THE LANCET Diabetes & Endocrinology

Supplementary appendix

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Supplementary Material

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1. Supplementary methods

1.1 *Construction of the genetic scores*

The interleukin-1 receptor antagonist (IL-1Ra) is a naturally occurring inhibitor of interleukin-1α/β signalling. Anakinra, the recombinant form of this protein, is licensed for the treatment of rheumatoid arthritis[1] (**S-Figure 1**). We selected two single-nucleotide polymorphisms (rs6743376 and rs11687782) upstream of the *IL1RN* gene because they had previously been reported to be independently associated with circulating IL-1Ra concentration in a genome-wide association study (GWAS) with imputation[2]. As rs11687782 was not present on the customised gene arrays we had used for *de novo* genotyping, we selected rs1542176 as a proxy, since it is very strongly correlated with rs11687782 (r^2=0.99, D'=1.0 in 1000 Genomes Europeans). We used rs6761276 as a proxy for rs6743376 (r^2=0.69, D'=1.0 in 1000 Genomes Europeans), since rs6743376 had not been genotyped or imputed in a few of the GWAS consortia we accessed. rs6761276 was the second strongest SNP reported in association with IL-1Ra levels

1.2 *Properties of the genetic scores*

1.2.1 *Properties of our main genetic score*

The SNPs we selected had several properties that made them suitable for use in the construction of a genetic score, reflecting IL-1α/β inhibition. First, our analysis of the Encyclopedia of DNA Elements (ENCODE) suggested that both SNPs are located in a likely gene regulatory region, suggested by the presence of features such as histone modification marks, DNase hypersensitivity sites and transcription factor binding sites (**S-Figure 2**). Second, the two SNPs are un-correlated and have statistically independent effects on IL-1Ra concentration. Third, both SNPs have broadly similar-sized effects on IL-1Ra concentration, ie, per allele effects in standard deviations (95% confidence interval) are: 0.18 (0.13-0.23) for rs1542176, and 0.25 (0.20-0.30) for rs6743376. Hence, combining information on both SNPs by constructing a genetic score should both enhance power and be biologically informative. Fourth, partly as a result of the properties mentioned above, we observed approximately linear associations between the genetic score and IL-1Ra concentration (**S-Figure 3**), which should enhance the power and interpretability of findings. Fifth, because the SNPs we used to construct our genetic score are un-correlated with each other, this independence should reduce the likelihood that our genetic score reflects a pathway other than IL-1α/β signalling (since for confounding by a common alternative pathway to occur it would require that these un-correlated SNPs are both associated with the actual causal trait, either directly or through linkage disequilibrium with a third SNP).

Sixth, we could validly derive our genetic score by involving only aggregated summary-level results from GWAS consortia (using fixed-effect meta-analysis of the summary estimates for the two individual SNPs). This derivation was possible because there is no correlation between the two SNPs in our genetic score in European and South Asian ancestry populations[3]. An important practical implication was our ability to access results from a variety of GWAS consortia that have available only aggregated, consortium-wide summary-level results (ie, most such consortia cannot provide access to summary results from each of their component studies).

1.2.2 *Using an alternative score as a validity test*

To test the validity of our genetic score, we constructed an alternative genetic score consisting of two further SNPs (rs6759676 and rs4251961) recently identified in a separate GWAS of IL-1Ra concentration[4]. As with the SNPs used in our main genetic score, the SNPs used in the alternative score were: i) located upstream of the *IL1RN* gene, ii) largely un-correlated with each other, and iii) broadly similar in their respective effects on IL-1Ra concentration. However, the SNPs used in the alternative score did not provide completely independent information to those used in the main genetic score because the former were strongly correlated with the SNPs used in our main score, ie, r^2 was 0.67 and D'=0.99 for the correlation between rs6759676 and rs6743376; and r^2 was 0.42 and D'=0.85 for the correlation between rs4251961 and rs1542176 (1000 Genomes, Europeans). A further rationale to use the alternative score was that it enabled analysis of additional data on two of the study's principal outcomes, ie, type 2 diabetes and CHD (Section 2.3).

1.3 Investigating the biological mechanism of the genetic score

We accessed publicly available data from multi-tissue gene expression resources: i) the Multiple Tissue Human Expression Resource (MuTHER) through http://www.muther.ac.uk/ and ii) the Genotype Tissue Expression project through http://www.gtexportal.org/home/.

We downloaded summary statistics from the MuTHER consortium for the associations of rs6743376 and rs1542176 with any nearby gene (transcription start site within 1MB of the SNP of interest) and derived the association of our score with mRNA levels by performing a fixed-effect meta-analysis of these two SNPs. Data were available on 28 probes, representing 19 genes in the region, in three tissues (skin, fat and lymphoblastoid cell lines) in 850 individuals. We applied a Bonferroni correction for the

number of tissues and probes tested, yielding a significance threshold of $P=6x10^{-4}$ (=0.05/[3*28]).

The score was associated with increased *IL1RN* mRNA levels in subcutaneous adipose tissue and in lymphoblastoid cell lines (**S-Table 1**). Both SNPs in our gene score had associations of similar size and significance levels with *IL1RN* mRNA in both tissues. Furthermore, an examination of this broader region suggested that genetic associations with *IL1RN* mRNA levels were confined to the location near rs6743376 and rs1542176 (dashed lines in **S-Figure 3A**). We observed similar associations to those described above for the alternative genetic score we used.

By contrast, whereas rs6743376 was associated with *IL36B* mRNA in skin, rs1542176 was not associated with *IL36B* mRNA levels (P>0.05). Furthermore, an examination of this broader region suggested that genetic associations with *IL36B* mRNA were strongest further upstream of rs6743376 and rs1542176 (**S-Figure 2B**). This observation suggests that the association between rs6743376 and *IL36B* mRNA levels is unlikely to reflect a direct causal relationship. Instead, it is likely to reflect that rs6743376 is in in linkage disequilibrium with these upstream variants. Hence, we examined associations of the lead SNP of this upstream region (ie, rs4849144, which was highly significantly associated with *IL36B* mRNA levels; $P=1.45x10^{-17}$) with the same medical conditions and traits for which we had observed highly significant associations with our genetic score. We found that rs4849144 was not associated with rheumatoid arthritis (P=0.22), coronary disease (P=0.51), or abdominal aortic aneurysm (P=0.31) or other traits. Hence, these observations suggest that pathways related to *IL36B* could not materially confound the associations we observed between our genetic score association and the study's outcomes.

We also observed no significant associations between either rs6743376 or rs1542176 with nearby genes in any of 13 different tissues derived from 60 to 170 people in the Genotype Tissue Expression project (i.e. the GTEx webportal returned: "No significant eQTLs were found in all eQTL Tissues").

1.4 *Description of the 5 studies involved in* de novo *genotyping providing individual-participant data on cardiovascular risk factors*

1.4.1 CIHDS/CGPS This case-control study involved two components, as described previously[5]:

The Copenhagen Ischaemic Heart Disease Study (CIHDS)

This study comprised 5185 cases with myocardial infarction and other major acute coronary syndromes and 10,368 controls matched by age and sex from the Copenhagen General Population Study (CGPS) described below. The cases were recruited from Copenhagen University Hospital during the period from 1991 to 2009. In addition to a diagnosis of acute coronary syndrome, these cases also had stenosis or atherosclerosis on coronary angiography and/or positive results on exercise electrocardiography. Cases were classified by World Health Organization International Classification of Diseases-Eighth Revision, codes 410 to 414; International Classification of Diseases-Tenth Revision, codes I20 to I25, and through review of all hospital admissions and diagnoses entered in the national Danish Patient Registry and all causes of death entered in the national Danish Causes of Death Registry, as previously described[6].

The Copenhagen General Population Study (CGPS)

The CGPS is a population-based prospective study initiated in 2003 with ongoing enrolment[6]. Participants were selected on the basis of the national Danish Civil Registration System to reflect the adult Danish population age 20 to ≥80 years. Data were obtained from a questionnaire, a physical examination, and blood samples including deoxyribonucleic acid extraction. Follow-up was 100% complete; that is, no participant was lost to follow-up. As noted above, individuals free of coronary heart disease at the time of examination were selected to serve as controls for CIHDS (Copenhagen Ischaemic Heart Disease Study). Body-mass index was calculated as weight (kg) divided by height squared (m^2). Non-fasting plasma levels of total cholesterol, high-density lipoprotein cholesterol (HDL-C), triglycerides and glucose were measured in fresh samples using colorimetric assays. Lipoprotein(a) was measured in the same samples using a turbidimetric assay (DiaSys Diagnostic Systems, Holzheim, Germany). High-sensitivity CRP was measured using nephelometry (Dade Behring, Deerfield, Ill). Fibrinogen, apolipoprotein-A1 and B were measured using colorimetric and turbidimetric assays. The hematologic cell counts were assayed using flow cell and impedance measurements on an ADVIA 2120 Hematology System (Siemens).

1.4.2 Copenhagen City Heart Study (CCHS)

CCHS is a population-based prospective study initiated in 1976 with follow-up examinations from 1981 to 1983, 1991 to 1994, and 2001 to 2003[7]. Selection of individuals for the CCHS was based on the same criteria as for the CGPS. Information on diagnosis of CHD (defined as WHO ICD 8 410 to 414 and WHO-ICD 10 I20 to I25) was collected and verified from 1976 until 2010 by reviewing all hospital admissions and diagnoses entered in the national Danish Patient Registry, and by reviewing all causes of death entered in the national Danish Causes of Death Registry[5,7]. Again, follow-up was 100% complete for both non-fatal coronary outcomes and mortality. All parameters were assessed in the same fashion as described for the CGPS study, with the exception of high-sensitivity CRP, which was measured by turbidimetry (Dako, Glostrup, Denmark).

1.4.3 European Investigation into Cancer and Nutrition-CVD (EPIC-CVD)

EPIC is a multi-centre prospective cohort study[8] of 519,978 participants (366,521 women and 153,457 men, mostly aged 35–70 years) recruited between 1992 and 2000 in 23 centres located in 10 European countries. Participants were invited mainly from population-based registers (Denmark, Germany, certain Italian centres, the Netherlands, Norway, Sweden, UK)[9]. Other sampling frameworks included: blood donors (Spain and Turin and Ragusa in Italy); screening clinic attendees (Florence in Italy and Utrecht in the Netherlands); people in health insurance programmes (France); and health conscious individuals (Oxford, UK) [9]. About 97% of the participants were of white European ancestry. Prevalent CHD was ascertained through self-reported history of MI or angina, or registry-ascertained CHD event prior to baseline. Height, weight, waist circumference were measured at baseline according to standardized protocols, and/or self-report. Measurements of all serum biomarkers were performed using a Roche MODULAR ANALYTICS EVO analyser by SHL groep in the Netherlands. HbA1c was measured in erythrocytes. Glomerular filtration rate was estimated based on creatinine levels using the formula developed by the Modification of Diet in Renal Disease Study Group. EPIC-CVD employs a nested case-cohort design, analogous to the EPIC-InterAct study for type-2 diabetes[10] which established a common set of referents through selection of a random sample of the entire cohort ("subcohort"). Incident CHD cases have been defined as fatal and non-fatal MI and other major acute coronary events, according to ICD-10 codes I20-I25. All centres have recorded cause-specific mortality through mortality registries and/or active follow-up, and have ascertained and validated incident fatal and non-fatal CHD through a combination of methods (eg, morbidity registers, general practice records, MONICA registries, self-report, clinical records[9]).

1.4.4 Bangladesh Risk of Acute Vascular Events (BRAVE)

BRAVE is a retrospective case-control study of first-ever confirmed acute myocardial infarction (MI) in Bangladesh. Patients (male or female; age between 30-80 years) admitted to the emergency rooms of the collaborating hospital in Dhaka, Bangladesh were eligible for inclusion as MI cases if they fulfilled all of the following criteria: i) presented within 24 hours of the onset of sustained clinical symptoms suggestive of MI lasting longer than 20 minutes, including chest pain and breathlessness; ii) had ECG changes indicative of MI (new pathologic Q waves, at least 1 mm ST elevation in any 2 or more contiguous limb leads or a new left bundle branch block, or new persistent ST-T wave changes diagnostic of a non-Q wave MI) with a subsequent confirmation by troponin-I measurements; and iii) had no previous cardiovascular diseases; defined as self-reported history of angina, MI, coronary revascularisation, transient ischaemic attack, stroke or evidence of CHD on prior ECG or in other medical records. Participants were not recruited into BRAVE if any of the following features had been evident: i) a previous history of cardiovascular disease (including self-reported MI, angina, coronary revascularization, stroke, transient ischaemic attack, or peripheral vascular disease, and, in cases, presence of cardiogenic shock); ii) a history of a viral or bacterial infection in the previous 2 weeks; iii) current hospitalization for acute cerebrovascular events; iv) MI secondary to any surgery; v) documented chronic conditions, such as malignancy, any chronic infection, leprosy, malaria or other bacterial/parasitic infections, chronic inflammatory disorders, hepatitis or renal failure on past medical history; vi) pregnancy or related conditions; or vii) unable to provide consent. Controls were hospital based and frequency-matched to cases on age (within 5 year age bands) and sex, and without a self-reported history of cardiovascular disease. Commercial assay kits manufactured by Roche Diagnostics (GmbH, D-68298 Mannheim, Germany) were used to determine total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglycerides. All analyses were done on Roche automated clinical chemistry analysers, Hitachi 902, Hitachi Ltd, Tokyo, Japan. Blood pressure was measured using a standard sphygmomanometer.

1.4.5 Pakistan Risk of Myocardial Infarction Study (PROMIS)

PROMIS is a retrospective case-control study of first-ever confirmed acute MI in Pakistan. Patients aged 30-80 years who were admitted to the emergency rooms of nine recruitment centres across Pakistan [11] were eligible for inclusion as cases if they fulfilled the same inclusion criteria as described for BRAVE. The controls in PROMIS were recruited using a similar approach as described above for BRAVE[11]. Nonfasting blood samples were drawn from each participant and centrifuged within 45 minutes of venepuncture. Serum samples were stored at -80°C. Total cholesterol, HDL-C, and

triglyceride concentrations were measured using enzymatic methods (Roche Diagnostics, USA) at the Center for Non-Communicable Diseases, Pakistan. Blood pressure was measured using a standard sphygmomanometer.

Baseline characteristics of the contributing studies are summarized in **S-Tables 2 & 3.**

1.5 *Genotyping methods and quality control procedures for studies with* de novo *genotyping*

In the five studies described above, we genotyped two variants (rs6743376 and rs1542176) contained in customised versions of the CardioMetabochip and OmniExpress array (both manufactured by Illumina, San Diego, USA) in two Illumina-certified laboratories located in Cambridge, UK, and Copenhagen, Denmark. Genetic quality control was performed on a chip-wide basis, separately for each study. Individuals were excluded for any of the following reasons: an average heterozygosity of >+/-3 standard deviations from the mean; a sample call rate <0.97; a mismatch between genotypic and reported gender; cryptically related individuals (ie duplicates, twins or first-degree relatives), including duplicates between the two studies from Copenhagen; and population outliers, based on manual inspection of principal component cluster plots. For each study, the numbers of individuals failing the quality control steps are shown in **S-Table 4**. Hardy-Weinberg-Equilibrium for both SNPs was assessed in controls using Fisher's exact test and the P-values are provided in **S-Table 3**. For each SNP and study, cluster plots were inspected manually. Similar methods were used for genotyping and quality control of studies which provided tabular information on an extended set of cases and controls, which had not been included previously in the largest meta-analysis of GWAS of CHD[12]. Such additional data were made available on 8678 cases and 34742 controls from the deCODE study, 3051 cases and 2432 controls from the German MI Family Study, and 2974 cases and 1643 controls from the Ottawa Heart Genomics Study / Cleveland Clinic GeneBank.

1.6 Measurement and analyses of inflammation biomarkers

Details of inflammation biomarkers and other relevant phenotypic characteristics recorded in the five studies with *de novo* genotyping are summarized in **S-Table 2**. IL-1Ra levels were measured in 3081 individuals of the Cardiovascular Health Study using the Mescoscale chemiluminescent multiplex system (Mesoscale Discovery Technology, Gaithersburg, MD,USA) as described previously[2]. Mean levels (standard deviation) of natural log transformed IL-1Ra, measured in pg/mL, were 5.35 (0.54). Additional data on inflammatory biomarkers have been contributed by the Cardiovascular Health Study, the SardiNIA study and the UK 10K consortium. Measurement of inflammation biomarkers was done using commercial assays, as described previously for the Cardiovascular Health Study and SardiNIA studies[2,13]. Measurement of inflammation biomarkers in the UK10K consortium were done with the Human Cardiovascular Disease (CVD) Panel 2 (acute-phase proteins) LINCOplex Kit (HCVD2-67BK) from Linco (Millipore) and with the Extracellular Protein Buffer Reagent Kit (LHB0001) from Invitrogen, or similar approaches. The UK10K consortium provided summary results

from a meta-analysis of several discovery and replication cohorts, comprising 7,311 individuals for IL-6 and 33,911 for CRP (of which, the ALSPAC study provided results on IL-6 for 4259 individuals and on CRP for 3393 individuals).

1.7 *Systematic review of randomised IL-1α/β treatment trials*

We searched the Medline electronic library by combining the following terms related to the IL-1α/β blocking agents anakinra, rilonacept, sIL1R1, AMG108 and randomised clinical trials (see **SFigure 4**), without language restriction:

(anakinra OR kineret OR rilonacept OR "IL-1 trap" OR Arcalyst OR IL-1RII OR rhuIL-1Ra OR (recombinant AND human AND ((Interleukin-1 receptor type I) OR IL-1R1 OR IL-1RI) OR AMG108) AND (((randomised OR randomized OR randomization OR Randomisation) AND (trial OR study)) OR ((prospective OR follow-up OR "follow up" OR observational OR phase I OR phase II OR phase IIa OR Phase IIb OR Phase III OR Phase IV) AND (Study OR Trial)) OR (meta analysis OR systematic review OR cochrane review))

Titles, abstracts and full text versions of identified articles were reviewed independently by two investigators (DF & PW). Randomised placebo controlled clinical trials (≥ 2 weeks, ie excluding trails of very short term administration) of an IL-1α/β blocking agent were included. Serious adverse events indicating a potential diagnosis of coronary heart disease were abstracted from parallel group trials only (i.e. no cross-over studies). Information on treatment effect or changes from baseline in cardiovascular risk factors (blood pressure, lipids) and inflammatory mechanism biomarkers (IL-1Ra, IL-6 and CRP) was abstracted from trials reporting on anakinra doses of 75mg or 100mg (the most commonly used dose for treatment of rheumatoid arthritis) from text, tables, figures or supplementary material where available. When not provided in a report, treatment effect was calculated as difference in baseline-corrected group specific differences in biomarkers, or post-treatment levels of biomarkers. The standard error of this difference was calculated by combining the group specific standard deviations [14]. All treatment effects were standardized by dividing effects and standard errors by the combined baseline standard deviations of IL-1Ra, IL-6 or CRP respectively. Results were combined across trials using fixed-effects meta-analysis.

1.8 *Definitions of principal disease endpoints*

Details on the definitions of principal endpoints are provided in **S-Table 5**.

Rheumatoid arthritis: All cases included in this analysis fulfilled the 1987 criteria of the American College of Rheumatology for RA diagnosis [15].

Type 2 diabetes: Case definition and characteristics of the DIAGRAM consortium included eg. American Diabetes Association (ADA) or WHO criteria, and have been described in detail previously[16]. For EPIC-InterAct, ascertainment of incident type 2 diabetes involved a review of the existing EPIC datasets at each centre using multiple sources of evidence including self-report, linkage to primary-care registers, secondary-care registers, medication use (drug registers), hospital admissions and mortality data. Information from any follow-up visit or external evidence with a date later than the baseline visit was used. To increase the specificity of the case definition we sought further evidence for all cases with information on incident type 2 diabetes from two independent sources at a minimum, including individual medical records review in some centres. Cases in Denmark and Sweden were not ascertained by self-report, but identified via local and national diabetes and pharmaceutical registers and, hence, all ascertained cases were considered to be verified.

Coronary disease: The large majority of patients with coronary disease in studies involving *de novo* genotyping had MI or other major acute coronary events. For the two GWAS consortium included in our analysis (ie, CARDIoGRAM and C4D), definitions of coronary disease used in the component studies have been described previously [17,18]. On the basis of descriptions of the component studies in these two GWAS consortia, we estimate that about 10% of the patients in our analysis of coronary heart disease were defined by angiographic evidence alone (eg, >50% coronary stenosis). Hence, about 90% of the cases included in this analysis had MI or other major acute coronary events. However, apart from the five studies for which we had access to participant-level data, we could not specifically disaggregate results by type of CHD. Nevertheless, our results should predominantly be driven by atherothrombotic coronary events, which comprise the large majority of CHD cases in this analysis.

Ischaemic stroke: Stroke subtyping was done with the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification system. Brain imaging (CT or MRI) was undertaken for more than 95% of cases.

Abdominal aortic aneurysm: An aneurysm (infrarenal aortic diameter of >30 mm) was diagnosed by either ultrasonography or by cross-sectional imaging, except for patients who presented with acute rupture and for whom the AAA was >55 mm. As we had access only to genetic summary data for aneurysm endpoints, it was not possible to analyse subtype of disease, such as acute rupture or aneurysm progression.

Details on the definitions of exploratory endpoints are provided in **S-Table 6**. Numbers of individuals for principal and exploratory endpoints are provided in **S-Table 7 & 8**, respectively.

1.9 *Methods to assess dose response relationships*

We approached individual studies of the CARDIoGRAM and C4D consortia to provide tabular data on the number of cases and controls within each category of the genotype combinations for the primary score (rs6743376 vs rs1542176; or rs6761276 vs rs1542176 if the former was not available). This enabled calculation of the odds ratio for CHD for each of the score categories 1-4, comparing it to the reference category (score category 0) separately by study, as well as calculation of a per allele odds ratio, using logistic regression. Results were pooled across studies using fixed-effect inverse-variance weighted meta-analysis. Endpoint definitions, numbers of cases and controls are provided in **S-Table 9**.

1.10 *Details of additional risk factors and biomarkers*

Details of risk factors and biomarkers in studies providing individual-participant data have been described above and are summarized in **S-Table 2**. These data were supplemented with summary results from genetics consortia. Information on consortia contributing clinical endpoints and methodological details are provided in **S-Table 7 & 8**.

1.10.1 *Further details on complex phenotypes*

1.10.1.1 *NMR metabolomics methods*

The methods and results of this approach have been described in detail previously[19]. Briefly, metabolites and metabolite ratios were measured in five cohorts from Finland totalling 8330 individuals (**S-Table 10** provides numbers of participants studied for each trait) using a high-throughput serum NMR metabolomics platform[20]. This methodology provided information on 117 serum measures, including lipoprotein subclass distribution and lipoprotein particle concentration, low molecular weight metabolites, such as amino acids, 3-hydroxybutyrate and creatinine, and detailed molecular information on serum lipids, including free and esterified cholesterol, sphingomyelin and fatty acid saturation, and a further 19 characteristics derived from the original measures.

1.10.1.2 *Mass spectrometry metabolomics methods*

The methods and results of this approach have been described in detail previously[21]. Briefly, metabolites were measured in two population based cohorts from Germany (KORA study) and the UK (TwinsUK) using a mass-spectrometry based approach (Metabolon Inc). Overall, information on 452 unique metabolites was available in up to 7824 individuals. The metabolites quantified in this study encompass a wide range of relevant biochemical classes (eg, amino acids, acylcarnitines, sphingomyelins, glycerophospholipids, carbohydrates, vitamins, lipids, nucleotides, peptides, xenobiotics and steroids). Further details on the metabolites and the association of the genetic score with each are provided in **S-Table 10**.

1.10.1.3 *Imaging markers*

Ultrasound of the common carotid artery

The methods and results of this approach have been described in detail previously[22]. Briefly, analyses were performed within nine population based cohorts of the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium. Each study evaluated the carotid arteries with high-resolution B-mode ultrasonography using previously described reading protocols. For these analyses, we used data from the baseline examination or the first examination in which carotid ultrasonography was obtained. Our primary analysis concerned the common carotid artery using the intima-

media thickness, typically summarized as the mean of the maximum of several measurements. For most studies, this was an average of multiple measurements from both the left and right arteries. All studies measured the far wall and several also included the near wall. Up to 31,207 individuals were included in these analyses (**S-Table 10**). We also examined the atherosclerotic thickening of the carotid artery wall, defined in seven of the nine studies by either the presence of plaque or the proxy measure of stenosis >25%. Data were available for up to 25,176 participants (**S-Table 10**). Specific details for each study's ultrasound, reading and plaque definition protocols have been published previously[22].

Carotid-femoral pulse wave velocity

The methods and results of this approach have been described in detail previously[23]. Briefly, analyses were performed within the AortaGen consortium. Measurement of Carotid-Femoral Pulse Wave Velocity (CFPWV) was conducted according to standardized protocols described in detail previously[23]. Nine population based cohorts which had measured CFPWV based on the carotid-to-femoral transit time and distance were included in the meta-analysis. CFPWV increases nonlinearly and exhibits marked variance inflation with advancing age, resulting in a strongly right skewed distribution. In addition, differences in the method used to ascertain transit distance can alter values by up to 30% and the amount of error may be influenced by sex and other anthropomorphic factors such as height and weight. Thus, genetic association analyses were performed using a sex-specific standardized residual that was based on the inverse of CFPWV, which normalizes the distribution, and that was further adjusted for age, age squared, height, and weight. 20,634 participants were included in the present analysis (**S-Table 10**).

1.10.1.4 *Immune cell subsets*

The methods and results of this approach have been described in detail previously[24]. Briefly, detailed flow cytometric measurements were conducted in up to 1,629 participants of the population based SardiNIA study in Sardinia, Italy. Immunophenotyping was carried out by flow cytometry on fresh blood samples, and cell phenotyping was performed within 2 hr after collection to avoid any time-dependent artefacts. A set of multiplexed fluorescent antibodies was used to characterize the major leukocyte cell populations in peripheral blood, including monocytes, granulocytes, circulating dendritic cells, and lymphocytes subdivided into NK, B, and T cells and their subsets. In particular, regulatory T cells (CD25hi, CD127-), subdivided into resting, activated, and cytokine-secreting nonsuppressive cells were assessed. The HLA-DR marker was used to assess the activation status of T and NK cells and both the

chemokine receptor CCR7 and the phosphatase CD45RA antigens to distinguish between naive, central memory (CM), effector memory (EM), and terminally differentiated (TD) T cell subsets. Moreover, in selected T cell subpopulations, the positivity for the ectoenzyme CD39 and the CD28 costimulatory antigen was assessed. Finally, cDCs were separated into myeloid (mDCs) and plasmacytoid (pDCs) cells and were further subdivided by the expression of the adhesion molecule CD62L and the co-stimulatory ligand CD86. Summary data from this study on the association of genetic variants with immune cell phenotypes was downloaded from http://www.irgb.cnr.it/facsdataexplorer.

2. Supplementary results

2.1 *Analysis of randomised trials*

We analysed eight randomised placebo-controlled trials of anakinra involving a total of 1125 individuals (**S-Figure 4** & **S-Table 11**). One of those trials reported on circulating IL-1Ra, four trials on IL-6, and all reported on CRP (**S-Figure 5 & S-Table 11**). None of the trials reported on other relevant cardiovascular risk factors, such as blood pressure or lipids. Overall, treatment with 75/100mg Anakinra resulted in increased IL-1Ra concentration (in standard deviations [SD] [95% CI]: 4.22 [3.04, 5.40]), decreased IL-6 concentration (in SD [95% CI]: -0.23 [-0.39, -0.07]) and decreased CRP concentration (in SD [95% CI]: -0.17 [-0.21, -0.14]). There was between-trial heterogeneity of treatment effects (I^2=75-82%; **S-Figure 5**). However, removal of results from a few trials with outlying effects did not affect the overall results.

Our review identified 22 randomised parallel group trials of IL-1α/β inhibitors reporting on serious adverse events (**S-Figure 4**). However, none was designed specifically to evaluate cardiovascular safety. In total, these trials reported on 3654 individuals receiving an IL-1α/β inhibitor and 1583 individuals receiving placebo. The maximum trial duration was 52 weeks (**S-Table 12**). Overall, there were 34 serious adverse events reported that could represent coronary heart disease events. Of these 34 outcomes, 21 (0.6%) were recorded in treatment arms and 13 (0.8%) in placebo groups (**S-Table 12**). However, as most trials did not report the criteria used to diagnose coronary heart disease outcomes, this analysis may be of limited value.

2.2 *Genetic analyses with CHD*

Using the maximum available dataset, the per-allele odds ratio was 1.03 (95% CI: 1.02-1.04; P=3.9×10^{-10}) for CHD (**S-Figure 7**). In studies that provided tabular data (**S-Table 9**), we observed an approximately log-linear relationship for the association of the genetic score with risk of CHD (**S-Figures 8 & 9**). There was no good evidence for heterogeneity between studies (**S-Figure 8**).

2.3 *Alternative genetic score*

The variants rs6759676 and rs4251961, recently reported in association with IL-1Ra[4] concentration, are on the CardioMetabochip. As a result, we were able to capitalise on additional data on CHD endpoints from a larger consortium (CARDIoGRAMplusC4D consortium[12]) than the separate CARDIoGRAM and C4D GWAS consortia (ie, the alternative score was studied in 78,171 CHD cases and 148,236 controls, whereas the main score was studied in 70,532 CHD cases and 126,374 controls). For the same reason, we were also able to capitalize on additional data on type 2 diabetes endpoints, from a larger collection from the DIAGRAM consortium[25] (i.e. the alternative score was studied in a total of 41,653 type 2 diabetes cases and 123,521 controls, while the main score was studied in a total of 18,715 type 2 diabetes cases and 61,692 controls).

The per-allele odds ratio for the association of this score with rheumatoid arthritis was 0.96 (0.94-0.98; $P=4.7x10^{-4}$; **S-Figure 10**), very similar to the corresponding odds ratio of 0.97 (95% CI: 0.95-0.99; $P=9.9x10^{-4}$) with our main genetic score.

We used results from CARDIoGRAMplusC4D, which includes a total of 63,746 CHD cases and 130,681 controls, as well as from the five studies for which we conducted *de novo* genotyping. The per-allele odds ratio was 1.03 (1.02-1.04; $P=3.7x10^{-8}$; **S-Figure 11**), which was, again, very similar to the corresponding odds ratio of 1.03 (1.02-1.04; $P=3.9x10^{-10}$) with our main genetic score.

The per-allele odds ratio for the association of this score with abdominal aortic aneurysm was 1.04 (1.01-1.08; P=0.011: **S-Figure 10**), somewhat weaker, yet similar to the corresponding odds ratio of 1.08 (1.04-1.12; $P=1.7x10^{-5}$) with our main genetic score.

The per allele odds ratio for the association of this score with type 2 diabetes was 1.00 (0.98-1.01; P=0.53), very similar to the corresponding odds ratio of 0.99 (0.97-1.01); P=0.47) with our main genetic score.

It is of interest that, although rs6759676 was previously reported to be associated with fasting insulin levels [4] (P=0.009; n=13,616), we did not find evidence to support this association, despite our involvement of three times as many participants as in the earlier study (P=0.55; n= 38,238).

2.4 *Exploratory endpoints*

We observed no clear associations of the genetic score with subtypes of ischaemic stroke (**S-Figure 12**). As discussed in the main text, the genetic score was associated with small increases in total- and LDL-cholesterol, but there was no clear evidence of

associations with any of the other cardiometabolic risk factors studied (**S-Figure 13**). Furthermore, there were no clear associations observed with any of the additional, complex phenotypes, including metabolomics profiles, cardiovascular imaging markers or immune cell subsets (**S-Table 10**). There were also no clear associations observed with any of the other clinical endpoints we studied (**S-Figure 14**), including conditions that might represent potential safety concerns for long-term IL-1 inhibition (**S-Figure 15**). Individual SNP associations for all endpoints are presented in **S-Figure 16**. However, as noted in the main text, the power to study these conditions varied considerably, reflecting differences in amount of information in various disease-specific GWAS consortia.

2.5 *Modelling impact of potential mediation by pro-atherogenic lipids*

We observed that the genetic score was associated with small increases in total cholesterol (per allele in SD [95% CI]:0.016 [0.009-0.022]), LDL-cholesterol concentration (per allele in SD [95% CI]: 0.014 [0.007-0.022]), and triglycerides (per allele in SD [95% CI]: 0.009 [0.003-0.015]). To estimate how much of the association we observed between the genetic score and CHD could be explained by LDL-cholesterol concentration, we estimated the causal effect of life-long alteration in LDL-cholesterol concentration in two ways. First, our genetic estimation used published reports that identified genetic variants robustly and exclusively associated with LDL-cholesterol levels [26]. The odds ratio for CHD was 0.33 per 30% lifelong genetic reduction (equivalent to a -0.357 unit change on the log-scale) in LDL-cholesterol concentration[26]. The standard deviation of log-transformed LDL-c was estimated as 0.267 in the subcohort participants of EPIC-CVD. On this basis, the odds ratio for a 0.014 standard deviation increase in LDL-c would be expected to be 1.012 (=exp(log(0.33)/-0.357*0.267*0.014)), which is approximately 38% of the increase in CHD risk associated with the genetic score (odds ratio: 1.032). Secondly, our phenotypic estimation used individual-participant data on serum lipid concentrations from 302,430 participants in the Emerging Risk Factors Collaboration[27]. We found that a 1-SD higher long-term average ("usual") non-HDL-cholesterol concentration (ie, corrected for regression dilution bias) is associated with a hazard ratio of 1.56 (1.47-1.66)[27]. An increase of 0.016 standard deviations in total cholesterol would therefore be expected to result in a hazard ratio of 1.007, which is approximately 22% of the observed increase in CHD risk of the genetic score. Hence, these two complementary approaches yielded broadly concordant findings, suggesting that LDL-cholesterol concentration could account for 20-40% of the association we observed between the genetic score and CHD.

Our rationale to conduct modelling for LDL-C but not triglycerides was two-fold. First, as we conducted exploratory analyses of the genetic score in relation to several cardiovascular traits, cautious interpretation is needed. The P-value for the LDL-C result was more extreme than the P-value for the triglyceride result. Hence, our modelling of LDL-C as a potential mediator is less speculative than it would have been for triglycerides. Second, whereas LDL-C concentration is itself regarded as a causal risk factor in CHD, triglyceride concentration in itself is unlikely to be a causal risk factor. Instead, there is good evidence that triglyceride-related pathways are causally relevant to CHD, but the exact causal component(s) of this pathway awaits identification[28,29]. Hence, a modelling analysis for triglyceride concentration would have involved extra assumptions compared to that for LDL-C concentration.

3. Supplementary tables & figures

S-Table 1: Association of the genetic score with expression levels of nearby genes

Gene	Tissue	Probe	Main score				Alternative score			
			Direction*	P	I^2	P heterogeneity	Direction	P	I^2	P heterogeneity
IL1RN	Subcutaneous adipose	ILMN_1689734	+	3.9×10^{-6}	0	0.47	+	2.3×10^{-5}	0	0.62
		ILMN_1774874	+	1.1×10^{-5}	0	0.72	+	2.3×10^{-6}	0	0.63
	Lymphoblastoid cell lines	ILMN_1689734	NA	0.07	0	0.78	NA	0.15	0	0.71
		ILMN_1774874	+	1.7×10^{-4}	0	0.76	+	2.2×10^{-6}	0	0.57
	Skin	ILMN_1689734	NA	0.91	0	0.52	NA	0.16	0	0.69
		ILMN_1774874	NA	0.60	80	0.02	NA	0.76	44	0.18
IL36B	Subcutaneous adipose	ILMN_1799519	NA	0.44	0	0.49	NA	0.23	0	0.51
	Lymphoblastoid cell lines	ILMN_1799519	NA	0.42	0	0.63	NA	0.62	0	0.74
	Skin	ILMN_1799519	+	3.3×10^{-6}	82	0.019	+	1.3×10^{-5}	74	0.047

* Direction relates to change in mRNA expression with increasing number of IL-1Ra increasing alleles. Regional association plots are provided in **S-Figures 2 & 3**.

S-Table 2: Summary information on biomarkers and cardiovascular risk factors for all five studies with participant level data

Variable	Category	CGPS		CCHS		EPIC-CVD		BRAVE		PROMIS*		PROMIS+	
		n	Mean (SD) / %	n	Mean (SD) / %	n	Mean (SD) / %	n	Mean (SD) / %	n	Mean (SD) / %	n	Mean (SD) / %
IL1Ra score	0	*293*	10.5	*692*	11.5	*2015*	12.0	*132*	8.0	*692*	12.7	*437*	10.9
	1	*884*	31.5	*1959*	32.4	*5536*	32.9	*568*	34.5	*2085*	38.4	*1611*	40.1
	2	*1019*	36.4	*2177*	36.1	*5925*	35.2	*822*	50.0	*2258*	41.6	*1661*	41.3
	3	*522*	18.6	*1046*	17.3	*2813*	16.7	*117*	7.1	*362*	6.7	*294*	7.3
	4	*85*	3.0	*163*	2.7	*549*	3.3	*5*	0.3	*31*	0.6	*19*	0.5
rs6743376	AA	*1139*	40.6	*2586*	42.8	*7578*	45.0	*924*	56.2	*3490*	64.3	*2555*	63.5
	AC	*1300*	46.4	*2727*	45.2	*7306*	43.4	*610*	37.1	*1693*	31.2	*1286*	32.0
	CC	*364*	13.0	*724*	12.0	*1954*	11.6	*110*	6.7	*245*	4.5	*181*	4.5
rs1542176	TT	*694*	24.8	*1571*	26.0	*4276*	25.4	*359*	21.8	*1321*	24.3	*898*	22.3
	TC	*1418*	50.6	*3004*	49.8	*8317*	49.4	*817*	49.7	*2586*	47.6	*2005*	49.9
	CC	*691*	24.7	*1462*	24.2	*4245*	25.2	*468*	28.5	*1521*	28.0	*1119*	27.8
Age at survey (yrs)		*2803*	58.0(12.6)	*6037*	63.3(14.7)	*16838*	56.6(10.1)	*1644*	50.1(10.0)	*5428*	54.5(9.2)	*4022*	55.1(7.6)
Gender	Male	*1230*	43.9	*2438*	40.4	*8403*	49.9	*1455*	88.5	*4424*	81.5	*3228*	80.3
SBP (mmHg)						*13353*	137.6(20.6)	*1644*	118.7(17.5)	*5272*	128.0(17.9)	*4002*	128.4(16.3)
DBP (mmHg)						*13353*	83.6(11.1)	*1644*	77.1(9.8)	*5272*	80.9(9.9)	*3999*	81.4(9.0)
Height (m)		*2800*	1.7(0.1)	*3962*	1.7(0.1)	*16402*	1.7(0.1)	*1644*	1.6(0.1)	*5363*	1.7(0.1)	*4001*	1.7(0.1)
BMI (kg/m2)		*2796*	26.1(4.1)	*3962*	26.0(4.3)	*16358*	26.9(4.4)	*1644*	22.7(7.0)	*5327*	25.6(4.6)	*3977*	26.6(5.6)
Waist (cm)						*14253*	90.2(12.9)			*5318*	91.9(11.9)	*3977*	93.9(12.7)
Waist/hip ratio						*14225*	0.9(0.1)	*1644*	1.0(0.1)	*5332*	0.9(0.1)	*4005*	1.0(0.1)
Total cholesterol (mmol/l)		*2730*	5.6(1.0)	*3896*	5.6(1.1)	*14103*	6.2(1.2)	*1638*	4.6(1.0)	*5214*	4.6(1.4)	*3942*	4.8(1.3)
HDL cholesterol (mmol/L)		*2730*	1.5(0.5)	*3890*	1.5(0.5)	*14099*	1.4(0.4)	*1638*	0.9(0.2)	*5203*	0.9(0.3)	*3939*	0.9(0.3)
Non-HDL cholesterol (mmol/L)		*2730*	4.1(1.0)	*3890*	4.1(1.1)	*14098*	4.8(1.2)	*1638*	3.7(1.0)	*5203*	3.7(1.3)	*3939*	3.9(1.3)
ln(Triglycerides [mmol/L])		*2730*	0.3(0.5)	*3896*	0.3(0.5)	*14098*	0.3(0.6)	*1638*	0.7(0.5)	*5213*	0.7(0.5)	*3937*	0.8(0.5)
Apolipoprotein A1 (g/l)		*2730*	1.7(0.3)	*3893*	1.5(0.3)	*14147*	1.5(0.3)						
Apolipoprotein B (g/l)		*2730*	1.1(0.3)	*3887*	1.1(0.3)	*14135*	1.1(0.3)						
ln(Lp(a)[mg/dL])				*3837*	3.0(1.0)	*13605*	0.4(0.9)						
ln(CRP [mg/l])		*2727*	0.6(0.6)	*3806*	0.5(1.1)	*14100*	0.4(1.1)						
ln(Leukocyte count [1e9/L])		*2733*	1.9(0.2)	*3906*	1.9(0.3)								
ln(Eosinophil count [1e9/L])		*2730*	-1.9(0.6)	*3881*	-1.7(0.6)								
ln(Basophil count [1e9/L])		*2704*	-3.6(0.5)	*2867*	-2.8(0.4)								
ln(Lymphocyte count [1e9/L])		*2733*	0.7(0.3)	*3904*	0.6(0.3)								
ln(Neutrophil count [1e9/L])		*2722*	1.4(0.3)	*3903*	1.3(0.4)								
Monocyte count (1e9/L)		*2733*	0.4(0.1)	*3904*	0.4(0.1)								
Fibrinogen (mmol/L)		*2725*	10.3(2.0)	*3918*	11.7(3.1)								
Albumin (g/l)						*13726*	46.2(2.9)						
ln(Creatinine [mg/dL])						*13774*	-0.2(0.2)						
Glucose (mmol/l)		*2730*	5.4(1.2)	*3896*	5.9(1.9)	*13071*	5.1(2.4)			5182	7.3(4.2)	3920	7.0(4.1)
HbA1c (%)						*14643*	5.8(0.9)			2626	6.5(1.7)	3470	6.8(1.9)
ln(Alkaline Phosphatase [iu/l])						*13099*	4.2(0.3)						

ln(Alanine Transaminase [iu/l])	*14069*	3.0(0.5)
ln(Aspartate Aminotransferase [iu/l])	*13778*	3.3(0.3)
Calcium (mmol/l)	*13081*	2.5(0.1)
ln(Ferritin [pmol/l])	*13751*	5.3(1.0)
ln(Gamma-Glutamyl Transferase [iu/l])	*14098*	3.2(0.6)
Iron (µmol/l)	*13112*	17.2(6.0)
Magnesium (mmol/l)	*13126*	0.9(0.1)
ln(Total bilirubin [µmol/l])	*13608*	1.9(0.5)
Transferrin (µmol/l)	*13071*	69.3(10.4)
Uric acid (µmol/l)	*13821*	306.1(83.9)
estimated glomerular filtration rate (eGFR) (ml/min/1.73m2), MDRD	*13774*	93.7(21.5)

CIHDS = Copenhagen Ischaemic Heart Disease Study, CGPS = Copenhagen General Population Study, CCHS = Copenhagen City Heart Study, EPIC-CVD = European Prospective Investigation into Cancer and Nutrition Study, BRAVE = Bangladesh Risk of Acute Vascular Events Study, PROMIS = Pakistan Risk of Myocardial Infarction Study, HWE = Hardy-Weinberg Equilibrium (in controls), * Subset of PROMIS genotyped using a customised version of the CardioMetabo array, + Subset of PROMIS genotyped using a customised version of the OmniExpress array.

S-Table 3: Summary information on CHD cases and controls for all five studies with participant level data

Variable	Category	CIHDS/CGPS					CCHS					EPIC				
		Cases		Controls			Cases		Controls			Cases		Controls		
		n	Mean (SD) / %	n	Mean (SD) / %	P HWE	n	Mean (SD) / %	n	Mean (SD) / %	P HWE	n	Mean (SD) / %	n	Mean (SD) / %	P HWE
Total		2703		2803			1999		6559			9587		7251		
IL1Ra score	0	266	9.8	293	10.5		221	11.1	748	11.4		1097	11.4	918	12.7	
	1	890	32.9	884	31.5		648	32.4	2154	32.8		3080	32.1	2456	33.9	
	2	965	35.7	1019	36.4		701	35.1	2359	36.0		3399	35.5	2526	34.8	
	3	489	18.1	522	18.6		367	18.4	1096	16.7		1681	17.5	1132	15.6	
	4	93	3.4	85	3.0		62	3.1	202	3.1		330	3.4	219	3.0	
rs6743376	AA	1119	41.4	1139	40.6	0.84	833	41.7	2788	42.5	0.35	4155	43.3	3423	47.2	0.09
	AC	1223	45.2	1300	46.4		906	45.3	2978	45.4		4233	44.2	3073	42.4	
	CC	361	13.4	364	13.0		260	13.0	793	12.1		1199	12.5	755	10.4	
rs1542176	TT	644	23.8	694	24.8	0.55	506	25.3	1731	26.4	0.54	2411	25.1	1865	25.7	0.24
	TC	1404	51.9	1418	50.6		1013	50.7	3252	49.6		4742	49.5	3575	49.3	
	CC	655	24.2	691	24.7		480	24.0	1576	24.0		2434	25.4	1811	25.0	
Age (years)		2703	60.4(11.9)	2803	58.0(12.6)		1999	66.1(10.8)	6559	55.4(15.4)		9587	59.7(8.9)	7251	52.5(10.2)	
Gender	Male	1979	73.2	1230	43.9		1045	52.3	2756	42.0		5686	59.3	2717	37.5	

CIHDS = Copenhagen Ischaemic Heart Disease Study, CGPS = Copenhagen General Population Study, CCHS = Copenhagen City Heart Study, EPIC = European Prospective Investigation into Cancer and Nutrition Study, BRAVE = Bangladesh Risk of Acute Vascular Events Study, PROMIS = Pakistan Risk of Myocardial Infarction Study, HWE = Hardy-Weinberg Equilibrium

S-Table 3 (continued): Summary information on CHD cases and controls for all five studies with participant level data

Variable	Category	BRAVE					PROMIS*					PROMIS+				
		Cases		Controls			Cases		Controls			Cases		Controls		
		n	Mean (SD) / %	n	Mean (SD) / %	P HWE	n	Mean (SD) / %	n	Mean (SD) / %	P HWE	n	Mean (SD) / %	n	Mean (SD) / %	P HWE
Total		1820		1495			2102		1903			3736		3483		
IL1Ra score	0	121	6.6	119	8.0		269	12.8	245	12.9		446	11.9	373	10.7	
	1	630	34.6	518	34.6		799	38.0	729	38.3		1451	38.8	1414	40.6	
	2	917	50.4	750	50.2		867	41.2	786	41.3		1545	41.4	1436	41.2	
	3	150	8.2	103	6.9		158	7.5	134	7.0		277	7.4	246	7.1	
	4	2	0.1	5	0.3		9	0.4	9	0.5		17	0.5	14	0.4	
rs6743376	AA	981	53.9	851	56.9	0.19	1329	63.2	1220	64.1	1.00	2355	63.0	2225	63.9	0.23
	AC	733	40.3	541	36.2		667	31.7	608	31.9		1225	32.8	1103	31.7	
	CC	106	5.8	103	6.9		106	5.0	75	3.9		156	4.2	155	4.5	
rs1542176	TT	384	21.1	323	21.6	1.00	508	24.2	462	24.3	0.02	897	24.0	785	22.5	0.81
	TC	895	49.2	744	49.8		1024	48.7	901	47.3		1775	47.5	1729	49.6	
	CC	541	29.7	428	28.6		570	27.1	540	28.4		1064	28.5	969	27.8	
Age (years)		1820	51.9(10.6)	1495	50.2(10.1)		2102	53.7(10.0)	1903	56.2(8.1)		3736	53.8(10.2)	3483	55.6(7.3)	
Gender	Male	1609	88.4	1331	89.0		1774	84.4	1588	83.4		3140	84.0	2825	81.1	

CIHDS = Copenhagen Ischaemic Heart Disease Study, CGPS = Copenhagen General Population Study, CCHS = Copenhagen City Heart Study, EPIC-CVD = European Prospective Investigation into Cancer and Nutrition Study, BRAVE = Bangladesh Risk of Acute Vascular Events Study, PROMIS = Pakistan Risk of Myocardial Infarction Study, HWE = Hardy-Weinberg Equilibrium (in controls), * Subset of PROMIS genotyped using a customised version of the CardioMetabo array, + Subset of PROMIS genotyped using a customised version of the OmniExpress array.

S-Table 4: Genetic quality control for contributing studies with participant level data

	CIHDS/CGPS		CCHS		EPIC		BRAVE		PROMIS*		PROMIS+	
	n	***%***	**n**	***%***	**n**	***%***	**n**	***%***	**n**	***%***	**n**	***%***
Total pre-QC	6000	*100*	8908	*100*	18733	*100*	3649	*100*	12044	*100*	8842	*100*
Removed due to												
Heterozygosity	65	*1.1*	53	*0.6*	103	*0.5*	35	*1.0*	90	*0.7*	0	*0.0*
Sample call rate <0.97	134	*2.2*	36	*0.4*	260	*1.4*	22	*0.6*	220	*1.8*	119	*1.3*
Gender mismatches	27	*0.5*	33	*0.4*	7	*0.0*	6	*0.2*	75	*0.6*	78	*0.9*
Cryptic relatedness	221	*3.7*	212	*2.4*	765	*4.1*	111	*3.0*	264	*2.2*	195	*2.2*
Duplicates between CIHDS/CGPS and CCHS	33	*0.6*	removed from CIHDS/CGPS									
Population outliers	14	*0.2*	13	*0.1*	9	*0.0*	9	*0.2*	2	*0.02*	0	*0.0*
Remaining	5506	*91.8*	8561	*96.1*	17589	*93.9*	3466	*95.0*	11393	*94.6*	8450	*95.6*

Discrepancies in the total number of individuals passing genetic quality control (below) and the number of individuals contributing to analyses (Stables 1 & 2) are due to missing information on covariates age, sex and *IL1RN* SNPs (rs6743376, rs1542176) and/or due to removal of participants from PROMIS due to overlap with the C4D consortium. * Subset of PROMIS genotyped using a customised version of the CardioMetabo array, + Subset of PROMIS genotyped using a customised version of the OmniExpress array.

S-Table 5: Principal endpoint definitions

Disease/Trait	Consortium	Reference(s) (PMID)	Endpoint definition / diagnosis*
Rheumatoid Arthritis	Okada	24390342	All cases met 1987 criteria of the American College of Rheumatology for RA diagnosis (3358796)
Type 2 diabetes	DIAGRAM & EPIC-InterAct	22885922 21717116	Case definition and characteristics of the DIAGRAM consortium included eg. American Diabetes Association (ADA) or WHO criteria, and have been described in detail previously (20581827). In the InterAct study, ascertainment of incident type 2 diabetes involved a review of the existing EPIC datasets at each centre using multiple sources of evidence including self-report, linkage to primary-care registers, secondary-care registers, medication use (drug registers), hospital admissions and mortality data. Information from any follow-up visit or external evidence with a date later than the baseline visit was used. further evidence for all cases with information on incident type 2 diabetes was sought from two independent sources at a minimum, including individual medical records review in some centres.
Coronary heart disease	CARDIoGRAM	21378990	See S-Table 9 for study-specific definitions.
	C4D	21378988	See S-Table 9 for study-specific definitions.
	Studies with participant level data	Unpublished	See S-Table 9 for study-specific definitions.
Ischaemic stroke	Metastroke	23041239	Stroke was defined as a typical clinical syndrome with radiological confirmation. Stroke subtyping was done with the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification system. Where subtyping was done, brain CT or MRI was undertaken for more than 95% of cases in all the discovery cohorts.
Abdominal aortic aneurysm	AAA genetics consortium	22055160 20622881 23535823 15096456 23743551	Abdominal aortic aneurysm ascertainment (infrarenal aortic diameter of >30 mm) was by either ultrasonography or by cross-sectional imaging except for patients who presented with acute rupture and for whom it was assumed that the AAA was >5.5 cm.

* The descriptions used for criteria to define disease outcomes have, unless stated otherwise, been derived from those published by the relevant GWAS consortium. Numbers in parentheses indicate PubMed identifiers (PMID) of relevant publications.

S-Table 6: Exploratory endpoint definitions

Disease/Trait	Consortium	Reference(s) (PMID)	Endpoint definition / diagnosis*
Alzheimer's disease	IGAP	24162737	Definitions vary between cohorts and include, for example autopsy-confirmed (≥ 60y at death), clinically-confirmed (DSM-IV criteria or Clinical Dementia Rating (CDR) ≥ 1); MRI confirmed diagnosis; the NINCDS-ADRDA criteria for definite or probable Alzheimer's.
Amyotrophic lateral sclerosis	ALSGEN	22959728	All cases met the El Escorial criteria for probable or definite amyotrophic lateral sclerosis.
Ankylosing spondylitis	WTCCC2 & TASC	21743469	Modified New York criteria for ankylosing spondylitis (6231933)
Asthma	GABRIEL & AAGC	21907864	Clinical diagnosis or epidemiological questionnaire ascertained diagnosis of asthma
Atopic dermatitis			Atopic dermatitis was diagnosed on the basis of a skin examination performed by experienced dermatologists and pediatricians according to standard criteria, which included the presence of chronic or chronically relapsing pruritic dermatitis with the typical morphology and distribution (7918015).
Atrial fibrillation	CHARGE	22544366	Definitions predominantly based on electrocardiographically confirmed atrial fibrillation, with slight variations between cohorts.
Chronic kidney disease	CKD Gen	20383146	Chronic kidney disease was defined as eGFRcrea < 60 ml/min/1.73 m^2 according to National Kidney Foundation guidelines (11904577).
Heart Failure	CHARGE	20445134	Definitions varied between the four contributing studies: ARIC relied on ICD-9 codes collected from hospital discharge summaries and death certificates. For the remaining three studies (Cardiovascular Health Study [CHS], Framingham Heart Study [FHS], and Rotterdam study [RS]), heart failure events identified by self-report or administrative data were validated by physician's review of medical records. CHS and FHS applied their published criteria, and RS applied the European Society of Cardiology criteria.
Inflammatory bowel disease	IIBDGC	23128233	Ulcerative colitis and Crohn's disease
Juvenile idiopathic arthritis		unpublished	Patients with the two most common subtypes of International League of Associations for Rheumatolog (ILAR)-defined juvenile idiopathic arthritis, rheumatoid factor-negative polyarticular and oligoarticular juvenile idiopathic arthritis (both persistent and extended).
Multiple Sclerosis	IMSGC & WTCCC2	21833088	Diagnosis depends on meeting established and well-validated criteria that combine clinical and para-clinical laboratory-based information, introduced in 1983 and revised and updated between 2001 and 2005 (6847134; 11456302; 16283615). The principle of these criteria is to establish that focal areas consistent with inflammatory demyelination have occurred in more than one part of the brain and spinal cord and on more than one occasion, and for which there is no better explanation than the diagnosis of multiple sclerosis. In the majority of centres disease severity has been documented using the Expanded Disability Status Score (EDSS) (6685237) and its dependent derivative the Multiple Sclerosis Severity Score (MSSS).(15824338)
Osteoarthritis	arcOGEN	22763110	Primary osteoarthritis of the hip or knee of radiographic Kellgren-Lawrence grade ≥2, or clinical evidence of disease to a level requiring total joint replacement. The exclusion criteria included the need for joint replacement due to fracture, secondary osteoarthritis of any cause, and developmental, vascular, or infective causes of joint disease.
Parkinson's disease	IPDGC	21292315	Diagnosis criteria vary between cohorts and include for example, UK Brain Bank criteria (1564476).
Schizophrenia	PGC	23974872	Case inclusion criteria included ≥2 hospitalizations with a discharge diagnosis of schizophrenia, based on ICD coding.(ICD-8 295, ICD-9 295, and ICD-10 F20). The ICD-8 and ICD-9 diagnosis of latent schizophrenia (295.5 and 295F) was excluded.
Type 1 diabetes		21980299	Patients were included if they had type-1 diabetes diagnosed by a physician and were taking insulin continuously since diagnosis.
Breast cancer	Breast Cancer Association Consortium	23535729	Clinical diagnosis, identified by hospitals or through cancer registries
Childhood acute lymphoblastoid lymphoma		19684604; 23996088	Clinical diagnosis
Chronic lymphocytic		24292274	Clinical diagnosis in accordance with WHO guidelines

leukemia			
Colorectal cancer	COGENT	24737748	Cases were defined according to the ninth revision of the International Classification of Diseases (ICD) by codes 153–154.
Lung cancer		24880342	Non-small cell lung cancer (NSCLC), classified as adenocarcinoma, squamous cell carcinoma, large-cell carcinoma, mixed adenosquamous carcinoma and other NSCLC histologies following either the International Classification of Diseases for Oncology (ICD-O) or WHO coding.
Melanoma	GenoMEL	unpublished	Clinical diagnosis, identified by hospitals or through cancer registries
Multiple myeloma		23955597	Cases were defined according to the 10th revision of the ICD by code C90.0.
Renal cell carcinoma		23184150	Histologically proven renal cell carcinoma
Tuberculosis		unpublished	Pulmonary tuberculosis in HIV-negative adults (clinical diagnosis confirmed by culture of M. tuberculosis).

* The descriptions used for criteria to define disease oucomes have, unless stated otherwise, been derived from those published by the relevant GWAS consortium. Numbers in parentheses indicate PubMed identifiers (PMID) of relevant publications.

S-Table 7: Analytical details of consortia & studies contributing summary level data for principal pre-specified outcomes

Disease/Trait	Consortium	Reference(s) (PMID)	QC steps (cut-offs)	Analysis details	Studies	Cases	Controls
Rheumatoid Arthritis	Okada	24390342	Exclusion of closely related subjects and ancestry outliers, sample call rate (<0.95), MAF (<5%), Hardy-Weinberg-Equilibrium (P<10-7), Info score (<0.5)	Imputation to 1KG, logistic regression model adjusting for ancestry-informative principal components, fixed-effects, inverse variance-weighted meta-analysis	18	14361	43923
Type 2 diabetes	InterAct	21717116	Sample call rate (98%), SNP call rate (95%), removal of ethnic outliers by comparison to hapmap CEU, heterozygosity.	Imputation to 1KG, logistic regression model adjusting for ancestry-informative principal components, age, sex and centre of recruitment	1	6813	8540
	DiaGRAM	20581827 22885922	Individual study QC, SNPs with MAF<1%	Imputed using CEU Hapmap PhII samples	12	11902	53152
Coronary heart disease	CARDIoGRAM	21378990	Sample call rate (<0.95), cryptic related individuals (some studies), homozygosity (some studies), Hardy-Weinberg Equilibrium in controls (10-6), MAF (<1%), SNP call rate (<0.95)	Imputation, logistic regression adjusting for age and sex, fixed effects inverse variance weighted meta-analysis	14	16772	39919
	C4D	21378988	Sample call rate (<0.95), removal of cryptically related individuals, Exclusion of ethnic outliers by comparison with hapmap reference populations, SNP call rate (<0.975), MAF (<1%)	Logistic regression models using robust sandwich estimators of variance, adjusting for country of origin or ancestry-informative principal components to account for population structure, fixed effects inverse-variance weighted meta-analysis	4	15420	15062
Ischaemic stroke	METASTROKE	23041239	Removal of ancestry outliers using principal components, removal of low-quality DNA samples, MAF (<1%), SNP call rate (<0.95), Hardy-Weinberg equilibrium (~P<10-6)	Imputation to HapMap II, III or 1KG, logistic regression of cox-proportional hazards accounting for ancestry-informative principal components, fixed effects inverse-variance weighted meta-analysis	15	12389	62004
Abdominal aortic aneurysm	AAA genetics consortium	22055160 20622881 23535823 15096456 23743551	Sample call rate (<0.95); MAF (<1%), SNP call rate (<0.975), Hardy-Weinberg equilibrium (<P<10^{-6}), Imputation score <0.9	Imputation to 1000G in individual datasets, analysis by logistic regression (additive model), meta-analysis using generic inverse variance method followed by further genomic control step	6	4682	38739
CRP, IL-6, IL-1Ra	Cardiovascular Health study	24182552	SNP call rate (<0.95);), Hardy-Weinberg equilibrium (<P<10^{-5})	Imputation to CEU HapMap PhII and III samples, logistic regression model adjusting for ancestry-informative principal components, age, sex	1	IL-1Ra: IL-6: CRP:	3081 2917 3181
CRP, IL-6	SARDINia study	22291609	SNP call rate (<0.95), MAF (<1%) Hardy-Weinberg equilibrium (<P<10^{-6})	Additive effects model using a family-based association test implemented in Merlin (accounting for relatedness structure)	1	IL-6: CRP:	5924 5716
CRP, IL-6	UK10K consortium	Unpublished	Sample call rate (<0.95), homozygosity >3SD, exclusion of cryptically related individuals, MAF<0.1% or INFO score <0.4.	Imputation to 1kG and UK10K combined panel, each cohort excluded outliers and applied inverse normal transformation followed by standardization, fixed effects inverse-variance weighted meta-analysis	13	IL-6: CRP:	7311 33911

PMID = PubMed identifiers of relevant publications.

.S-Table 8: Analytical details of consortia & studies contributing summary level data for exploratory outcomes

Disease/Trait	Consortium	Reference(s) (PMID)	QC steps (cut-offs)	Analysis details	Studies	Cases	Controls
Alzheimer's disease	IGAP	24162737	Study specific cut-offs, Sample call rate, gender mismatches, heterozygosity, duplicates and related individuals, ancestry outliers, SNP call rate (<0.95); MAF (<1%)	Imputation to 1KG (2010 interim release); logistic regression model for case-control collections, Cox proportional hazards model for prospective cohorts, either model adjusting for age, sex and ancestry informative principal components; fixed-effects inverse variance weighted meta analysis	31	17008	37154
Amyotrophic lateral sclerosis	ALSGEN	22959728	Relatedness, gender ambiguities, heterozygosity outliers, samples call rates (<0.95), SNP call rate, differential SNP call rate between cases and controls, Hardy–Weinberg Equilibrium	Logistic regression model adjusting for ancestry informative principal components; fixed-effects, inverse variance-weighted meta-analysis	13	4240	5104
Ankylosing spondylitis	WTCCC2 & TASC	21743469	Bayesian clustering approach to exclude outlying individuals on the basis of call rate, heterozygosity, ancestry and average probe intensity. (pairwise IBD >5%), MAF (<0.1%), SNP call rate (<0.98); Hardy-Weinberg P value ($<5 \times 10^{-20}$ in cases or controls).	Imputation to HapMap2/3; logistic regression model adjusting for ancestry-informative principal components, fixed-effects, inverse variance-weighted meta-analysis	2	2000	5660
Asthma	GABRIEL & AAGC	21907864	Removal of duplicates or cryptically related individuals, removal of ancestry outliers, SNP call rate (<0.95), Hardy-Weinberg P value (10^{-6}), MAF (<1%)	Imputation to 1KG and HapMap3 (2009 release), Cochran-Mantel-Haenszel test, inverse variance weighted fixed effects meta-analysis	39	12475	19967
Atopic dermatitis		Unpublished	Sample call rate (<0.95), individuals with excess heterozygosity or homozygosity, duplicates or cryptically related individuals (>2^{nd} degree), SNP call rate (<0.95), Hardy-Weinberg Pvalue ($<10^{-8}$), MAF (<5%)	Imputation to 1KG (integrated variant set, release March 2012), Association analysis was carried out using logistic regression with allele dosage. Sex and the first 4 principal component scores were included in the models as covariates.	1	2115	3831
Atrial fibrillation	CHARGE	22544366	Study specific QC	Imputation to HapMap, logistic or cox regression models, adjusting for age, sex, and where appropriate ancestry-informative principal components, fixed-effects inverse variance weighted meta-analysis	14	6707	52426
Heart failure	CHARGE	20445134	Study specific QC	Imputation to HapMap, Cox-proportional hazards model adjusting for age and sex, fixed-effects inverse variance weighted meta-analysis	4	1835	11447
Chronic kidney disease	CKD Gen	20383146	Study specific cut-offs for SNP call rate, Hardy-Weinberg P value, MAF	Imputation to HapMap; logistic regression model adjusting for study site age and sex, fixed-effects inverse variance weighted meta-analysis	20	5807	61286
Inflammatory bowel disease	IIBDGC	23128233	Heterozygosity per individual ($\pm$0.2); SNP call rate (<0.98); difference in SNP call rate between cases and controls (>0.02); Hardy-Weinberg P value (controls $<10^{-6}$; cases $<10^{-10}$)	Imputation to HapMap 3; logistic regression model adjusting for ancestry informative principal components;	15	12882	21770

Juvenile idiopathic arthritis	Consortium for Juvenile Arthritis Genetics (CJAG)	Unpublished	Relatedness, gender ambiguities, heterozygosity outliers, samples call rates (<0.95), SNP call rate, differential SNP call rate between cases and controls, Hardy–Weinberg Equilibrium.	Imputation to 1K (IMPUTE2, June 2014 release). Logistic regression model adjusting for ancestry informative principal components; fixed effects, sample size weighted meta-analysis.	3	2750	15882
Multiple Sclerosis	IMSGC & WTCCC2	21833088	Bayesian clustering approach to exclude outlying individuals on the basis of call rate and heterozygosity; gender mismatches, removal of related or cryptically related individuals (IBD >5%), removal of ancestry outliers using principal component analysis; SNP call rate (<0.98), MAF (<0.1%); Hardy-Weinberg Pvalue ($<10^{-50}$), frequency differences between genotyping plates	Linear mixed model, accounting for ancestry informative principal components	NA	9772	17376
Osteoarthritis	arcOGEN	22763110	Sample call rate (<0.95-0.99); Genetic and phenotypic gender mismatch; Heterozygosity (visual removal of outliers); Removal of duplicates or cryptically related individuals (pairwise IBD>0.2); Removal of Non-European ancestry individuals based on comparison with HapMap populations; SNP call rate (<0.95-0.99), Hardy Weinberg P value ($<10^{-4}$),	Imputation to 1KG (2010 interim release); logistic regression model; fixed-effects, inverse variance-weighted meta-analysis	1	7406	11002
Parkinson's disease	IPDGC	21292315	Cut offs differ between cohorts, criteria include sample call rate, gender mismatch, sample duplicates or cryptically related individuals, ancestry outliers; SNP call rate, Hardy-Weinberg Pvalue, MAF , difference in SNP call rate between cases and controls	Imputation to 1KG (2009 low coverage release), logistic regression models adjusting for ancestry informative principal components, fixed effects inverse variance weighted meta-analysis	5	5333	12019
Schizophrenia	PGC	23974872	Sample call rate (<0.98), removal of duplicates or cryptically related individuals (IBD>0.2) heterozygosity ($F_{het} \pm 0.2$), ; SNP call rate (<0.98); differential SNP call rate between cases and controls (>0.02), Hardy-Weinberg P value (controls $<10^{-6}$, cases $<10^{-10}$)	Imputation to 1KG phase I, logistic regression including ancestry informative principal components, inverse variance weighted fixed effects meta-analysis	37	13,833	18,462
Type 1 diabetes		21980299	Sample call rate (<0.98), sample duplicates or cryptically related individuals using IBS, population outliers (>±6 SD on any of the top ten principal components); SNP call rate (<0.95); Hardy-Weinberg P value ($<10^{-5}$), MAF (<1%)	Imputation to HapMap, Logistic regression model adjusting for ancestry informative principal components; fixed-effects, inverse variance-weighted meta-analysis	5	9934	16956
Breast cancer	Breast Cancer Association Consortium	23535729	Exclusion of individuals genotypically not female, sample call rate (<0.95) low or high heterozygosity; genotypes discrepancies with previous BCAC genotyping; duplicates and cryptically related relatives (first-	Logistic regression, including study and principal components as covariates.	41	48155	43612

			degree based on IBS), removal of ancestry outliers based on comparison with HapMap 2 populations; SNP call rates (<0.95), Hardy-Weinberg equilibrium (P < 1 × 10-7 controls); SNPs with discrepancies in more than 2% of duplicate samples.				
Childhood acute lymphoblastoid lymphoma		19684604; 23996088	Removal of cryptically related individuals based on IBS (>80%); Exclusion of non-European individuals by comparison with CEU hapmap reference panel, Hardy-Weinberg equilibrium (P<10-5 in controls); MAF (<1%); SNP call rate (<95%)	Unconditional logistic regression, fixed effect inverse variance weighted meta-analysis	2	1987	7224
Chronic lymphocytic leukemia		24292274	Removal of cryptically related individuals based on IBS (>80%); Exclusion of non-European individuals by comparison with CEU hapmap reference panel, Hardy-Weinberg equilibrium (P<10-5 in controls); MAF (<1%); SNP call rate (<95%)	Unconditional logistic regression, fixed effect inverse variance weighted meta-analysis	2 consortia	1739	5199
Colorectal cancer		24737748	Removal of cryptically related individuals based on IBD (>6.25%); Exclusion of non-European individuals by comparison with CEU hapmap reference panel, GenCall score (<0.25), Info score (<0.4), Hardy-Weinberg equilibrium (P<10-4 in controls, 10-6 in cases); MAF (<1%); SNP call rate (<0.95)	1KG phase I imputation, unconditional logistic regression, fixed effect inverse variance weighted meta-analysis	5	5626	7817
Lung cancer		24880342	Sample call rate (<0.95), X-chromosme heterozygosity rate (different cut-offs across studies); Removal of first degree relatives (genome-wide IBD >0.2), Autosomal heterozygosity (>6 SD from sample mean); < 80% probability of being Caucasian ancestry; SNP call rate (<0.95); MAF (<1%), Hardy-Weinberg-Equilibrium ($P<10^{-4}$)	1KG phase I imputation, unconditional logistic regression, fixed effect inverse variance weighted meta-analysis	4	11348	15861
Melanoma	GenoMEL	Unpublished	Imputation was conducted genome-wide separately on each study, following a shared protocol. SNPs with either MAF<0.03 or MAF<0.01, control HWE p-value<10-4 (in controls) or missingness >0.03 were excluded, as were any individuals with call rates <0.97, identified as first degree relatives and/or European outliers (as identified by principal components analysis using PCA/Eigenstrat). In addition, in each study where samples were genotyped on more than one chip, any SNP not present on all chips were removed prior to	Imputed genotypes were analysed as expected genotype counts based on the posterior probabilities (gene dosage) using SNPTEST2 assuming an additive model with geographic region as a covariate. Only those with an imputation quality ('INFO') score >0.8 were analysed. Potential stratification was dealt with in the GenoMEL samples by including geographic region as a covariate (inclusion of principal components as covariates was previously found to make little difference) and elsewhere by including principal components as covariates.	10	12320	17576

			imputation to avoid bias. IMPUTEv2 was used for imputation	Heterogeneity of per SNP effect sizes in studies contributing to the meta-analyses was assessed using the I^2 metric. For all SNPs I^2 was less than 31% so a fixed effects model was used			
Multiple myeloma		23955597	Removal of cryptically related individuals based on IBS (>0.8); Exclusion of non-European individuals by comparison with CEU hapmap reference panel, Hardy-Weinberg equilibrium (P<10-6 in controls); MAF (<1%); SNP call rate (<0.95)	Fixed effect meta-analysis	2	2312	7298
Renal cell carcinoma		23184150	Sample call rate (<0.97), gender mismatch, cryptic relatedness based on IBD (>0.185), Exclusion of non-European individuals by comparison with CEU hapmap reference panel, Hardy-Weinberg equilibrium (P<10-5 in controls); MAF (<1%); SNP call rate (<0.95), different missing genotype rates between cases and controls (P<10-5)	1KG phase I imputation, unconditional logistic regression, fixed effect inverse variance weighted meta-analysis	5	2215	3369
Tuberculosis		unpublished	Sample call rate (<0.98), sample duplicates or cryptically related individuals using IBS (> 80%), heterozygosity (> 3.5 SD), ancestry outliers; SNP call rate (<0.98), Hardy-Weinberg P-value (< 10-6), missing rate per SNP difference in cases and controls (> 0.02), MAF (<1%).	Imputation to HapMap, Logistic regression model adjusting for ancestry informative principal components.	1	5530	5607
Anthropometric traits (Height, BMI, WHR, waist circumference)	GIANT	23754948	QC on study level according to standard protocols	Imputation to HapMap PhII CEU, linear regression model, fixed effect inverse variance weighted meta-analysis	Up to 46		Up to 75819
Glycemic traits (Glucose, fasting insulin, 2h glucose, Proinsulin, HbA1c)	MAGIC	21873549; 20858683; 20081857; 20081858	QC on study level according to standard protocols	linear regression model, fixed effect inverse variance weighted meta-analysis	Up to 26		Up to 46368
Lipids (Total-cholesterol, LDL-cholesterol, HDL-cholesterol, Triglycerides)	GLGC	20686565	Study specific QC, plus MAF (< 0.01), poor imputation quality (Rsq/Info < 0.3)	Imputation to HapMap PhII CEU, linear regression (or mixed linear regression in family based studies) on residuals obtained after adjustment for age, age^2, sex, and a ancestry informative principal components in some studies, fixed effect inverse variance weighted meta-analysis	Up to 51		Up to 94569
Lipid sub fractions and metabolites (NMR)		22286219	Sample call rate (<0.95), cryptically related individuals, gender mismatches, SNP call rate (<0.95),	Imputation to 1KG and HapMap PhIII, linear regression on standardised residuals, obtained after adjustment for age, sex and ancestry-informative principal components, fixed effect inverse variance weighted meta-analysis	5		8330
Metabolites		24816252	Sample call rate (<0.98), heterozygosity (±>2 SD from the mean), exclusion of non-European	Imputation to HapMap PhII, linear regression models adjusting for age, sex and batch effects,	2		7824

			ancestry individuals based on comparison with HapMAp3 populations; Hardy-Weinberg Pvalue ($<10^{-6}$), MAF (<1%), SNP call rate (<0.97),	fixed effect inverse-variance weighted meta-analysis		
Soluble adhesion molecules (sICAM1 & sP-selectin)	CHARGE	20167578	Study specific QC	linear regression (or mixed linear regression in family based studies), fixed effect inverse variance weighted meta-analysis	Up to 4	Up to 8984
White blood cell counts (differential)	CHARGE	21738480	Sample call rate (<0.95), exclusion of non-European ancestry individuals based on multiple dimensional-scaling vectors, gender mismatches, MAF (<1%), SNP call rate (<0.95), Hardy-Weinberg Pvalue (10^{-7})	Imputation to HapMap PhII, linear regression models adjusting for age, sex and smoking status, fixed effect inverse-variance weighted meta-analysis	Up to 7	Up to 19509
Carotid intima-media thickness and presence of carotid atherosclerotic plaque	CHARGE	21909108	Varying QC measures and cut-offs according to studies.	Imputation to HapMap, linear regression models (or linear mixed effects models) for carotid intima-media thickness; logistic regression models (or general estimating equations clustering on family to account for familial correlations) for presence of plaque.	9	31211
Carotid-femoral pulse wave velocity	AortaGen	22068335	Study specific QC	Imputation to HapMap, linear regression (or mixed linear regression in family based studies) standardized regression residual, adjusted for age, age^2, height, and weight, fixed effect inverse variance weighted meta-analysis	9	20634

PMID = PubMed identifiers of relevant publications.

S-Table 9: Details on CHD studies contributing tabular data for estimation of dose-response relationship

Acronym	Reference (PMID)	Full name	Case definition	SNPs provided			N cases	N controls
				rs6743376	rs6761276	rs1542176		
ADVANCE	18443000	Atherosclerotic Disease, VAscular functioN, and genetiC Epidemiology	Clinical non-fatal CAD including MI, typical angina with ≥1 artery with >50% stenosis, positive non-invasive test, or PCI or CABG		x	x	278	312
AGES-Reykjavik	17351290	Age, Gene/Environment Susceptibility-Reykjavik Study	Fatal and non-fatal confirmed MI	x		x	642	2542
BHF-FHS / WTCCC	17554300	British Heart Foundation Family Heart Study / Wellcome Trust Case Control Consortium	Validated MI, CABG, PTCA or angina with positive noninvasive testing <66 yrs	x		x	1873	2834
BRAVE	See above	Bangladesh Risk of Acute Vascular Events	Confirmed MI, see above	x		x	1820	1644
CCHS	See above	Copenhagen City Heart Study	Fatal and non-fatal MI and other major acute coronary events, according to ICD-10 codes I20-I25	x		x	1999	6559
CHS	1669507	Cardiovascular Health Study	MI, possible and definite fatal CHD, sudden death within an hour of symptoms	x		x	854	2417
CIHDS/CGPS	See above	Copenhagen Ischaemic Heart Disease Study / Copenhagen General Population Study	Fatal and non-fatal MI and other major acute coronary events, according to ICD-10 codes I20-I25	x		x	2703	2803
deCODE	17478679	deCODE genetics coronary heart disease study	MI (MONICA criteria) before the age of 75 in Iceland between 1981 and 2002, angiography and percutaneous coronary interventions (PCI) (nationwide clinical registries), additional subjects diagnosed with significant angiographic CAD (>50% stenosis), individuals with CAD discharge diagnoses (ICD 9 codes 410.*, 411.*, 412.*, 414.*, or ICD 10 codes I20.0, I21.*, I22.*. I23.*, I24.*, I25.*), from the Landspitali University Hospital in Reykjavik, individuals where cause of death or contributing cause of death listed as MI or chronic ischaemic heart disease (ICD 9 or 10 codes) in death	x		X	15,318	62,353

			registries, subjects undergoing coronary artery bypass grafting (CABG) procedures at Landspitali University Hospital in Reykjavik					
EPIC-CVD	See above	European Prospective Investigation into Cancer and Nutrition Study	Fatal and non-fatal MI and other major acute coronary events, according to ICD-10 codes I20-I25	x		x	10288	7292
GerMIFS I-V	17634449 19198612	German MI Family studies	MI MONICA criteria	x		x	6314	7071
HPS	12114036	Heart Protection Study	History of MI, unstable or stable angina, CABG, or angioplasty	x		x	2652	2717
ITH	20031563	Interheart Study	Incident acute MI, presenting to a hospital within 24 hours of symptom onset	x		x	387	437
LOLIPOP	21378988	London Life Sciences Prospective Population	History of MI, CABG, PTI or angiographically confirmed coronary artery stenosis greater than 50%		x	x	2794	3759
LURIC	11258203	The LUdwigshafen RIsk and Cardiovascular Health study	Angiography (>50% coronary stenosis)	x		x	2095	923
MedStar	21239051	-	Patients with one or more coronary vessels with ≥50% stenosis and a history or presentation of MI		x	x	408	442
MIGen	19198609	Myocardial Infarction Genetics Consortium	Confirmed MI		x	X	2957	3071
OHGS / CCGB	20729558 22319020	Ottawa Heart Genomics Study / Cleveland Clinic GeneBank	At least one of the following criteria: a stenosis in a major epicardial vessel of at least 50%; PCI; CABG or MI	x		X	4516	3098
PennCath	21239051	-	Patients with one or more coronary vessels with ≥50% stenosis and a history or presentation of MI		x	x	433	437
PROCARDIS	21378988	-	MI or acute coronary syndrome, unstable or stable angina, CABG	x		X	1189	1125
PROMIS	See above	Pakistan Risk of Myocardial Infarction study	Confirmed MI, see above	x		x	10235	9411
Rotterdam Study	20031568	-	Definite or probable MI, PTCA or CABG,	x		x	777	5127
Total							***70,532***	***126,374***

PMID = PubMed identifiers of relevant publications.

S-Table 10: Association of the genetic score with metabolites and imaging biomarkers

Available online at http://www.phpc.cam.ac.uk/ceu/il-1-genetics-consortium/

For all traits except Carotid-Femoral Pulse Wave Velocity, analyses combined the effects of primary score SNPs rs1542176 and rs6743376 using fixed-effects meta-analysis. For Carotid-Femoral Pulse Wave Velocity rs6761276 was used as proxy for rs6743376 instead. I2 values and heterogeneity p-values refer to between SNP heterogeneity.

S-Table 11: Summary of clinical trials of 75/100mg anakinra providing inflammatory biomarker information

First author	Year	Study ID	Dose	Frequency	Duration	Patient population	Location	Background medication	IL-1Ra		IL-6		CRP	
									N drug	N placebo	N drug	N placebo	N drug	N placebo
Bresnihan B	1998	N/R	75mg	Daily	24 weeks	Rheumatoid arthritis	41 centers in 11 European countries	NSAIDs and/or Corticosteroids					115	118
Cohen S	2002	N/R	75mg	Daily	24 weeks	Rheumatoid arthritis	36 centers (31 in the US, 3 in Canada, and 2 in Australia)	MTX, NSAIDs and or corticosteroids					44	38
Cohen SB	2004	990145 Study	100mg	Daily	24 weeks	Rheumatoid arthritis	Multicentre trial, US	MTX, NSAIDs and or corticosteroids					250	251
Larsen CM	2007	NCT00303394	100mg	Daily	13 weeks	Type 2 diabetic patients	2 centres in Denmark and Switzerland	Antidiabetics			34	33	34	33
Van Tassell BW	2014	NCT01542502	100mg	Daily	4 weeks	Patients with Heart failure according to New York Heart Association class II-III	Virginia Commonwealth University, US	Furosemide, ACE-inhibitors, b-blockers, spironolactone, statins, aspirin					12	12
Hung AM	2011	NCT00420290	100mg	3x/week	4 weeks	Maintenance haemodialysis patients	Single centre study, Nashville, US	NR			7	7	7	7
Moran A	2013	NCT00711503	100mg	Daily	36 weeks	Patients with recent-onset type 1 diabetes	Multicentre trial at 14 centres across Europe	Insulin	24	25	25	26	25	26
Morton AC)	2014	EUCTR: 2006-001767-31-GB; MRC ILA Heart Study	100mg	Daily	2 weeks	Patients with Non-STEMI	5 centres in the UK	aspirin, clopidogrel, statins, ACE inhibitors, angiotensin receptor blockers			76	70	80	73
								Total	**24**	**25**	**142**	**136**	**567**	**558**

S-Figure 4 provides a flow chart of the systematic review strategy used to create this table.

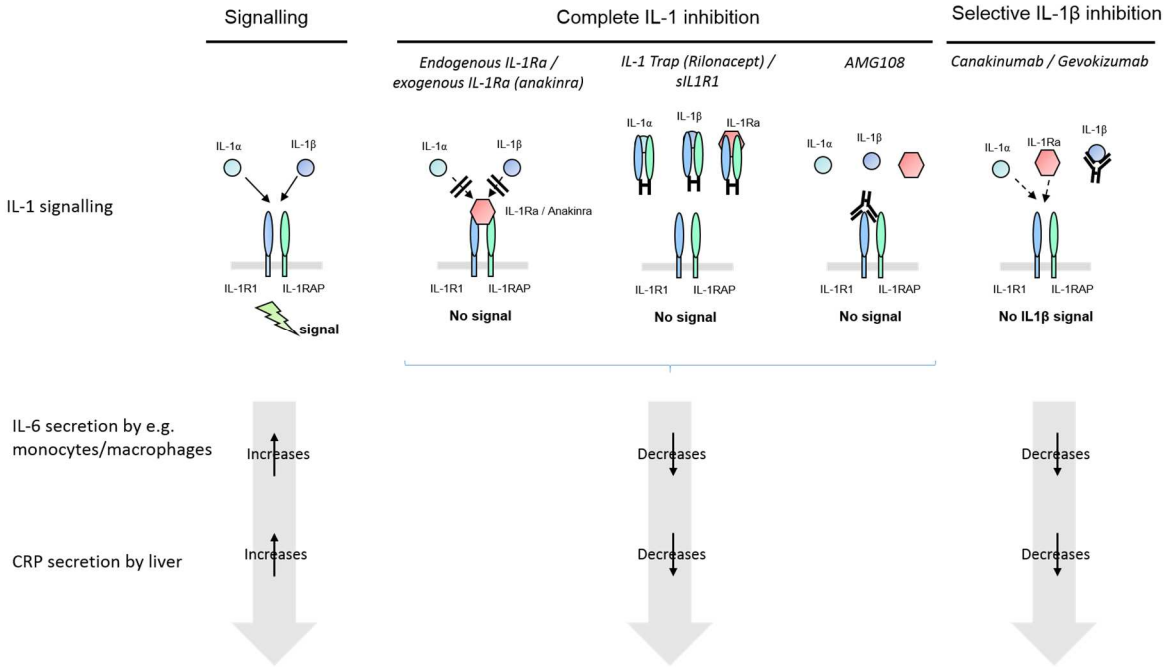
S-Table 12: Summary of clinical trials of IL-1α/β blocking agents and cardiovascular related serious adverse events (SAEs)

First author	Year	Study ID	Drug	Dose	Frequency	Duration	Patient population	n total drug	n total placebo	Type of cardiovascular serious adverse event	Events drug arm	Events placebo arm
Cardiel MH	2010	NCT00293826	AMG 108	50 / 125 / 250 mg	4 weekly	24 weeks	Rheumatoid arthritis	604	201	None reported	0	0
Cohen SB	2011	NCT00110942 -Part A & B	AMG 108	75, 100, 300mg	4 weekly	12 weeks	Patients with osteoarthritis	128	95	Unstable angina in AMG108 group, coronary artery disease in placebo group	1	1
Bresnihan B	1998		Anakinra	30, 75, 150mg	Daily	24 weeks	Rheumatoid arthritis	351	121	None reported	0	0
Cohen S	2002		Anakinra	0.04, 0.1, 0.4, 1, 2 mg/kg	Daily	24 weeks	Rheumatoid arthritis	345	74	Chest pain (unclear whether cardiac or not)	2	0
Fleischmann RM	2003	990757 Study	Anakinra	100mg	Daily	24 weeks	Rheumatoid arthritis patients	1116	283	Death due to MI	0	1
Schiff MH	2004									Chest pain	2	2
Cohen SB	2004	990145 Study	Anakinra	100mg	Daily	24 weeks	Rheumatoid arthritis patients	250	251	None reported	0	0
Genovese MC	2004	20000223 Study	Anakinra	100mg	Daily	24 weeks	Rheumatoid arthritis patients	162	80	Chestpain, cardiac	1	0
Charatcharoenwitthaya N	2007		Anakinra	100mg	Daily	3 weeks	Healthy postmenopausal women	14	13	None reported	0	0
Larsen CM	2007	NCT00303394	Anakinra	100mg	Daily	13 weeks	Type 2 diabetic patients	34	35	None reported	0	0
Ilowite N	2009	NCT00037648	Anakinra	1mg/kg; 100mg max	Daily	16 weeks	Juvenile rheumatoid arthritis patients	25	25	None reported	0	0
Abbate A	2010	NCT00789724	Anakinra	100mg	Daily	2 weeks	Patients with suspected STEMI	5	5	Acute coronary syndrome	1	1
										Unstable angina	1	0
Niu X	2011		Anakinra	80mg	Daily	24 weeks	Rheumatoid arthritis patients	38	12	None reported	0	0
Quartier P	2011	NCT00339157	Anakinra	2mg/kg, max 100mg	Daily	4 weeks	Juvenile idiopathic arthrithis	12	12	None reported	0	0
Abbate A	2013	NCT01175018	Anakinra	100mg	Daily	2 weeks	Patients with STEMI	15	15	Recurrent MI	1	0
										Cardiac death	0	1
										Repeat coronary revascularization (urgent & elective)	3	5
Moran A	2013	NCT00711503	Anakinra	100mg	Daily	36 weeks	Patients with recent-onset diabetes (diagnosed <100d before enrollment)	35	34	None reported	0	0
Morton AC	2014	EUCTR: 2006-001767-31-GB; MRC ILA Heart Study	Anakinra	100mg	Daily	52 weeks	Patients with Non-STEMI	93	89	Myocardial infarction	8	2

Hoffman HM	2008	NCT00288704	Rilonacept	160mg	Weekly	6 + 9 weeks	CAPS patients	23	24	None reported	0	0
Schumacher HR Jr	2012	NCT00610363	Rilonacept	160mg	Weekly	16 weeks	Patients with with hyperuricemia and gout	41	42	None reported	0	0
Schumacher HR Jr	2012	NCT00829829	Rilonacept	80mg / 160mg	Weekly	20 weeks	Patients with acute arthritis of primary gout or MSU crystals in the joint fluid	161	79	Coronary artery disease (nighttime angina)	1	0
Mitha E	2013	NCT00958438	Rilonacept	80mg / 160mg	Weekly	16 weeks	Patients with acute arthritis of primary gout or MSU crystals in joint fluid	166	82	None reported	0	0
Lovell DJ	2013	NCT01803321	Rilonacept	2.2mg/kg / 4.4mg/kg; 320mg max	5 applications during 4 weeks (not regular)	4 weeks	Patients with systemic idiopathic juvenile arthrithis	17	7	None reported	0	0
Drevlow BE	1996		sIL1R1	125,250,500,100 ug/m2	Daily	4 weeks	Rheumatoid arthritis	19	4	None reported	0	0
							Total	**3654**	**1583**		**21**	**13**

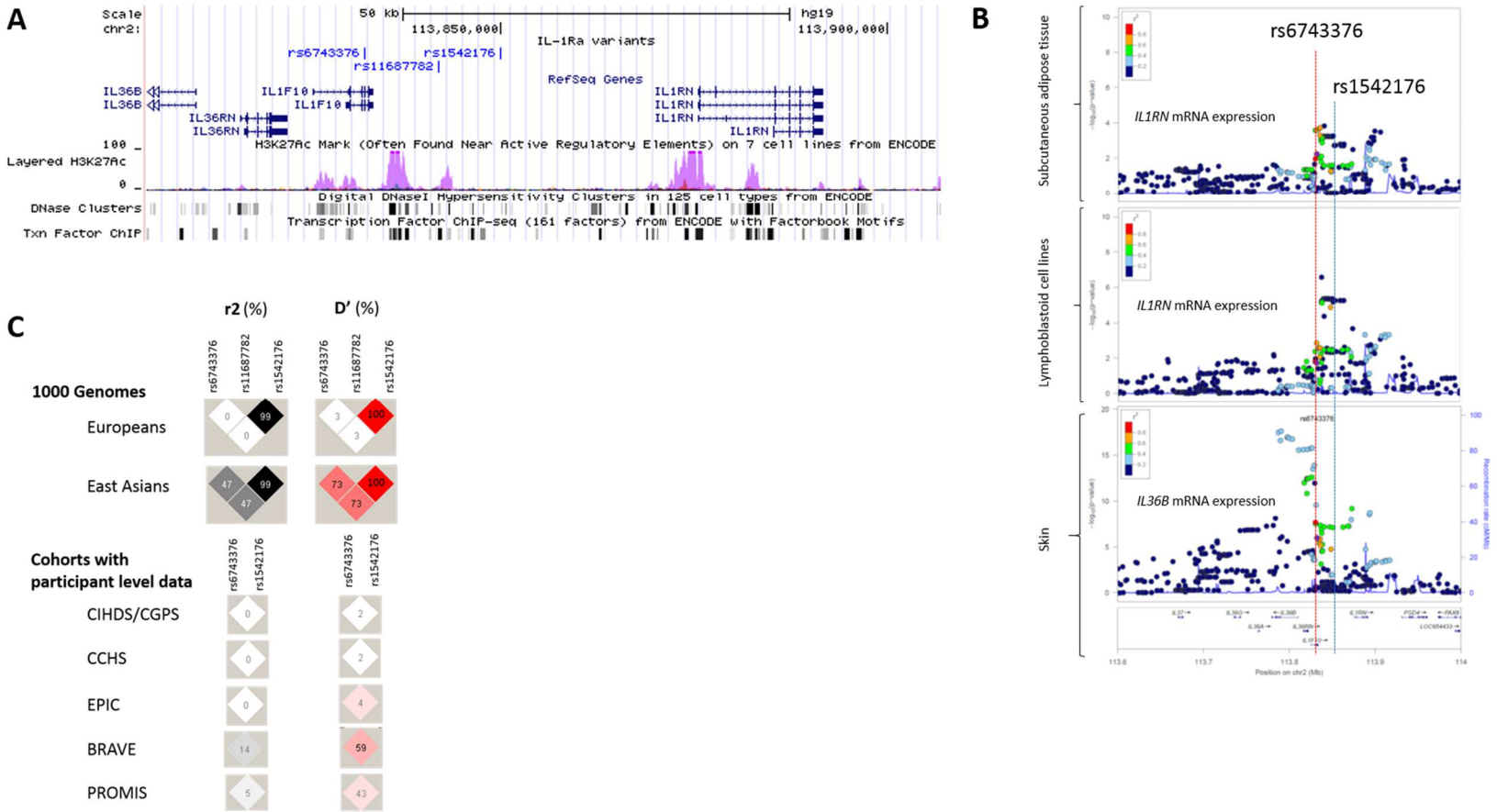
S-Figure 4 provides a flow chart of the systematic review strategy used to create this table.

S-Figure 1: Interleukin-1 (IL-1) signalling and blockage by IL-1Ra / anakinra and other agents.



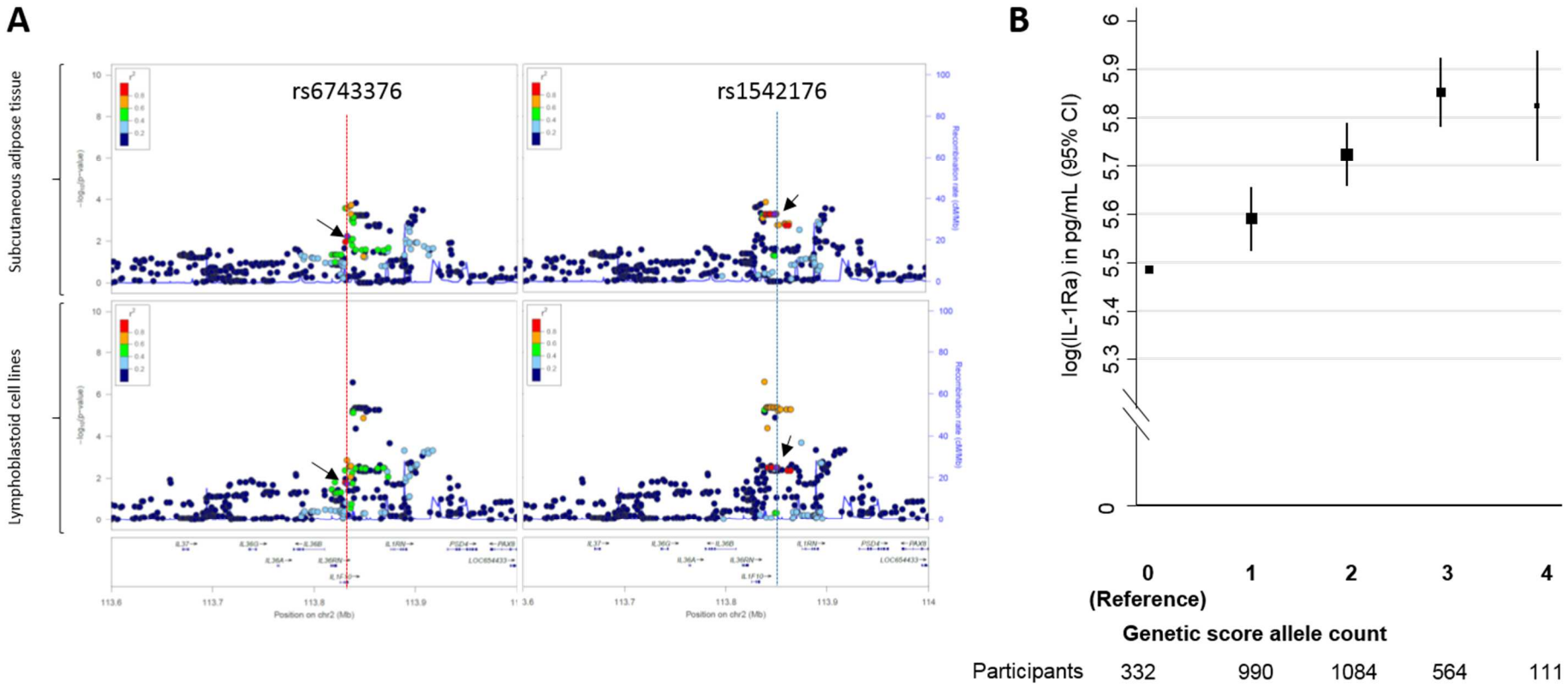
IL-1 isoforms IL-1α and IL-1β promote signalling by binding to the heterodimeric IL-1 receptor composed of the IL-1 receptor 1 (IL-1R1) and IL-1 receptor accessory protein (IL-1RAP), leading to stimulation of interleukin-6 (IL-6) secretion and further stimulation of the release of systemic inflammatory markers like C-reactive protein (CRP) (left panel). IL-1 receptor antagonist (IL-1Ra) or the recombinant form anakinra competitively inhibit actions of IL-1α and IL-1β, thereby reducing the increase in downstream inflammatory markers IL-6 and CRP. IL-1 Trap (Rilonacept) and soluble IL1R1 serve as decoy receptors, binding IL-1α. IL-1β and IL-1Ra, while AMG108 specifically binds IL1R1. Similar to anakinra, these agents block broad IL-1 activity, in contrast to canakinumab and gevokizumab, which specifically bind and inhibit IL-1β actions only.

S-Figure 2: *IL1RN* region, gene expression and linkage disequilibrium (LD) between SNPs.



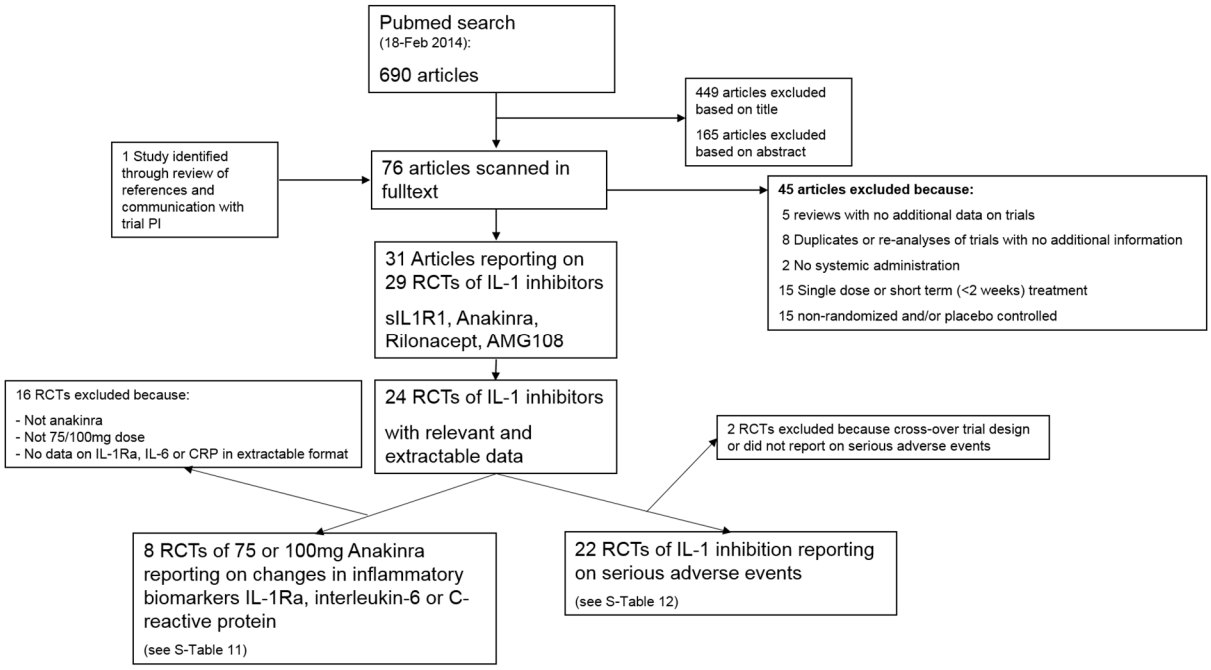
A) Functional genomic data, visualized using UCSC genome browser, showing location of SNPs (top), genetic context of *IL1RN* (middle) and Encyclopedia of DNA Elements (ENCODE) annotation (bottom). ENCODE annotation includes: i) histone acetylation marks (H3K27Ac) reflecting active genetic enhancer regions in 7 different cell lines. The only acetylation marks present in this region are found in Normal Human Epidermal Keratinocytes (represented by the purple peaks); ii) DNase I hypersensitivity clusters, indicating accessible DNA elements, hence likely to be of regulatory character and iii) transcription factor binding chromatin immuno-precipitation (ChIP) peaks indicating genetic regions found to bind to transcription factors. B) Regional association plots, showing association of genetic variants with mRNA expression of the *IL1RN* (top two panels) and the *IL36B* gene (bottom panel) in 850 individuals from the MuTHER consortium. Numerical values for the association of the genetic score are provided in **S-Table 1**. Plots were produced using LocusZoom (http://csg.sph.umich.edu/locuszoom/). Linkage disequilibrium plotted in relation to rs6743376. Positions of rs6743376 and rs1542176 indicated by dashed red and blue lines respectively. C) LD between the three key SNPs for 1000 Genomes phase I Europeans and East Asians (top) and studies with participant level data (bottom). Grey shading corresponds to r^2 between SNPs, red shading corresponds to D' values between SNPs.

S-Figure 3 Relationship of the genetic score variants with *IL1RN* mRNA expression and soluble interleukin-1 receptor antagonist concentration



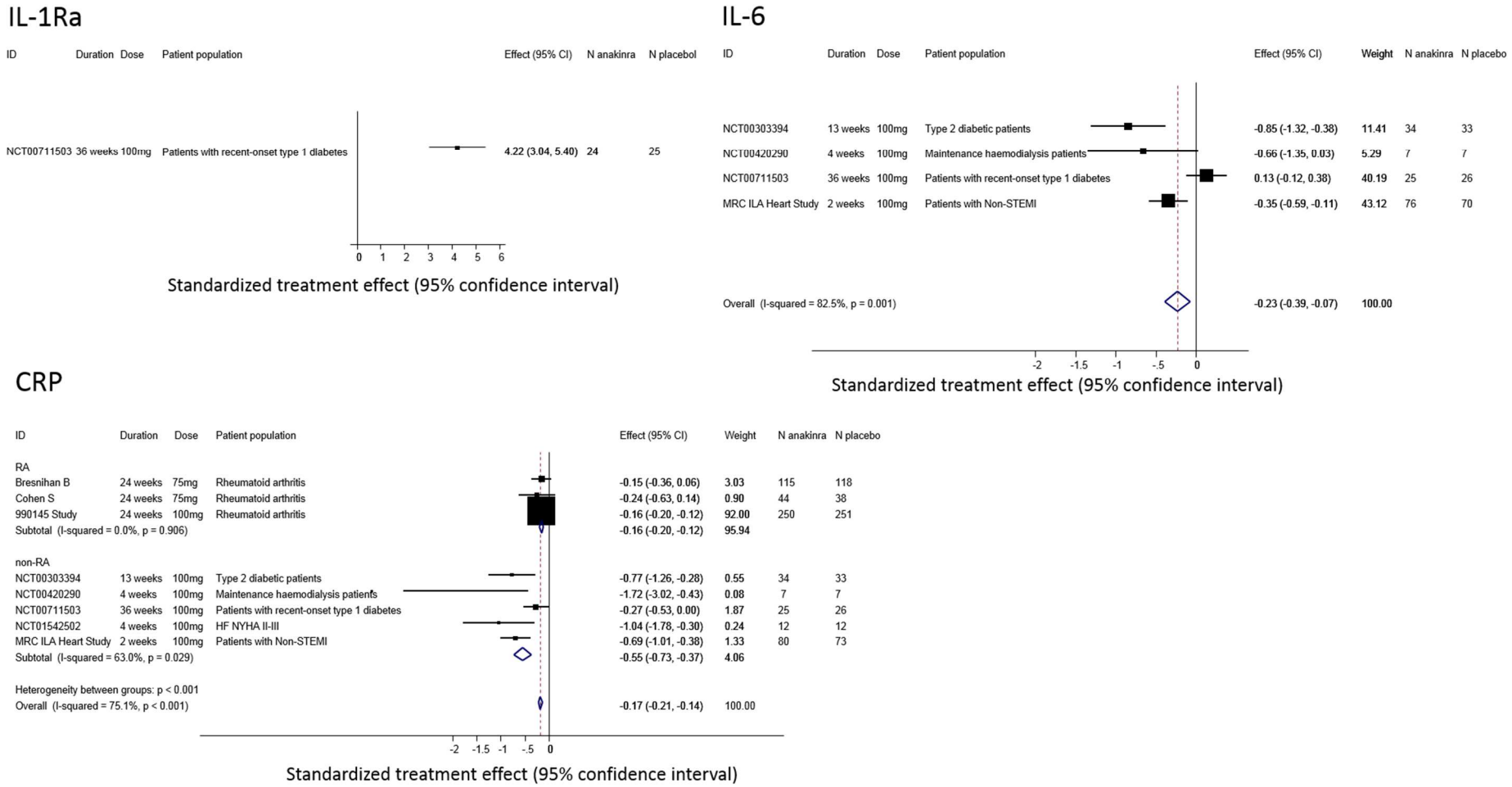
A) Regional association plot showing the association of genetic variants with *IL1RN* mRNA expression levels in subcutaneous adipose tissue (top row) and lymphoblastoid cell lines (bottom row) from 850 individuals in the Multiple Tissue Human Expression Resource consortium. Left column shows linkage disequilibrium pattern for variants in relation to rs6743376 (shown as purple marker and indicated by arrow-head), right column shows the same data but linkage disequilibrium in relation to rs1542176 (also shown as purple marker indicated by arrow-head). Numerical values for the association of the genetic score are provided in **S-Table 1**.
B) Relationship of allele counts of the genetic score (constructed from rs6743376 and rs1542176) with soluble interleukin-1 receptor antagonist concentration. Box sizes reflect number of participants.

S-Figure 4: Flow chart of the systematic literature review for anakinra and other IL-1α/β blocking drugs



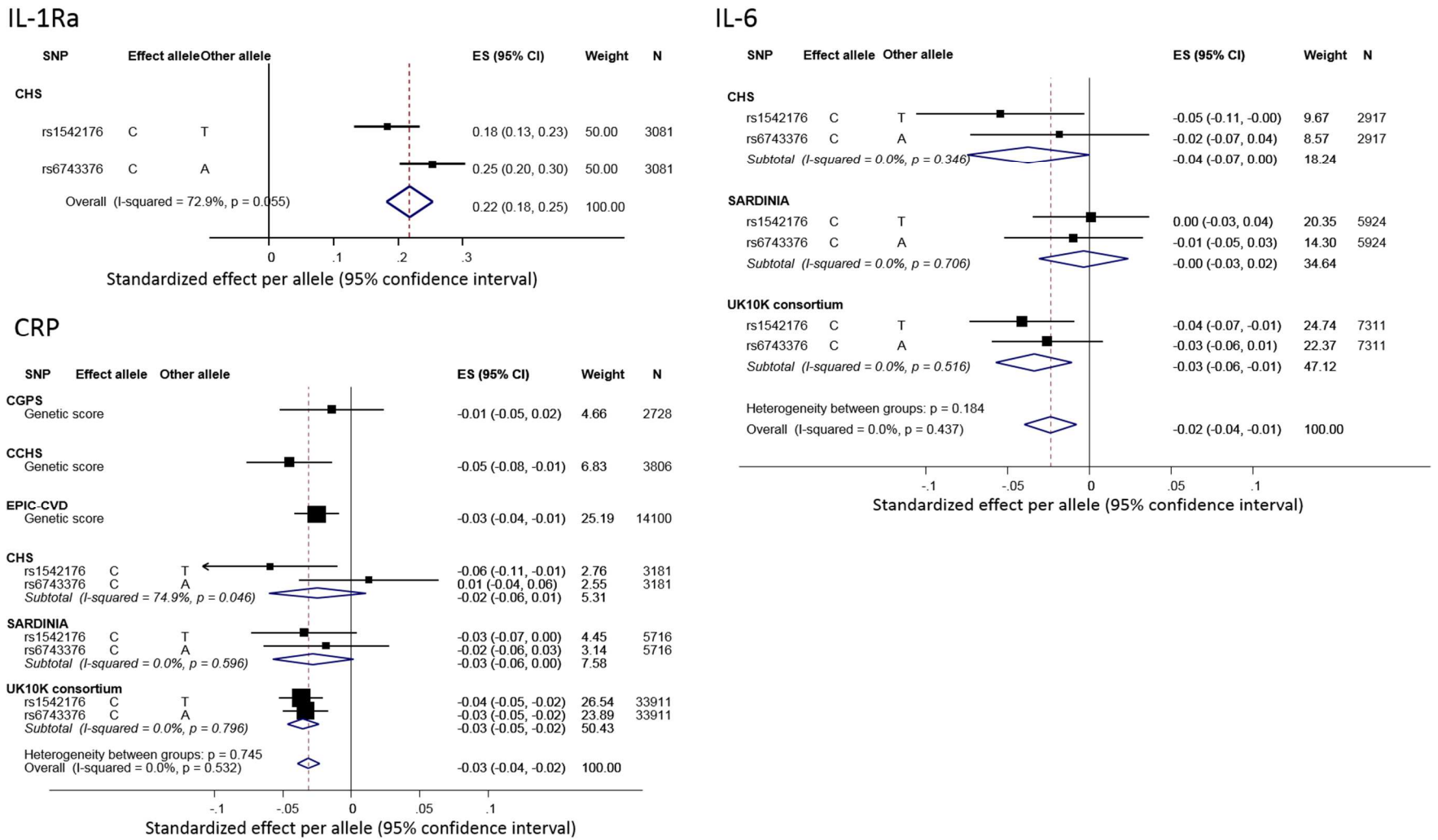
Details on studies identified through this systematic search are provided in **S-Tables 11 & 12.** Study level and meta-analysis results from the analysis of 75 or 100mg anakinra and inflammatory biomarkers are provided in **S-Figure 5**.

S-Figure 5: Effect of 75/100 mg dose of anakinra on inflammation biomarkers in clinical trials



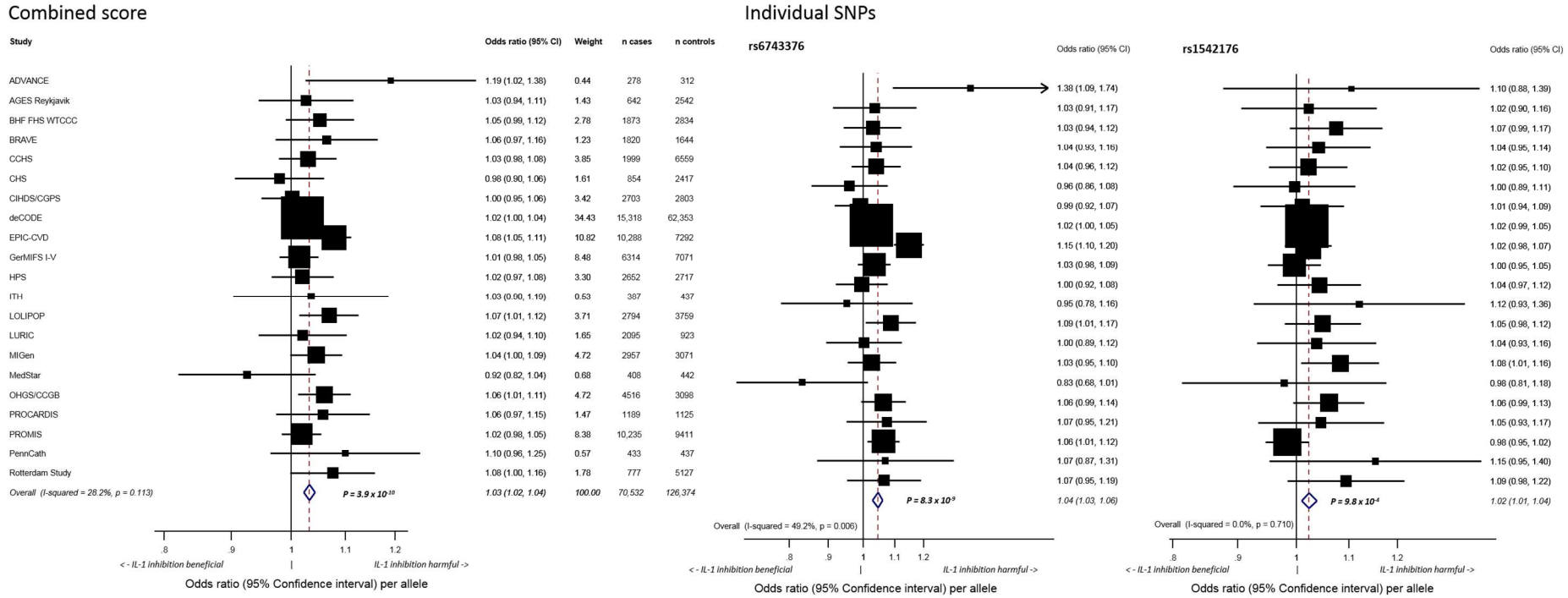
Blue diamonds reflect combined estimate from fixed effects inverse variance weighted meta-analysis. The combined estimates correspond to those in **Figure 2**. The corresponding study level characteristics are provided in **S-Table 11**.

S-Figure 6: Individual and combined associations of the genetic score with inflammation biomarkers



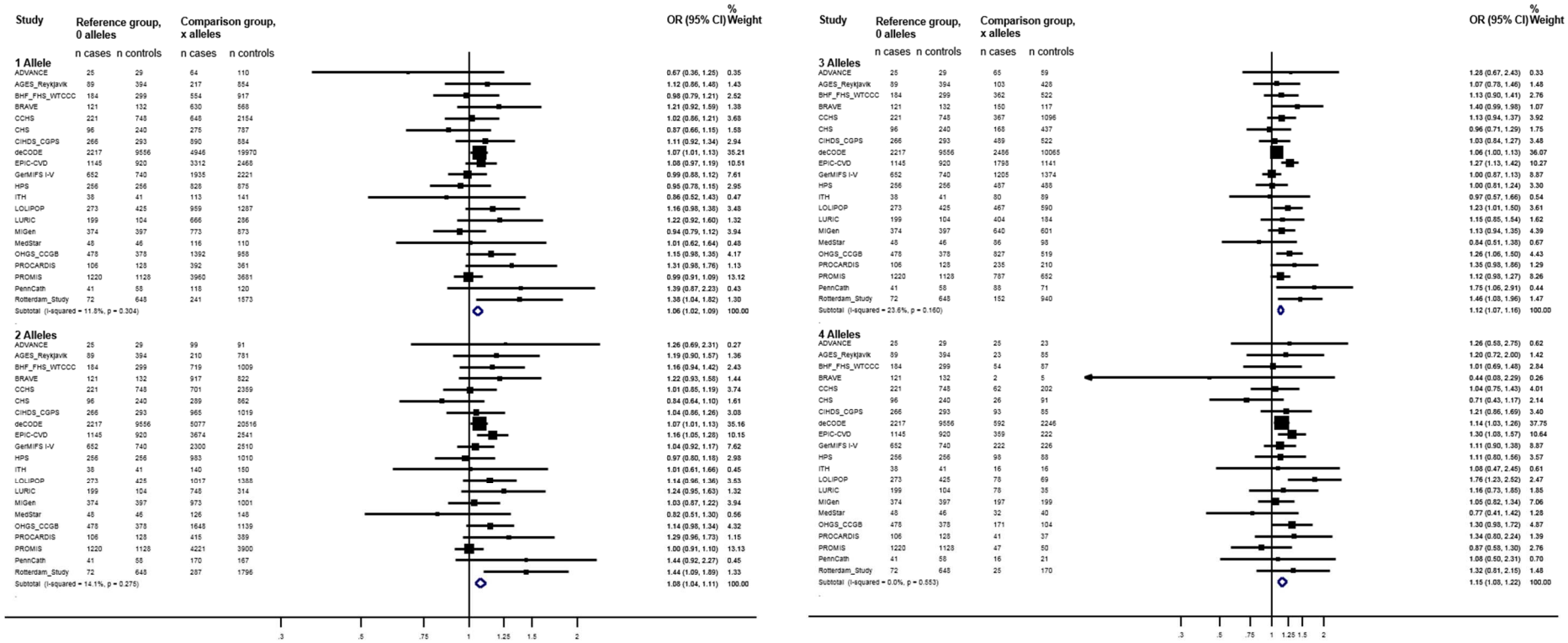
Blue diamonds reflect combined estimate from fixed effects inverse variance weighted meta-analysis. The combined estimates correspond to those in **Figure 2**. The corresponding study details are provided in **Table 1**, **S-Table 2** and **S-Table 7**.

S-Figure 7: Individual and combined associations of the genetic score and individual SNPs with coronary disease risk using allele count data



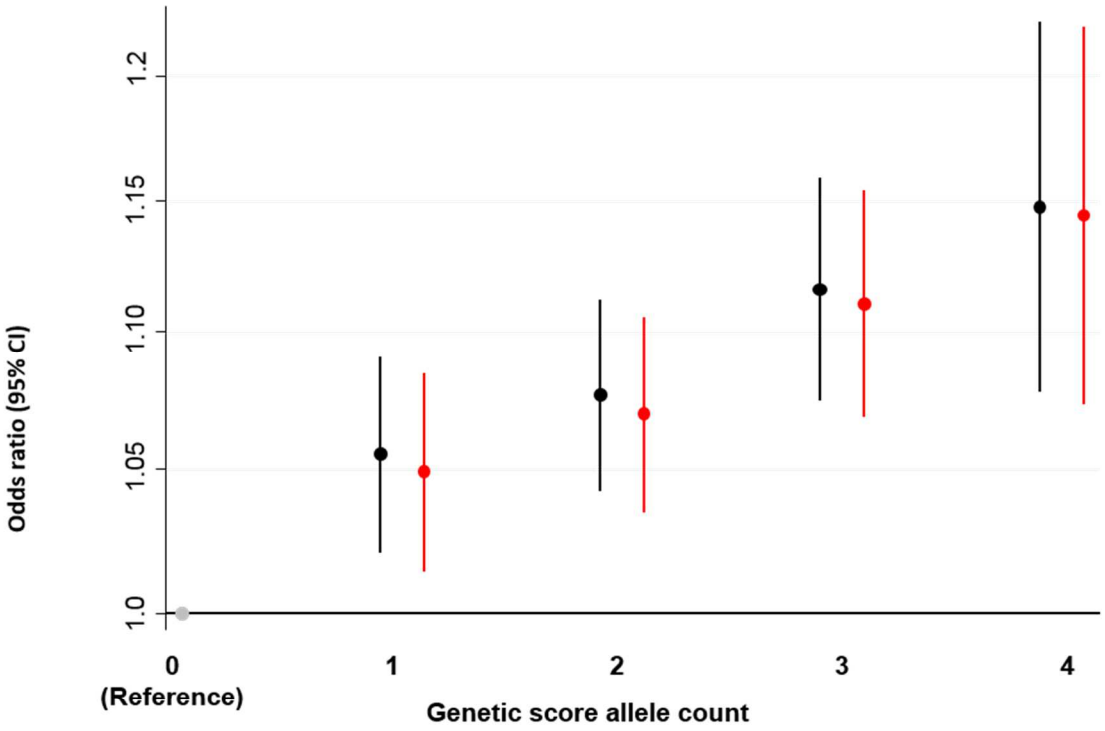
Blue diamonds reflect combined estimate from fixed effects inverse variance weighted meta-analysis. The overall estimate for the combined score analysis corresponds to the estimate provided for CHD in **Figure 3**. Analyses are based on tabular data on allele counts, using a per allele model. For rs6743376, between study heterogeneity is reduced considerably upon exclusion of the two small studies with the most extreme results (ADVANCE and MedStar, I^2=37.4%, P=0.05), while the overall results remained unchanged (OR=1.04, 95% CI: 1.03-1.06). Details of the contributing studies are provided in **S-Table 9**.

S-Figure 8: Relationship of the genetic score allele count with risk of CHD - individual study estimates



Blue diamonds reflect combined estimate from fixed effects inverse variance weighted meta-analysis. The overall estimate for each score category (1-4) corresponds to the estimates plotted in **Figure 4**. Details on studies contributing allele count data are provided in **S-Table 9.**

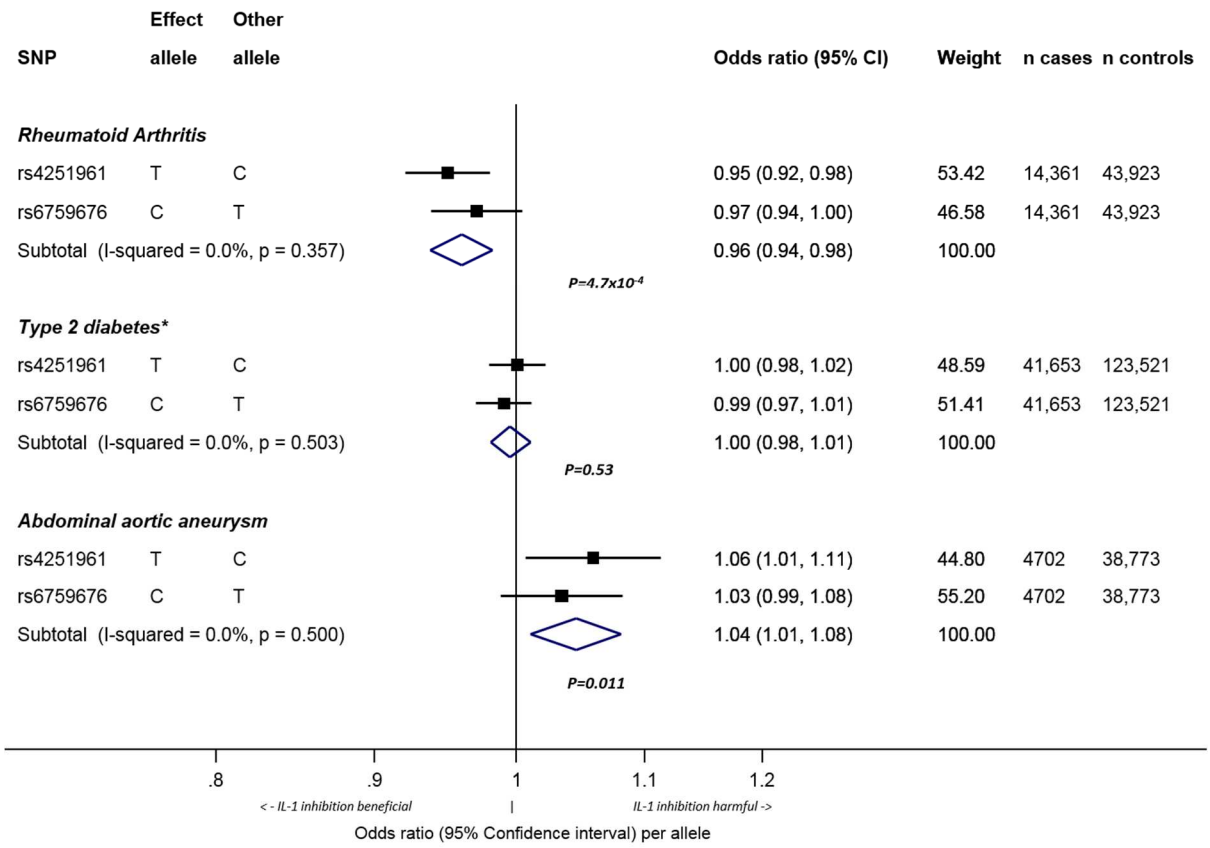
S-Figure 9: Relationship of the genetic score allele count by type of CHD



All endpoints ●					
n cases	8121	23,029	25,679	11,446	2257
n controls	16,960	41,198	43,912	20,203	4101
"Hard" CHD endpoints only ●					
n cases	7850	22,122	24,644	10,890	2154
n controls	16,208	39,339	41,802	19,079	3896

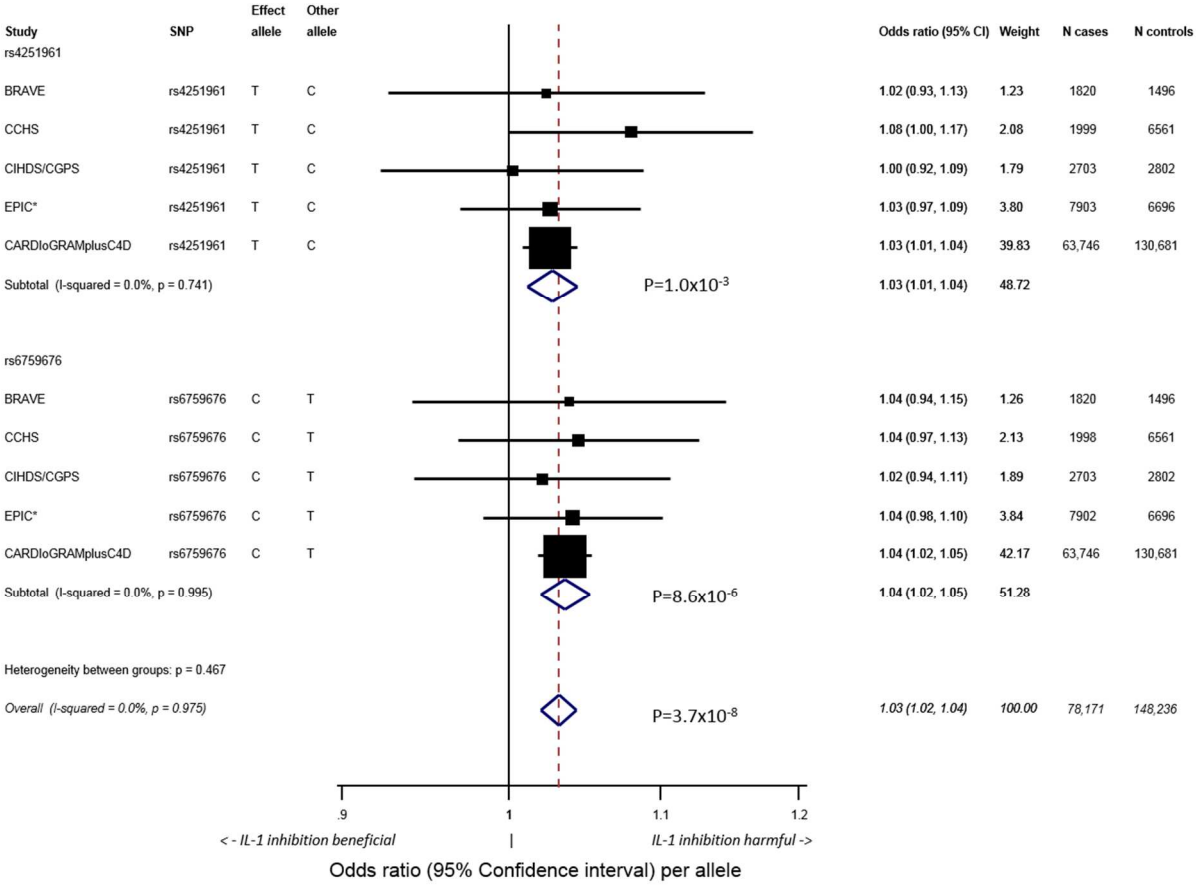
Details on studies contributing allele count data are provided in **S-Table 9**. Individual study estimates of the "all endpoints" analysis are provided in **S-Figure 8**. "Hard" CHD endpoints refer to studies that included predominantly CHD endpoints defined as myocardial infarction and other major acute coronary events. This analysis omitted results from studies that predominantly involved CHD endpoints defined by angiographic coronary stenosis.

S-Figure 10 Associations with rheumatoid arthritis, type 2 diabetes and abdominal aortic aneurysm of variants in alternative genetic score



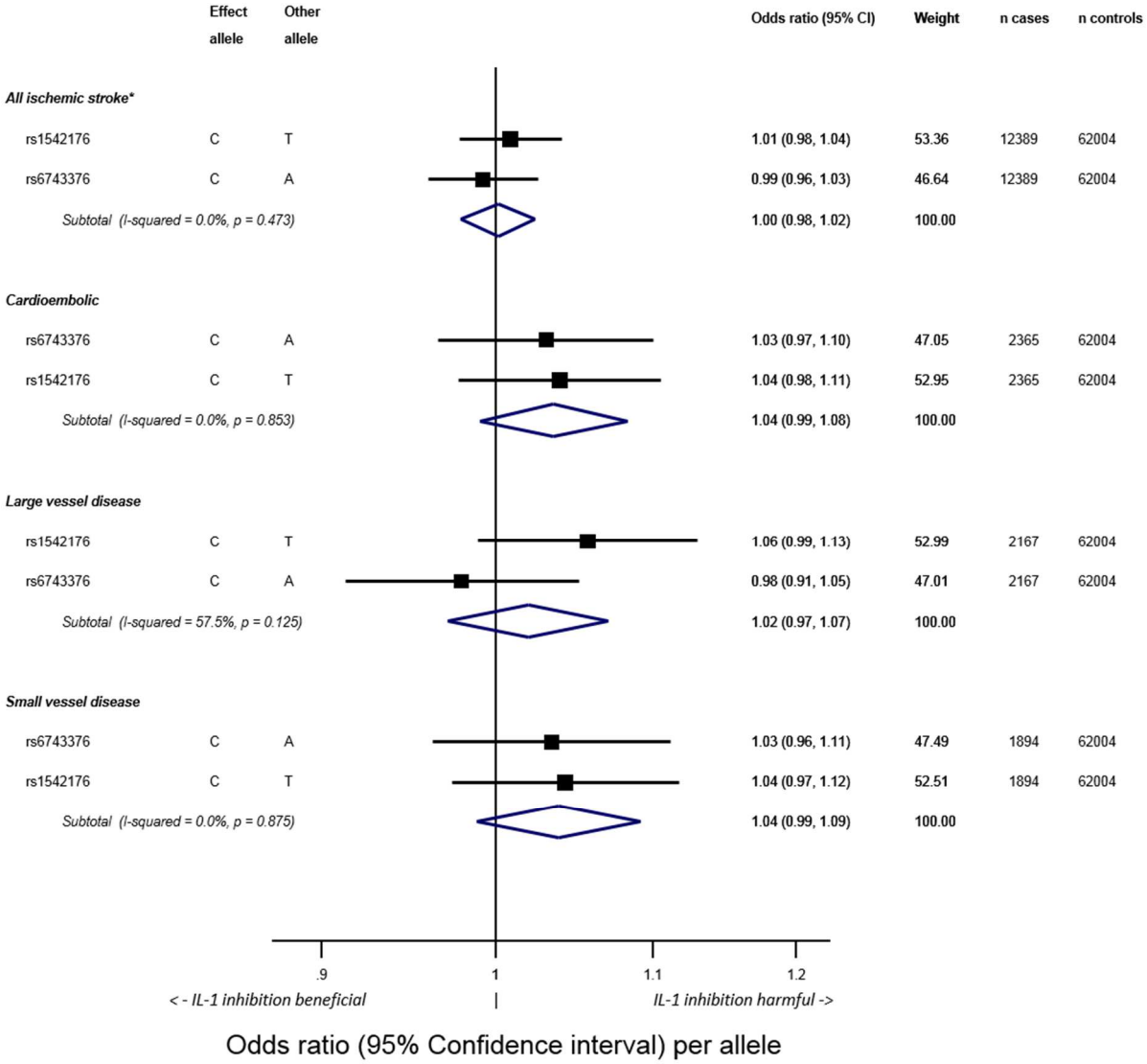
The alleles rs4251961[T] and rs6759676[C] are associated with higher IL-1Ra levels[4].
* Since the two SNPs are on the CardioMetabo array, the Type 2 diabetes analysis could capitalise on a bigger sample size than the primary score analyses.

S-Figure 11: Associations with CHD of variants in alternative genetic score



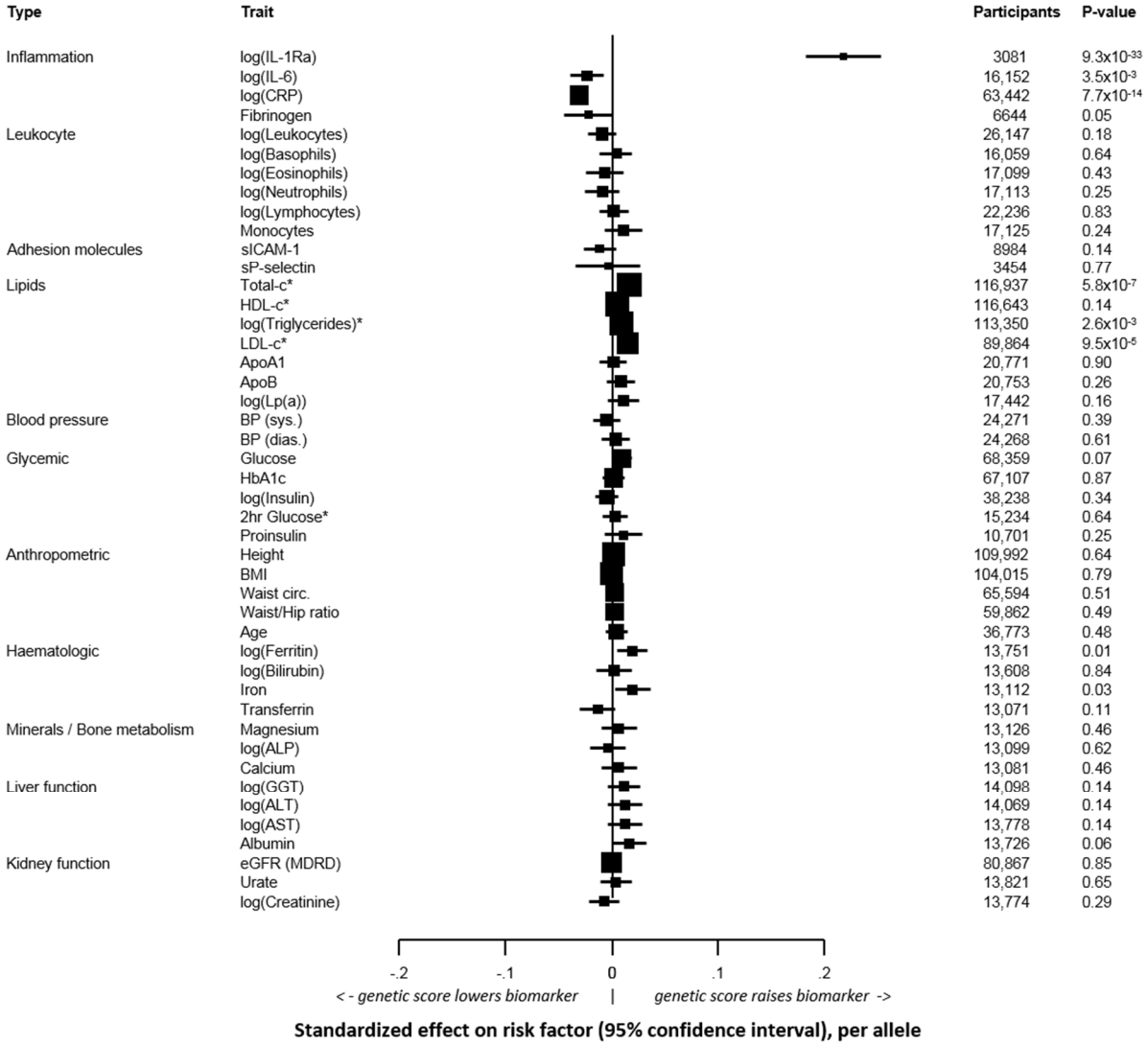
The alleles rs4251961[T] and rs6759676[C] are associated with higher IL-1Ra levels[4]. Individuals from the PROMIS study are included in the CARDIoGRAMplusC4D consortium. *Individuals from EPIC Norfolk have been excluded, due to overlap with CARDIoGRAMplusC4D. Since the two SNPs are on the CardioMetabo array, the Type 2 diabetes analysis could capitalise on a bigger sample size than the primary score analyses.

S-Figure 12: Individual and combined SNP associations with ischaemic stroke subtypes



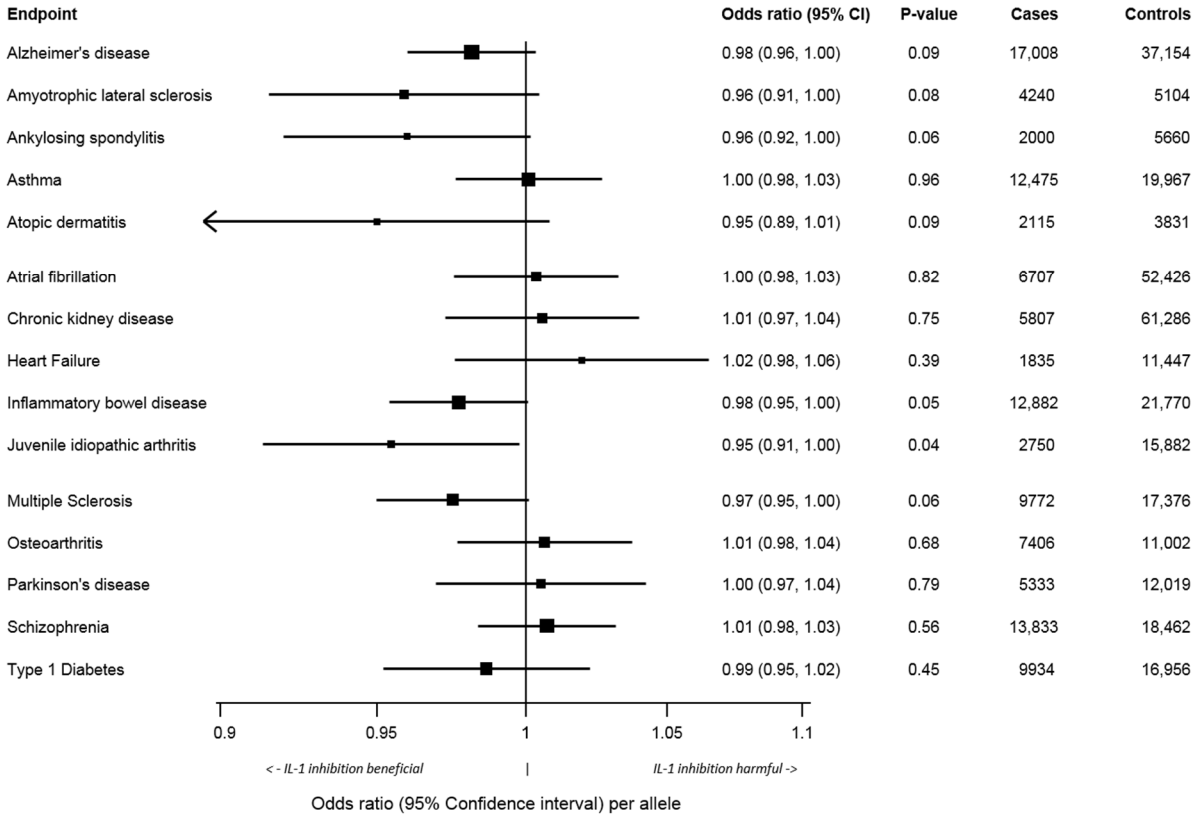
* As stroke subtyping information was not available for all ischaemic stroke cases, the numbers of cases in the subtotals do not sum to equal the grand total of cases. Further details have been provided in **S-Tables 5 & 7.**

S-Figure 13: Exploratory analysis of the genetic score with a range of cardiometabolic risk factors and biomarkers



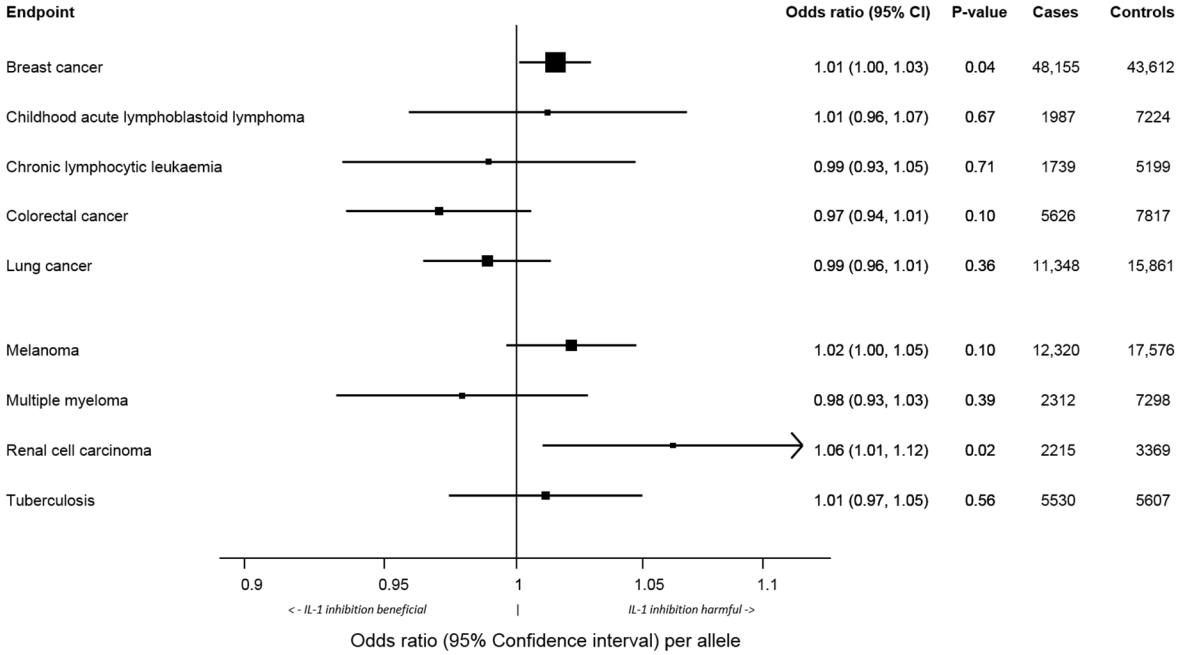
To enable comparison of the magnitude of associations across several different markers analyses were undertaken with standardised units of measurement for each marker. Associations are presented as per allele change in the biomarker expressed as standard deviations. Box sizes reflect number of participants contributing to analyses. * contributing data include in part data on rs6761276[T] as proxy for rs6743376[C]. These analyses include data from studies with participant level data (**S-Table 2**) as well as summary data from consortia (**S-Table 8**).

S-Figure 14: Exploratory analysis of the genetic score with selected additional disease endpoints.



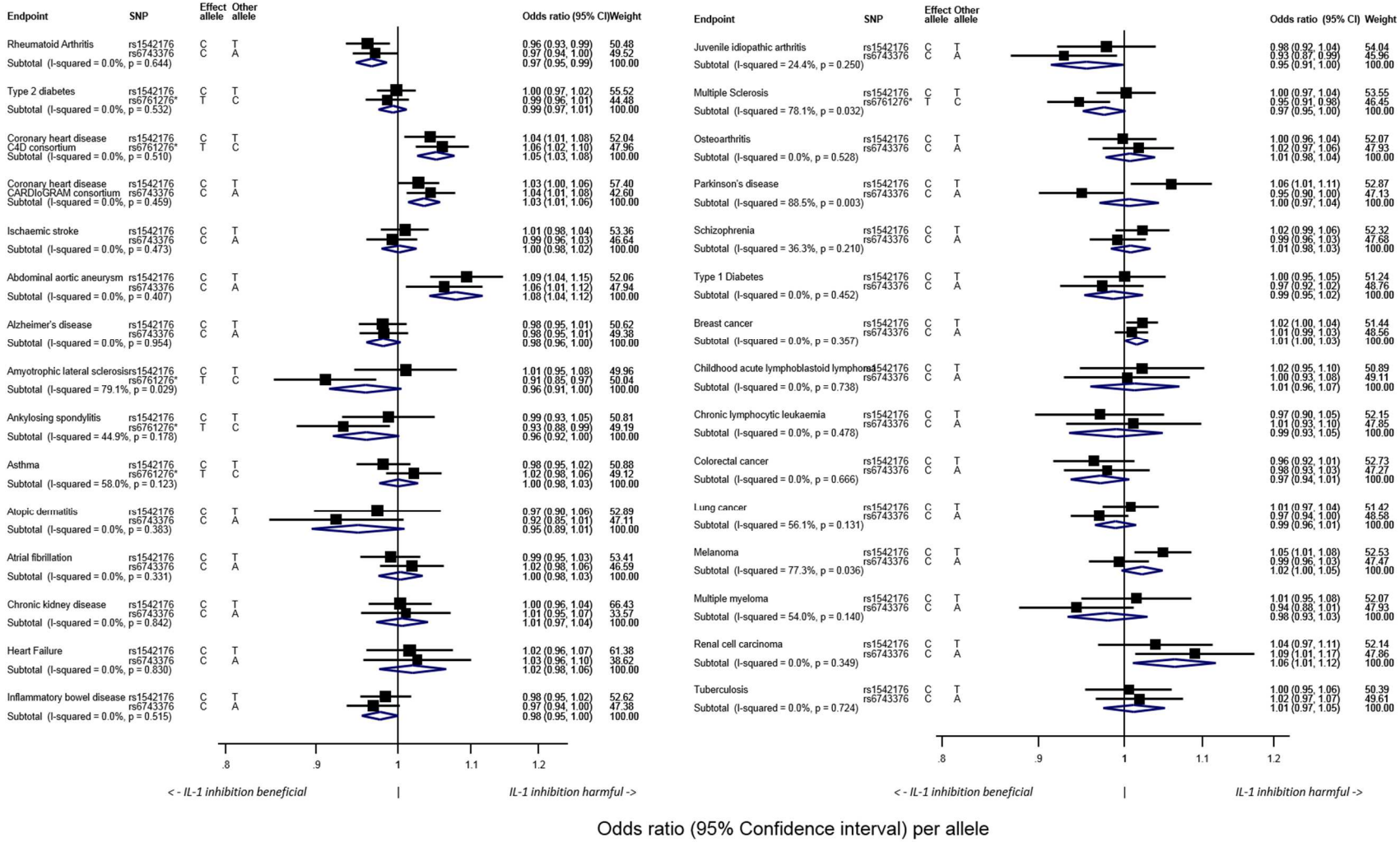
Box sizes reflect number of cases contributing to analyses. * contributing data include rs6761276[T] as proxy for rs6743376[C]. Endpoint definitions have been provided in **S-Table 6**, and further details on methods in **S-Table 8**. Individual SNP results and meta-analysis are provided in **S-Figure 16**.

S-Figure 15: Exploratory analysis of the genetic score with disease endpoints potentially relevant to safety of IL-1 inhibition.



Box sizes reflect number of cases contributing to analyses. * contributing data include rs6761276[T] as proxy for rs6743376[C]. Endpoint definitions have been provided in **S-Table 6**, and further details on methods in **S-Table 8**. Individual SNP results and meta-analysis are provided in **S-Figure 16**.

S-Figure 16: Individual and combined SNP – disease endpoint associations



*rs6761276[T] tags rs6743376[C], r^2=0.69, D'=1.0 and is the second strongest SNP for association with IL-1Ra levels. Blue diamonds reflect combined score estimate, derived from inverse variance weighted fixed-effect meta-analysis of individual SNP estimates. The combined score estimates correspond to those provided for each endpoint in **S-Figures 14 & 15**. Endpoint definitions have been provided in **S-Tables 5 & 6**, and further details on methods in **S-Tables 7 & 8**.

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