclusion of 1 outlying trial - the AMBITION trial, the only trial to use methotrexate in a "methotrexate-naïve" population in its placebo arm, pooled mean differences (95% CI) and heterogeneity statistics were:

Total cholesterol: *0mg/kg* 0.13 (0.05,0.20), I^2=45%,p=0.14. *4mg/kg* 0.44 (0.37,0.51), I^2=0%,p=0.81. *8mg/kg* 0.81 (0.73,0.89), I^2=53%,p=0.10.

LDL-C: *0mg/kg* 0.08 (0.01,0.14), I^2=46%,p=0.14. *4mg/kg* 0.34 (0.28,0.40), I^2=0%,p=0.85. *8mg/kg* 0.54 (0.48,0.61), I^2=38%,p=0.18.

HDL-C: *0mg/kg* 0.03 (0.01,0.05), I^2=0%,p=0.51. *4mg/kg* 0.08 (0.05,0.10), I^2=0%,p=0.749. *8mg/kg* 0.12 (0.10,0.15), I^2=35%,p=0.20.

Triglycerides: *0mg/kg* 0.03 (-0.02,0.07), I^2=0%,p=0.94. *4mg/kg* 0.08 (0.01,0.15), I^2=38%,p=0.20. *8mg/kg* 0.34 (0.29,0.39), I^2=0%,p=0.78.

Supplementary Appendix.

List of acronyms for the genetic studies

Study Acronym	Study Name
ADVANCE	Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified-Release Controlled Evaluation
AGES	AGES Reykjavik Study: The Reykjavik Study of Healthy Aging for the New Millennium
BHF-FHS	British Heart Foundation Family Heart Study
BLOODOMICS-1	Bloodomics Consortium, Dutch Part
BLOODOMICS-2	Bloodomics Consortium, German Part
CIHDS	Copenhagen Ischemic Heart Disease Study
COPEN	Copenhagen City Heart Study
COROGENE	Genetic Predisposition of Coronary Heart Disease in Patients Verified with Coronary Angiogram?
CUDAS / CUPID	Carotid Ultrasound Disease Assessment Study / Carotid Ultrasound in Patients with Ischaemic Heart Disease Study
DECODE	Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe
DILGOM	Dietary, Lifestyle and Genetic Determinants of Obesity and Metabolic Syndrome Study
EPIC-NL	European Prospective Investigation into Cancer and Nutrition, Netherlands Centre
FHS-G3	Framingham Generation Three Cohort
FHS-offspring	Framingham Offspring Cohort
Framingham	Framingham Heart Study
FUSION_1	Finland-United States Investigation of NIDDM Genetics Study 1
FUSION_2	Finland-United States Investigation of NIDDM Genetics Study 2
GerMIFS_1	German MI Family Study 1
GerMIFS_2	German MI Family Study 2
GLACIER	Gene x Lifestyle Interactions And Complex Traits Involved in Elevated Disease Risk Study
Guangzhou	Guangzhou Biobank Cohort Study
HealthABC	Health, Aging, and Body Composition Study
HPS	Heart Protection Study
HUNT	Nord-Trøndelag Health Study
HVHS	Heart and Vascular Health Study
INCHIANTI	Invecchiare in Chianti Study
InterHeart-1	InterHeart Study, Indian Asian Part
InterHeart-2	InterHeart Study, European Part
ISIS	International Study of Infarct Survival
LOLIPOP	London Life Sciences Prospective Population Study
LURIC	Ludwigshafen Risk and Cardiovascular Health Study
METSIM	Metabolic Syndrome In Men Study
MOGERAUG	MONICA/KORA Augsburg
MrOS	Osteoporotic Fractures in Men Study
NHS	Nurses' Health Study
ORCADES	Orkney Complex Disease Study
PennCATH	University of Pennsylvania Catheterization Study
PIVUS	Prospective Investigation of the Vasculature in Uppsala Seniors Study
PROCARDIS	Precocious Coronary Artery Disease Study
PROMIS	Pakistan Risk of Myocardial Infarction Study
ROTT	The Rotterdam Study
SARDINIA	Sardinia Study of Aging
SCARF	Stockholm Coronary Artery Risk Factor Study
SHEEP	Stockholm Heart Epidemiology Program
ULSAM	Uppsala Longitudinal Study of Adult Men
WGHS	Women's Genome Health Study

List of acronyms for the observational studies (ERFC)

Study Acronym	Study Name
ATTICA	ATTICA Study
BRHS	British Regional Heart Study
BRUN	Bruneck Study
CAPS	Caerphilly Study
CHS1	Original cohort of the Cardiovascular Health Study
CHS2	Supplemental African-American cohort of the Cardiovascular Health Study
COPEN	Copenhagen City Heart Study
FIA	First Myocardial Infarction in Northern Sweden
FINRISK92	Finrisk Cohort 1992
FINRISK97	Finrisk Cohort 1997
FLETCHER	Fletcher Challenge Blood Study
HPFS	Health Professionals Follow-Up Study
KIHD	Kuopio Ischaemic Heart Disease Study
LEADER	Lower Extremity Arterial Disease Event Reduction Trial
MESA	Multi-Ethnic Study of Atherosclerosis
MOGERAUG2	MONICA/KORA Augsburg Surveys S2
MOGERAUG3	MONICA/KORA Augsburg Surveys S3
MOSWEGOT	MONICA Göteborg Study
NHANES3	Third National Health and Nutrition Examination Survey
NHS	Nurses' Health Study
NSHS	Nova Scotia Health Survey
PRIME	Prospective Epidemiological Study of Myocardial Infarction
QUEBEC	Québec Cardiovascular Study
ROTT	The Rotterdam Study
SHS	Strong Heart Study
SPEED	Speedwell Study
TARFS	Turkish Adult Risk Factor Study
ULSAM	Uppsala Longitudinal Study of Adult Men
WHI-HaBPS	Women's Health Initiative (Hormones and Biomarkers Predicting Stroke in Women)
WHS	Women's Health Study

Search strategy used to identify published reports on tocilizumab

Published studies were identified through electronic searches using Medline and by scanning reference lists of articles identified for all relevant studies (including review articles). The computer-based searches combined search terms related to tocilizumab without language restriction.

Pubmed strategy:
atlizumab OR tocilizumab OR Actemra OR RoActemra OR (MRA AND ("Interleukin 6" OR "Plasmacytoma Growth Factor" OR "Growth Factor, Plasmacytoma" OR "B-Cell Differentiation Factor-2" OR "B Cell Differentiation Factor 2" OR "B-Cell Stimulatory Factor 2" OR "B-Cell Stimulatory Factor-2" OR "BSF-2" OR "Differentiation Factor, B-Cell" OR "Differentiation Factor, B Cell" OR "Differentiation Factor-2, B-Cell" OR "Differentiation Factor 2, B Cell" OR "Hepatocyte-Stimulating Factor" OR "Hepatocyte Stimulating Factor" OR "Hybridoma Growth Factor" OR "Growth Factor, Hybridoma" OR "IFN-beta 2" OR "IL-6" OR "IL6" OR "MGI-2" OR "Myeloid Differentiation-Inducing Protein" OR "Differentiation-Inducing Protein, Myeloid" OR "Myeloid Differentiation Inducing Protein" OR "B Cell Stimulatory Factor-2" OR "B Cell Stimulatory Factor 2" OR "B-Cell Differentiation Factor" OR "B Cell Differentiation Factor"))

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Search strategy used to identify reports of *IL6R* variant associations

Published studies were identified through electronic searches using Medline and by scanning reference lists of articles identified for all relevant studies (including review articles). The computer-based searches combined search terms related to the interleukin-6 receptor and relevant genetic variants without language restriction.

Pubmed strategy:
genetic[tw] OR genetic research[mh] OR genetics[tw] OR medical genetics[mh:noexp] OR genetics, population[mh] OR genomics[mh:noexp] OR genomic[tw] OR genomics[tw] OR molecular epidemiology[tw] OR molecular epidemiology[mh] OR molecular association[tw] OR genes[mh] OR genes[tw] OR gene[tw] OR allele[tw] OR alleles[tw] OR allelic[tw] OR polymorphism[tw] OR polymorphisms[tw] OR polymorphic[tw] OR SNP[tw] OR mutation[tw] OR mutations[tw] OR mutant[tw] OR mutants[tw] OR homozygote[tw] OR homozygotes[tw] OR homozygotic[tw] OR heterozygote[tw] OR heterozygotes[tw] OR heterozygotic[tw] OR genotype[mh] OR genotype[tw] OR genotypes[tw] OR genotypic[tw] OR genotyped[tw] OR phenotype[mh] OR phenotype[tw] OR phenotypes[tw] OR phenotypic[tw] OR phenotyped[tw] OR haplotype[tw] OR haplotypes[tw] OR haplotypic[tw] OR haplotyped[tw] OR genetic variant*[tw] OR genetic variation[tw] OR variation genetics[mh] OR DNA[mh:noexp] OR DNA[tw] OR locus[tw] OR loci[tw] OR penetrance[tw]

AND

"interleukin 6 receptor"[tiab] OR receptor, interleukin-6[MeSH] OR IL6R[tiab] OR IL6-receptor[tiab] OR "IL-6 receptor"[tiab] OR rs4537545[tiab] OR rs8192284[tiab] OR rs4129267[tiab] or rs2228145[tiab]

Investigators in the Cardiogenics Consortium

Tony Attwood[1], Stephanie Belz[2], Peter Braund[3], Jessy Brocheton[4], François Cambien[4], Jason Cooper[5], Abi Crisp-Hihn[1], Patrick Diemert (formerly Linsel-Nitschke)[2], Panos Deloukas[6], Jeanette Eardman[2], Nicola Foad[1], Tiphaine Godefroy[4], Alison H Goodall[3,11], Jay Gracey[3], Emma Gray[6],, Rhian Gwilliams[6], Susanne Heimerl[7], Christian Hengstenberg[7], Jennifer Jolley[1], Unni Krishnan[3], Heather Lloyd-Jones[1], Ulrika Liljedahl[8], Ingrid Lugauer[7], Per Lundmark[8], Seraya Maouche[2,4], Jasbir S Moore[3] , Gilles Montalescot[4], David Muir[1], Elizabeth Murray[1], Chris P Nelson[3], Jessica Neudert[9], David Niblett[6], Karen O'Leary[1], Willem H Ouwehand[1,6], Helen Pollard[3], Carole Proust[4], Angela Rankin[1], Augusto Rendon[12], Catherine M Rice[6], Hendrik B Sager[2], Nilesh J Samani[3,11], Jennifer Sambrook[1], Gerd Schmitz[10], Michael Scholz[9], Laura Schroeder[2], Heribert Schunkert[2], Jonathan Stephens[1], Ann-Christine Syvannen[8], Stefanie Tennstedt (formerly Gulde)[2], Chris Wallace[5].

[1] Department of Haematology, University of Cambridge, Long Road, Cambridge, CB2 2PT, UK and National Health Service Blood and Transplant, Cambridge Centre, Long Road, Cambridge, CB2 2PT, UK;

[2] Medizinische Klinik 2, Universität zu Lübeck, Lübeck Germany

[3] Department of Cardiovascular Sciences, University of Leicester, Glenfield Hospital, Groby Road, Leicester, LE3 9QP, UK

[4] INSERM UMRS 937, Pierre and Marie Curie University (UPMC, Paris 6) and Medical School, 91 Bd de l'Hôpital 75013, Paris, France

[5] Juvenile Diabetes Research Foundation/Wellcome Trust Diabetes and Inflammation Laboratory, Department of Medical Genetics, Cambridge Institute for Medical Research, University of Cambridge, Wellcome Trust/MRC Building, Cambridge, CB2 0XY, UK

[6] The Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Hinxton, Cambridge CB10 1SA, UK

[7] Klinik und Poliklinik für Innere Medizin II, Universität Regensburg, Germany

[8] Molecular Medicine, Department of Medical Sciences, Uppsala University, Uppsala, Sweden

[9] Trium, Analysis Online GmbH, Hohenlindenerstr. 1, 81677, München, Germany

[10] Institut für Klinische Chemie und Laboratoriumsmedizin, Universität, Regensburg, D-93053 Regensburg, Germany

[11] Leicester NIHR Biomedical Research Unit in Cardiovascular Disease, Glenfield Hospital, Leicester, LE3 9QP, UK

[12] European Bioinformatics Institute, Wellcome Trust Genome Campus, Hinxton, Cambridge, CB10 1SD, UK