The interplay between inflammatory cytokines and cardiometabolic disease: evidence from Mendelian randomization

Supplementary information

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Supplementary Methods

Genome-wide association study cohorts

Northern Finland Birth Cohort 1966

Northern Finland Birth Cohort 1966 (NFBC1966) recruited pregnant women with expected date of delivery between 1st January and 31st December 1966[1]. Overall, 12,055 mothers (over 96% of eligible women) were followed from pregnancy onwards, with 12,058 live-born children in the cohort. In the offspring 31-year data collection in 1997, all cohort members with known addresses in either the Northern Finland or Helsinki area were invited to a clinical examination[2]. In total, data were received for 6033 participants, and DNA was successfully extracted for 5753 participants from fasted blood samples. Cytokines were quantified from overnight fasting plasma samples using Bio-Rad's Bio-Plex 200 system (Bio-Rad Laboratories, California, USA) with Milliplex Human Chemokine/Cytokine and CVD/Cytokine kits (Cat# HCYTOMAG-60K-12 and Cat# SPR349; Millipore, St Charles, Missouri, USA) and Bio-Plex Manager Software V.4.3 as previously described[3,4]. Genotyping was conducted using Illumina HumanCNV-370DUO Analysis BeadChip (Illumina, California, USA) and imputed using Haplotype Reference Consortium imputation reference panel.

The Cardiovascular Risk in Young Finns Study

The Cardiovascular Risk in Young Finns (YFS) is an ongoing follow-up study of 3,596 children and adolescents aged 3, 6, 9, 12, 15, or 18 years. The subjects were randomly

chosen from five university cities and their rural surroundings using Finnish population register. The baseline survey was held in 1980 and subsequent follow-up visits involving all five centres have been arranged in 1983, 1986, 1989, 2001, 2007, 2011 and 2017. The latest follow-up included also children and parents of the original participants.

Genotyping have been performed using the blood samples drawn at 2001 follow-up visit. Genotyping was performed with custom-build Illumina 670K array. The custom content replaced some poor performing SNPs on the Human610 BeadChip and added more CNV content after which the customized chip shared 562,643 SNPs with Illumina Human610 chip. Genotyping was performed for 2,556 samples. Prior to imputation, samples and probes with high missingness were excluded (missingness-per-individual > 0.05 and missingness-per-variant > 0.05). To exclude poorly functioning probes, we excluded SNPs deviating from Hardy-Weinberg equilibrium (HWE p-value < 1×10^{-6}). To exclude related samples, we used $\hat{\pi}$ cut-off of 0.20. The pair with greater missingness was removed. After the QC steps, the data set included 2,443 individuals and 546,674 probes. The imputation was performed with IMPUTE2 software by using 1000 Genomes Phase 3 release as reference panel. After imputation, poorly imputed and rare variants (INFO < 0.7 and MAC < 3) were removed.

Biorad's Bio-Plex Pro Human Cytokine 27-plex Assay and 21-plex Assay were used to quantify circulating concentrations of 48 cytokines from serum samples drawn at 2007 follow-up visit as previously described[5]. Depending on the cytokine, imputed genotypes and cytokine concentrations were available for 116-2019 samples.

FINRISK

FINRISK surveys are population-based cross-sectional studies which began in 1972. A new sample is recruited every five years to monitor the health status of Finnish population. Subset of individual-level data from 1992-2012 surveys is available through THL Biobank. Cytokine quantification for FINRISK1997 and FINRISK2002 samples was performed similarly as in YFS, but quantification was done using EDTA plasma in FINRISK1997 and heparin plasma in FINRISK2002[6]. In FINRISK1997, a custom 20-plex array was used in cytokine quantification. In FINRISK2002, only participants between 51 and 74 years were selected for the analysis. Imputation was performed using 1000 Genomes Phase 3 as reference panel. Poorly imputed variants (INFO < 0.7) and variants with low minor allele count (MAC < 3) were excluded. Depending on the cytokine, imputed genotypes and cytokine concentrations were available for 3440-4613 samples from FINRISK1997 and 843-1705 samples from FINRISK2002.

Cytokine genome-wide association study

We conducted GWAS for 41 cytokines in FINRISK+YFS population and for 16 cytokines in NFBC1966 (Supplementary Table 6)[7]. The data pre-processing and transformations were done in a similar manner to previous GWAS analyses[7,8]. Inverse-normal rank transformation was first applied to the traits, before regressing the transformed measures on age, sex and the first 10 genetic principal components. In contrast to the previous analyses[7,8], we did not add body mass index (BMI) as a covariate, as this could potentially introduce collider bias into consequent MR analyses[9]. The inverse-normal rank transformation was again applied to the residuals of this regression, and these transformed residual estimates were used as response variables in the GWAS.

The GWAS was conducted in each study using an additive genetic model with SNPTEST2 software[10]. The results for variants which showed poor imputation quality (model info < 0.7) or low minor allele frequency (MAF, < 0.05) were discarded. For the ten cytokines available in both NFBC1966 and FINRISK+YFS (Supplementary Table 6), the summary statistics were pooled by inverse variance weighted fixed-effects meta-analysis using Metal software[11].

Genetic associations and instrument selection for cardiometabolic traits

The metabolic traits considered were: coronary artery disease, stroke, type 2 diabetes mellitus, BMI, waist circumference, waist-hip-ratio, systolic blood pressure, glycated haemoglobin, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, total cholesterol, triglycerides, C-reactive protein, glucose, fasting insulin and lifetime smoking. Genetic association estimates for these traits were obtained from large GWAS of mainly European ancestry participants[12–22] (Supplementary Table 2). We used GWAS summary statistics that were unadjusted for other heritable phenotypes to avoid potential collider bias in MR[9]. Single-nucleotide polymorphisms (SNPs) that associated with the corresponding trait at $P < 5\times10^{-8}$ and were independent ($r^2 < 0.001$) were chosen as instruments to proxy the exposure. For fasting insulin, we relaxed the selection threshold to $P < 1\times10^{-6}$ in order to have at least one instrument available. Clumping was performed using the TwoSampleMR package in R[23]. In clumping, a variant with the lowest p-value is detected within a specific genomic window, and any variants with r^2 above the pre-specified threshold with the lead variant are excluded. This procedure is iteratively

repeated for any other remaining variants, also excluding the lead variant from the previous iteration. The final list of instruments consists of the lead variants for each iteration. We used the window size of 10,000 kilobase pairs, which is the default value in ld_clump() function. To protect against potential reverse causation, any variants from within ±500 kb of the coding gene of the considered outcome cytokine were excluded.

Cytokine instrument selection

We further incorporated information from publicly available genetic associations to improve the instruments for cytokines in MR. These instruments are *a priori* biologically plausible, merging association summary statistics from two other pQTL sources, as well as eQTL data.

We sought GWAS summary statistics from INTERVAL[24] and SCALLOP[25] consortia for the same cytokines that were analysed in our current work. We first tested whether the genetic associations were comparable between our work, INTERVAL, and SCALLOP consortia considering the different measurement methods. Specifically, for each cytokine, we examined the correlation between the beta estimates between our work and INTERVAL study and between our work and SCALLOP consortium based on the SNPs associated with the cytokine at P-value$<10^{-5}$ and $r^2<0.1$. For 11 cytokines which beta estimates were correlated (regression coefficient P-value < 0.1 of regressing the beta estimates of the current study on the beta estimates of a previous study), we calibrated the beta estimates of the INTERVAL (3 cytokines) and SCALLOP (8 cytokines) consortium to match with the beta estimates from the current studies and performed the meta-analyses. For the rest of the cytokines, we used summary statistics from the GWAS with

the largest sample size (the current studies (26 cytokines), the INTERVAL study (2 cytokines), and SCALLOP consortium (8 cytokines); Supplementary Table 3).

Gene expression GWAS summary statistics were obtained from the Genotype-Tissue Expression (GTEx) project (release version 8), and related to 15,201 samples from a multi-ethnic group of 838 individuals[26]. Results from 49 tissues were pooled using fixed-effects meta-analysis to produce cross-tissue estimates of association with gene expression. To validate the relevance of the cross-tissue *cis*-eQTL instruments, we examined the correlation of the expression Z-scores of the *cis*-eQTL variants with the Z-scores in blood from eQTLGen consortium[27].

Two distinct instrument selection criteria were used to identify variants to proxy the effect of circulating cytokine levels in MR analyses. Firstly, variants located within ±500 kb of the gene locus corresponding to a cytokine under study that also related to circulating levels of that cytokine with association *P*-value < 1×10^{-4} were selected. These are referred to as *cis*-pQTL. Secondly, variants located within ±500 kb of the gene locus corresponding to a cytokine under study that related to both expression of that gene at $P < 1\times10^{-4}$ and circulating levels of that cytokine at $P < 0.05$ were selected. These are referred to as *cis*-eQTL. The gene locations were extracted per human genome build 19 (released February 2009) using UCSC Genome Browser (accessed on 18th June 2019) [28]. As we only considered variants from within a biologically relevant genomic locus, we did not use the conventional threshold of $P < 5\times10^{-8}$ (which is usually applied when instruments are selected across the full genome) in our main analysis.

Only variants for which both exposure and outcome genetic association estimates were available for any given MR analysis were considered as potential instruments for that analysis. All variants were clumped to a pairwise linkage disequilibrium threshold of r^2<0.1 using the TwoSampleMR package in R[23]. The F statistic was calculated as a measure of the strength of the instruments[29]. To protect from potential weak instrument bias, we only used variants with F>10 as instruments[30,31]. As a supplementary analysis, we also report the results considering cytokines as exposures and cardiometabolic traits as outcomes, when selecting the instruments at $P < 5\times10^{-8}$ across the full genome from the GWAS summary statistics of the three Finnish cohorts, clumping at $r^2 < 0.001$.

Mendelian randomization

The ratio method was used to obtain MR estimates, with first order weights used to generate standard errors[32]. Where more than one instrument variant was available for a given analysis, MR estimates obtained from different instruments were pooled using the multiplicative random-effects inverse-variance weighted (IVW) MR method. MR is prone to bias when the genetic variants used as instruments affect the outcome through some pathway that is independent of the exposure under consideration, a phenomenon termed pleiotropy[33]. To explore the possibility of the MR results being driven by such pleiotropic effects, MR methods that make distinct assumptions on the inclusion of pleiotropic variants were performed in sensitivity analyses where three or more instrument variants were available. Specifically, the weighted median, MR-Egger and MR-PRESSO methods were used[34,35]. The weighted median approach orders the MR estimates produced by each instrument by their magnitude weighted for their precision and produces an overall MR estimate based on the median value, with standard error

estimated by bootstrapping[34]. It is a consistent approach when more than half of the weight for the analysis is derived from valid instruments[34]. MR-Egger regresses the variant-outcome associations on the variant-exposure associations, weighted by the precision of the variant-outcome association estimates. The regression slope represents the MR estimate, and presence of directional pleiotropy can be assessed by testing whether the intercept differs from zero[36]. MR-Egger assumes that any pleiotropic effects of the genetic variants are uncorrelated with the variant-exposure associations, and the method may be biased due to outliers[37]. Therefore, we report MR-Egger results only for exposures with ≥10 variants available as instruments. The MR-PRESSO detects outliers using the squared residuals from the regression of the variant-outcome association estimates on the variant-exposure association estimates with the intercept fixed to zero, and repeats such regression-based MR analysis after excluding any identified outlier variants[35].

We accounted for multiple testing by applying a Bonferroni correction for the number of outcomes, resulting to $P<0.05/47 = 0.0011$ when cytokines were considered as outcomes, and $P<0.05/15 = 0.0033$ when considering the cardiometabolic traits as outcomes. The lenient approach to multiple testing correction was taken as the MR results were further validated in colocalization analysis, detailed below. The MR sensitivity analyses were only performed to explore the robustness of the main IVW analysis to potential pleiotropy and as such no multiple testing correction was applied for these.

Colocalization

The colocalization analysis method 'coloc' proposed by Giambartolomei et al.[38] as applied here investigates whether the data are consistent with a shared variant influencing both exposure and outcome trait. Under the assumption of a maximum of one causal variant per each trait within a genomic locus, the alternative hypotheses are:

H_0: No causal variants in the locus.

H_1: A causal variant on the exposure only.

H_2: A causal variant on the outcome only.

H_3: Distinct causal variants on exposure and outcome.

H_4: A shared causal variant on exposure and outcome.

Given data $D = \left(\hat{\beta}_j \ \mathrm{SE}\left(\hat{\beta}_j\right)\right), j = 1, \ldots, m$ for m variants from GWAS summary statistics, and prior probabilities p_1 for a variant being causal for the exposure, p_2 for a variant being causal for the outcome, and p_{12} for a variant being causal for both exposure and outcome, we can compute the posterior probabilities (PP) for all hypotheses. Specifically, the PP for a shared causal variant ($\mathrm{PP}_{\mathrm{shared}}$) is:

$$PP_{\mathrm{shared}} = P(H_4|D) = \frac{P(H_4|D)/P(H_0|D)}{1 + \sum_{k=1}^{4}\left(P(H_k|D)/P(H_0|D)\right)}$$

And the PP for distinct causal variants ($\mathrm{PP}_{\mathrm{distinct}}$) is:

$$PP_{\mathrm{distinct}} = P(H_3|D) = \frac{P(H_3|D)/P(H_0|D)}{1 + \sum_{k=1}^{4}\left(P(H_k|D)/P(H_0|D)\right)}.$$

In the above equations,

$$\frac{P(H_1|D)}{P(H_0|D)} = p_1 \times \sum_j ABF_j^{(1)} \qquad \frac{P(H_2|D)}{P(H_0|D)} = p_2 \times \sum_j ABF_j^{(2)}$$
$$\frac{P(H_3|D)}{P(H_0|D)} = p_1 p_2 \times \sum_{j \neq k} ABF_j^{(1)} ABF_k^{(2)} \quad \frac{P(H_4|D)}{P(H_0|D)} = p_{12} \times \sum_j ABF_j^{(1)} ABF_j^{(2)},$$

and *ABF* is the Approximate Bayes Factor[39]:

$$ABF = \sqrt{\frac{\mathrm{SE}(\hat{\beta})^2 + W}{\mathrm{SE}(\hat{\beta})^2}} \exp\{ -\frac{1}{2}\left(\frac{\hat{\beta}}{\mathrm{SE}(\hat{\beta})}\right)^2 \frac{W}{\mathrm{SE}(\hat{\beta}) + W}\}, \ \hat{\beta} \sim N(0, W),$$

where *W* is the prior variance for causal effect sizes, set here as $0.15 \times \mathrm{sd}(X)$ for continuous traits and 0.2 for binary traits (the default values used in coloc).

In colocalization, we are particularly interested in PP_{shared}. We only considered the gene region for the exposure cytokine for exposure-outcome pairs with MR evidence, and thus a high PP_{shared} would provide supporting evidence to our MR results. In contrast, a high $PP_{distinct}$ would imply that the MR results were confounded by LD, that is, the MR evidence of association is caused purely by LD between two distinct variants, one influencing the exposure, and the other influencing the outcome.

Colocalization may suffer from reduced power if the association with the outcome is weak, which is commonly the case when colocalization is done as a sensitivity analysis following MR. Additionally, when colocalization is conducted to examine the possibility of confounding by LD, already in the presence of MR evidence, it is of relevance to examine the probability of a shared causal variant conditioned on there being a causal

variant for both traits. Therefore, we defined colocalization as being present when (i) $PP_{shared} + PP_{distinct} > 0.5$ (to ensure sufficient power), and (ii) $PP_{shared} / (PP_{shared} + PP_{distinct}) > 0.5$ (to support that the posterior probability of a shared causal variant is greater than the posterior probability of distinct causal variants)[40].

We used the effect size estimates and their variances from the cytokine GWAS summary statistics, within ±500kb around the coding gene. The prior probabilities p_1, p_2 and p_{12} were all set at 10^{-4}.

Cytokine networks

To further visualize the clustering of the different cytokines based on the MR results, we applied network community structure algorithm for the cytokine-cytokine pairs that showed MR associations at $P<0.0011$. Briefly, without any prior information on the network structure, each node (cytokine) is initialized with a unique label, and the algorithm proceeds iteratively to label each node (cytokine) by majority voting in its neighborbood[41].

Evidence for causality

In examining the causality of circulating cytokine levels on cardiometabolic phenotypes, we merge the results from both MR and colocalization analyses for an overall summary. We infer *strong evidence for causality* as (i) MR association at $P<0.0033$ using either *cis*-pQTL or *cis*-eQTL instruments for the cytokine considered, with concordant effect size estimates if both types of instruments available, and (ii) colocalization ($PP_{shared} / (PP_{shared} + PP_{distinct}) > 0.5$) within the corresponding genomic locus of circulating protein levels and outcome.

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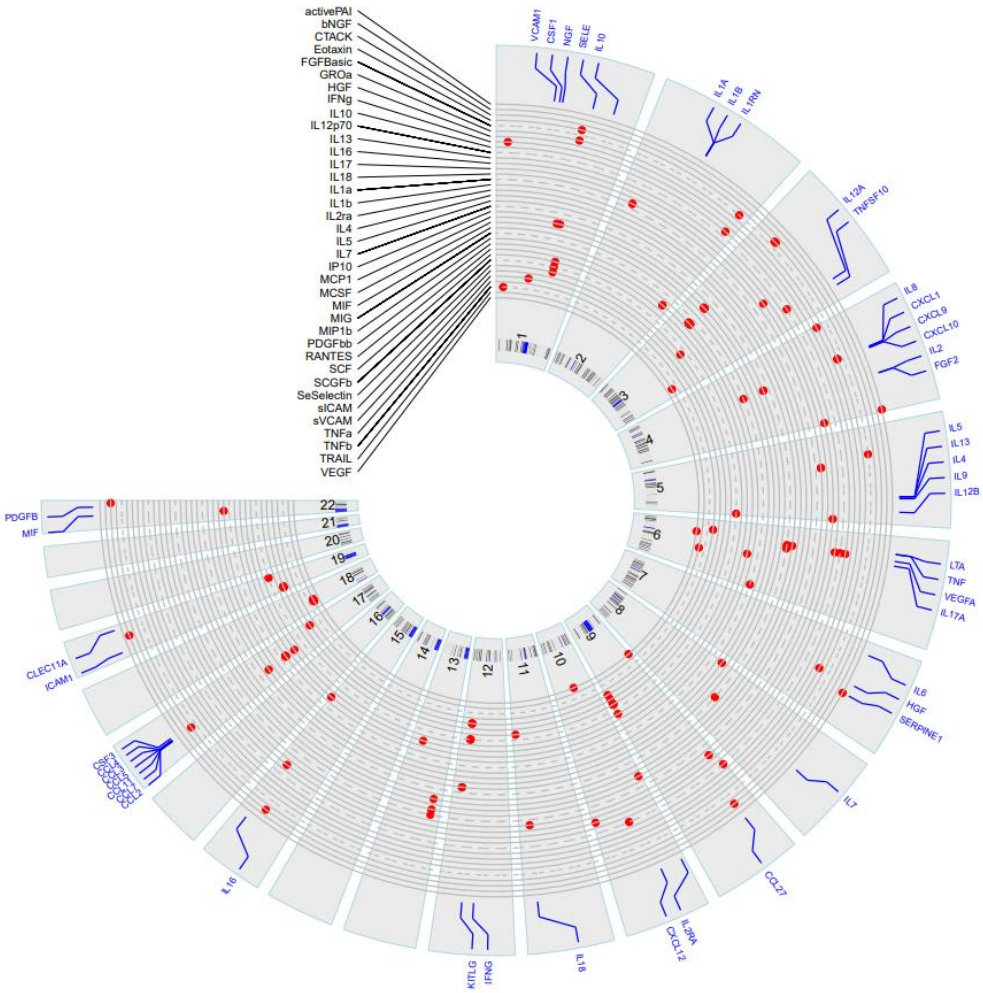
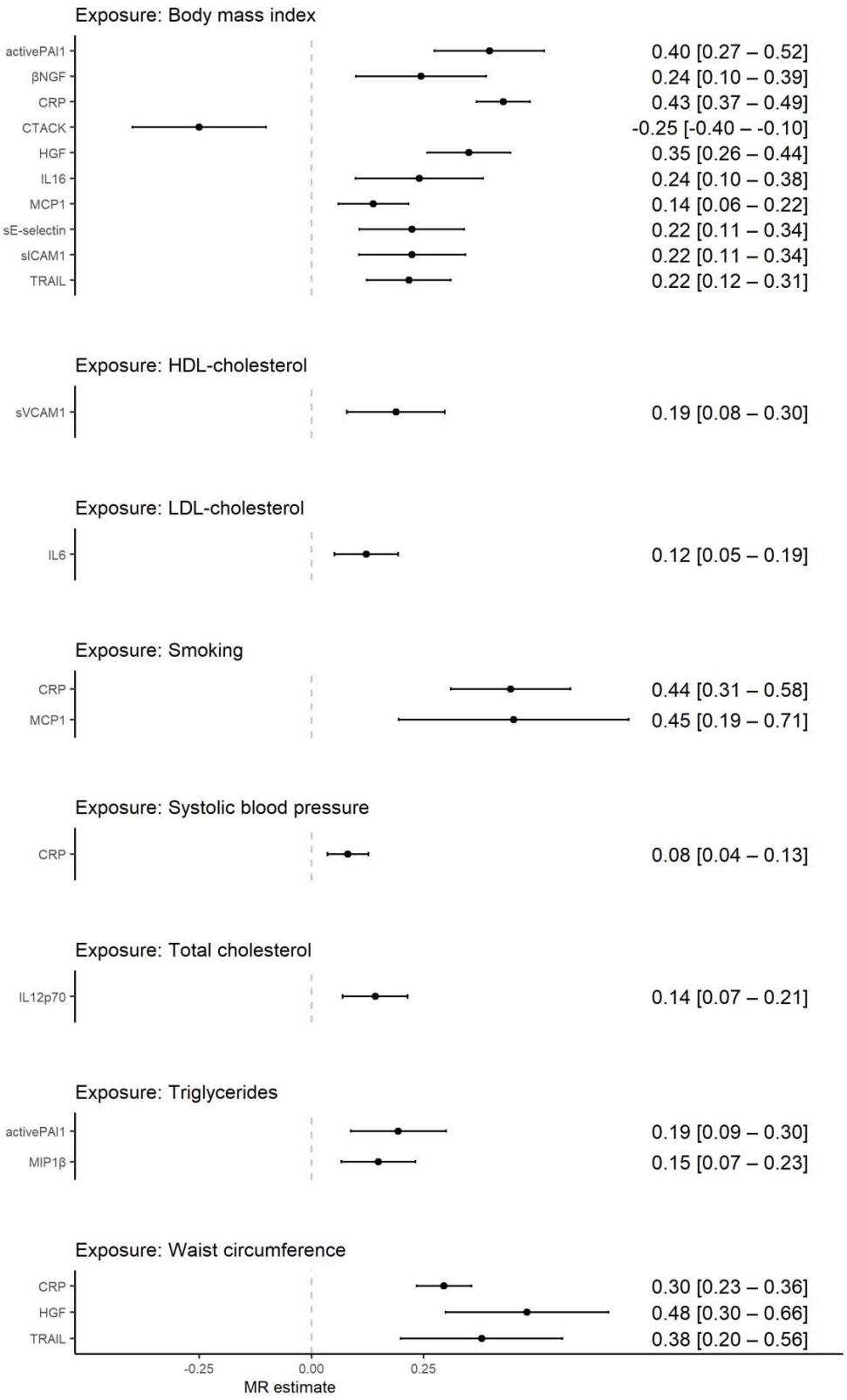


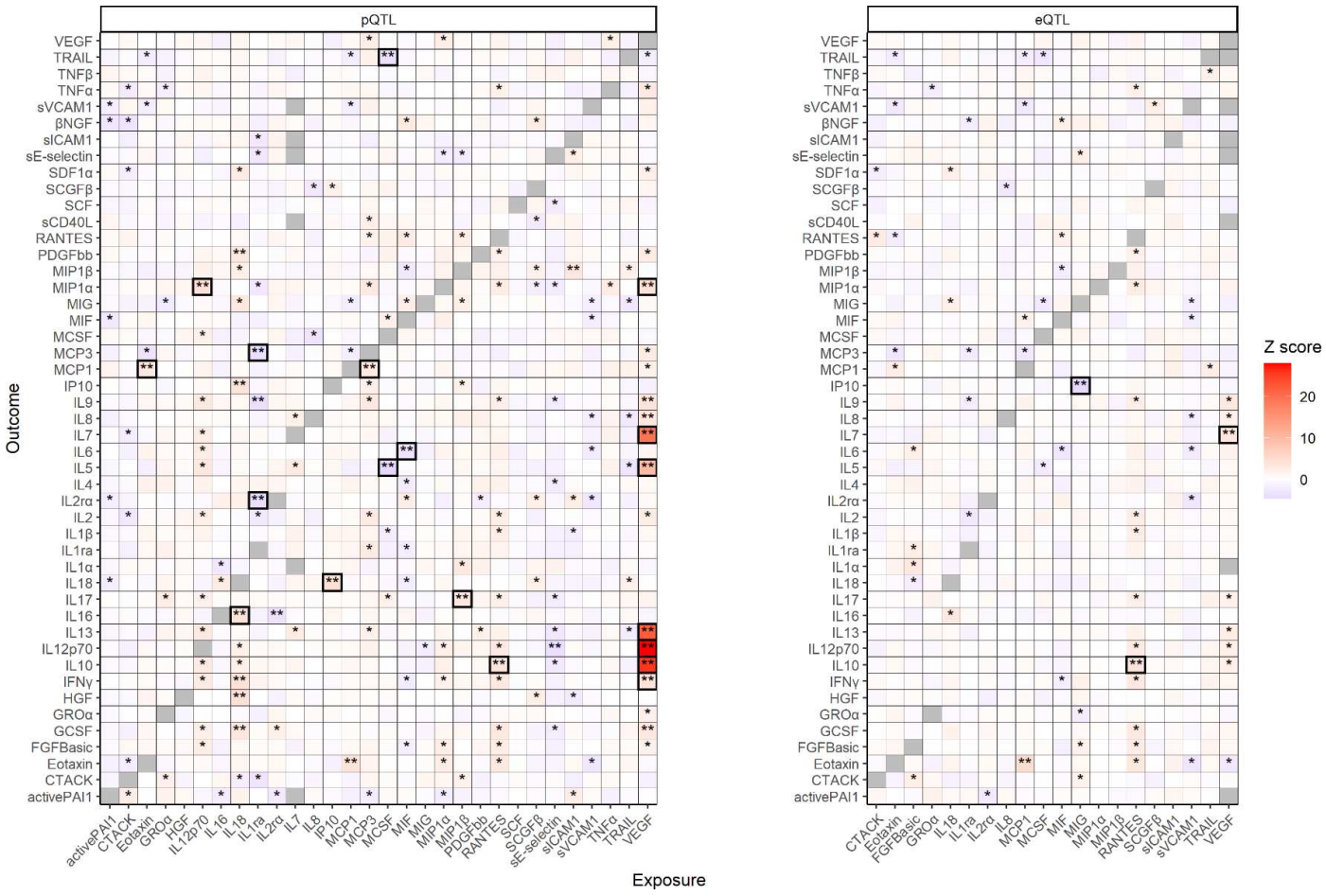
Supplementary Figure 1. Circos plot for the cytokine genome-wide association study results in the Finnish cohorts.

The red points indicate a variant-cytokine association of either $p<5\times10^{-8}$ anywhere in the genome, or $p<10^{-4}$ at the coding gene, pruned at ±500kb window. Cytokines with no such variants are omitted. The coding genes of the considered cytokines are given in the outer circle (see also Supplementary Table 3).


Exposure: Body mass index
activePAI1
βNGF
CRP
CTACK
HGF
IL16
MCP1
sE-selectin
sICAM1
TRAIL
0.40 [0.27 – 0.52]
0.24 [0.10 – 0.39]
0.43 [0.37 – 0.49]
-0.25 [-0.40 – -0.10]
0.35 [0.26 – 0.44]
0.24 [0.10 – 0.38]
0.14 [0.06 – 0.22]
0.22 [0.11 – 0.34]
0.22 [0.11 – 0.34]
0.22 [0.12 – 0.31]
Exposure: HDL-cholesterol
sVCAM1
0.19 [0.08 – 0.30]
Exposure: LDL-cholesterol
IL6
0.12 [0.05 – 0.19]
Exposure: Smoking
CRP
MCP1
0.44 [0.31 – 0.58]
0.45 [0.19 – 0.71]
Exposure: Systolic blood pressure
CRP
0.08 [0.04 – 0.13]
Exposure: Total cholesterol
IL12p70
0.14 [0.07 – 0.21]
Exposure: Triglycerides
activePAI1
MIP1β
0.19 [0.09 – 0.30]
0.15 [0.07 – 0.23]
Exposure: Waist circumference
CRP
HGF
TRAIL
0.30 [0.23 – 0.36]
0.48 [0.30 – 0.66]
0.38 [0.20 – 0.56]
-0.25
0.00
0.25
MR estimate

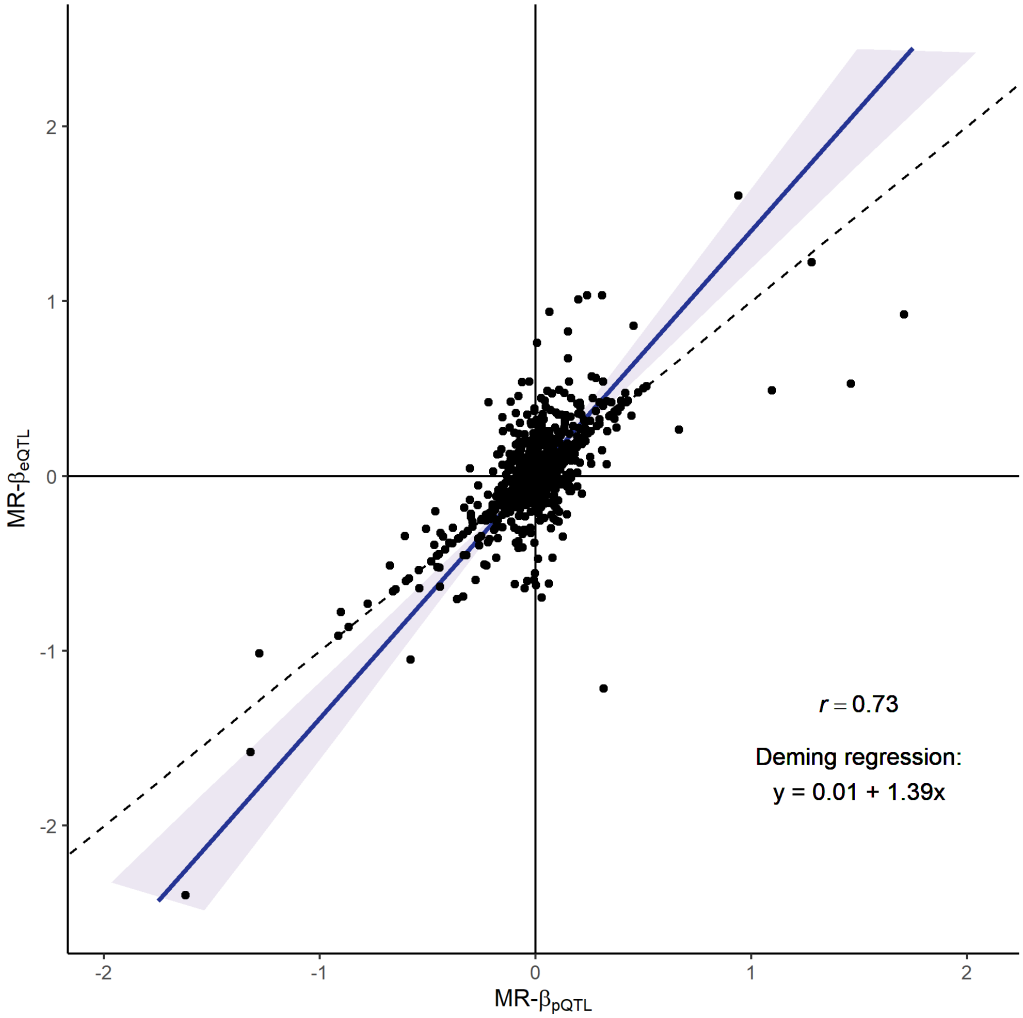
Supplementary Figure 2. Mendelian Randomization results (point estimates and their 95% confidence intervals) for the effect of genetically predicted cardiometabolic traits on circulating cytokine levels.

The results (given as effect size estimate [95% confidence interval]) are plotted only for effects with $P < 0.0011$ (0.05/47 cytokines) and are per 1-standard-deviation increase in genetically proxied exposure. HDL: high-density lipoprotein; LDL: low-density lipoprotein; CRP: C-reactive protein. The abbreviations for the cytokines are given in Supplementary Table 1.



Supplementary Figure 3. Mendelian randomization estimates for the effects of genetically predicted cytokine levels on other circulating cytokines when considering cis-pQTL (left panel) and cis-eQTL (right panel) instruments.

Associations with P < 0.05 are denoted with a single asterisk, and associations with P<0.0011 (0.05/number of cytokines) are denoted with a double asterisk. Those associations with additional colocalization evidence (PP_{shared} + $PP_{distinct}$ > 0.5 and PP_{shared} /(PP_{shared} + $PP_{distinct}$) > 0.5) are highlighted with a box. PP = posterior probability.

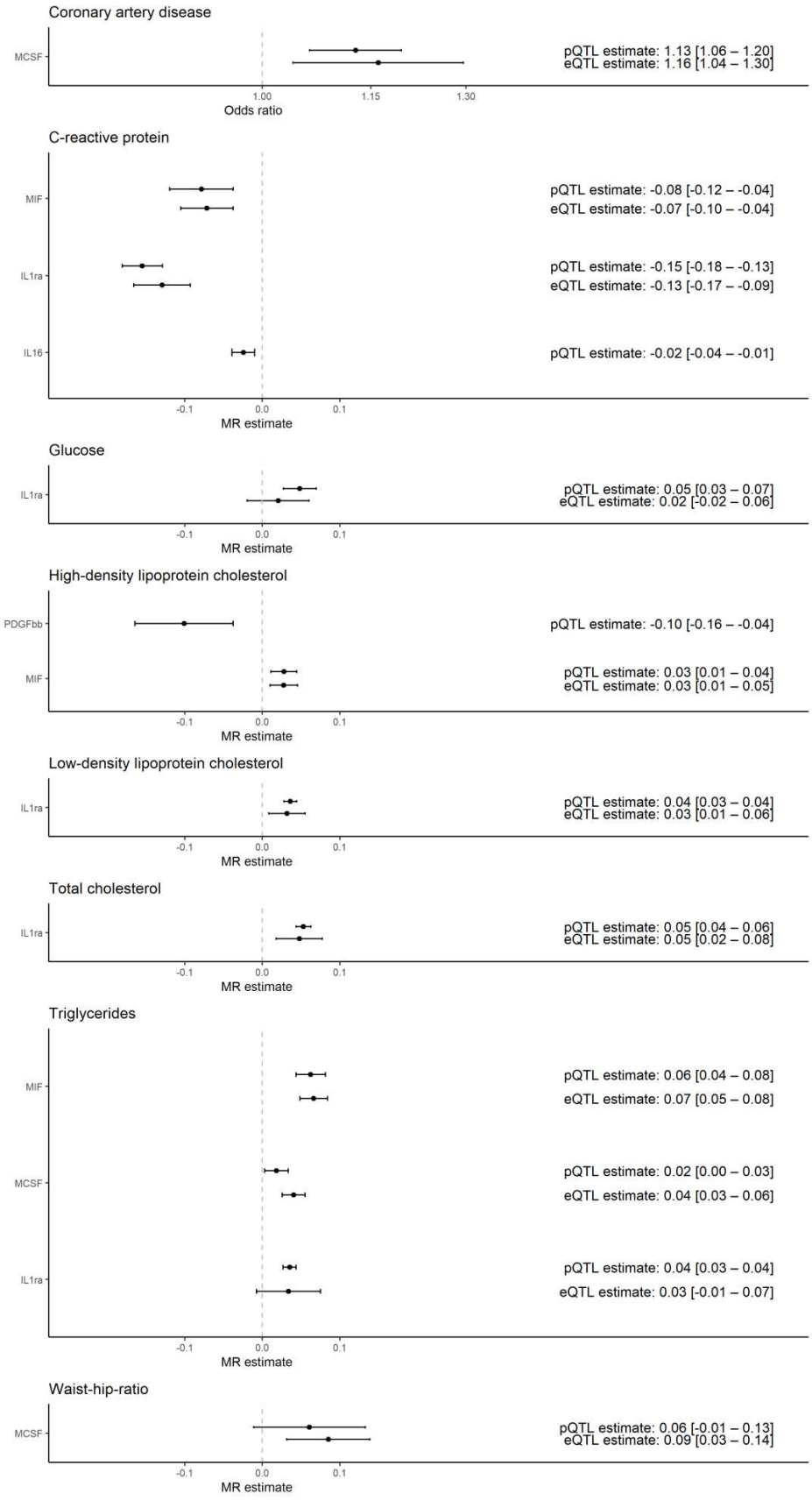


Supplementary Figure 4. Scatter plot comparing Mendelian randomization (MR) estimates for the effects of genetically predicted cytokine levels on other circulating cytokine levels when using the two different instrument selection criteria.

The correlation between the MR estimates was quantified using Pearson's coefficient. x-axis: MR effect estimates using *cis*-protein quantitative trait loci instrument selection; y-axis: MR effect estimates using *cis*-expression quantitative trait loci instrument selection. The dashed line is the line of equality, y=x. The blue line is the Deming regression line and the shaded area its 95% confidence band. r: correlation coefficient.

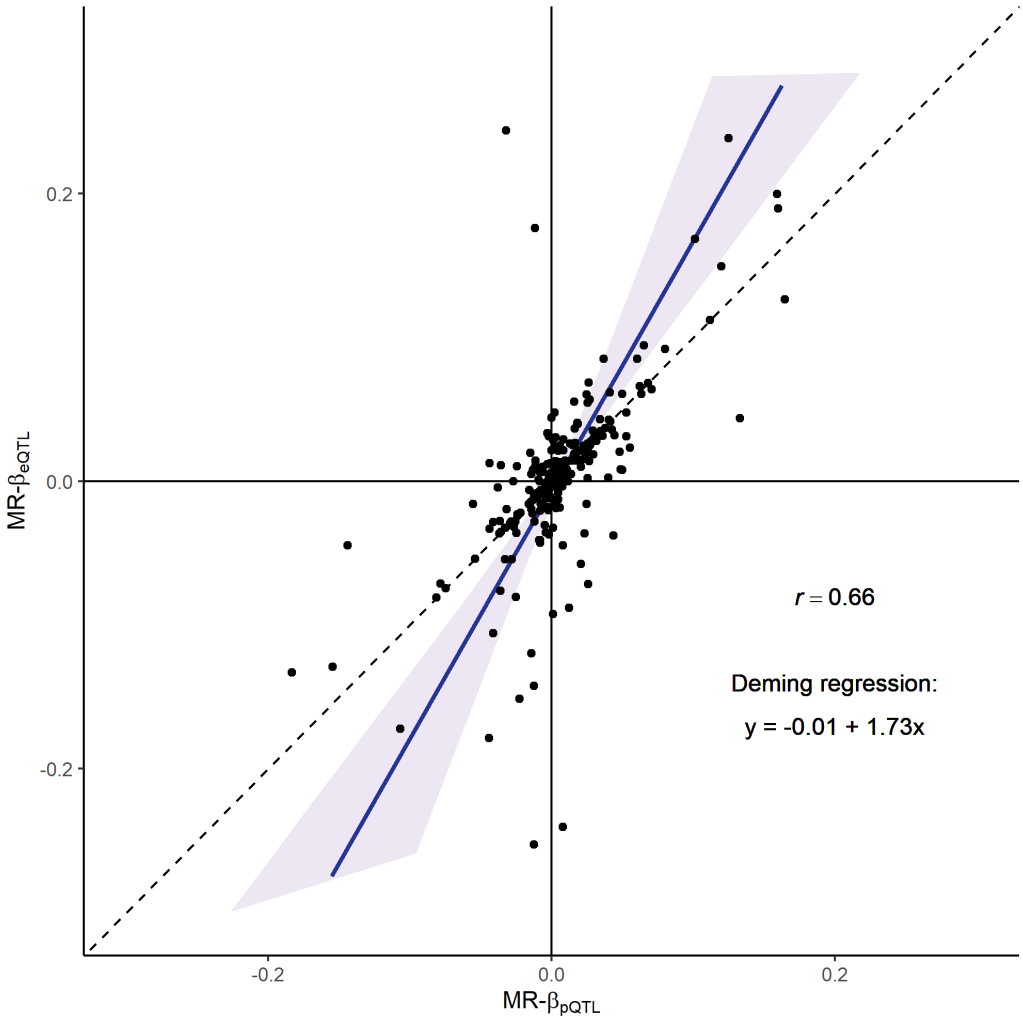
Supplementary Figures 5a-t. Colocalization plots for circulating cytokine levels.

Cytokine-cytokine pairs with evidence for colocalization (PP_{shared} + $PP_{distinct}$ > 0.5 and PP_{shared} /(PP_{shared} + $PP_{distinct}$) > 0.5) within ±500kb of the coding gene of the exposure cytokine. pQTL=protein quantitative trait loci. R^2 = linkage disequilibrium correlation based on the 1000Genomes European reference panel. PP = posterior probability. Available at: https://doi.org/10.5281/zenodo.7215468.


Coronary artery disease
MCSF
pQTL estimate: 1.13 [1.06 – 1.20]
eQTL estimate: 1.16 [1.04 – 1.30]
1.00
1.15
1.30
Odds ratio
C-reactive protein
MIF
pQTL estimate: -0.08 [-0.12 – -0.04]
eQTL estimate: -0.07 [-0.10 – -0.04]
IL1ra
pQTL estimate: -0.15 [-0.18 – -0.13]
eQTL estimate: -0.13 [-0.17 – -0.09]
IL16
pQTL estimate: -0.02 [-0.04 – -0.01]
-0.1
0.0
0.1
MR estimate
Glucose
IL1ra
pQTL estimate: 0.05 [0.03 – 0.07]
eQTL estimate: 0.02 [-0.02 – 0.06]
-0.1
0.0
0.1
MR estimate
High-density lipoprotein cholesterol
PDGFbb
pQTL estimate: -0.10 [-0.16 – -0.04]
MIF
pQTL estimate: 0.03 [0.01 – 0.04]
eQTL estimate: 0.03 [0.01 – 0.05]
-0.1
0.0
0.1
MR estimate
Low-density lipoprotein cholesterol
IL1ra
pQTL estimate: 0.04 [0.03 – 0.04]
eQTL estimate: 0.03 [0.01 – 0.06]
-0.1
0.0
0.1
MR estimate
Total cholesterol
IL1ra
pQTL estimate: 0.05 [0.04 – 0.06]
eQTL estimate: 0.05 [0.02 – 0.08]
-0.1
0.0
0.1
MR estimate
Triglycerides
MIF
pQTL estimate: 0.06 [0.04 – 0.08]
eQTL estimate: 0.07 [0.05 – 0.08]
MCSF
pQTL estimate: 0.02 [0.00 – 0.03]
eQTL estimate: 0.04 [0.03 – 0.06]
IL1ra
pQTL estimate: 0.04 [0.03 – 0.04]
eQTL estimate: 0.03 [-0.01 – 0.07]
-0.1
0.0
0.1
MR estimate
Waist-hip-ratio
MCSF
pQTL estimate: 0.06 [-0.01 – 0.13]
eQTL estimate: 0.09 [0.03 – 0.14]
-0.1
0.0
0.1
MR estimate

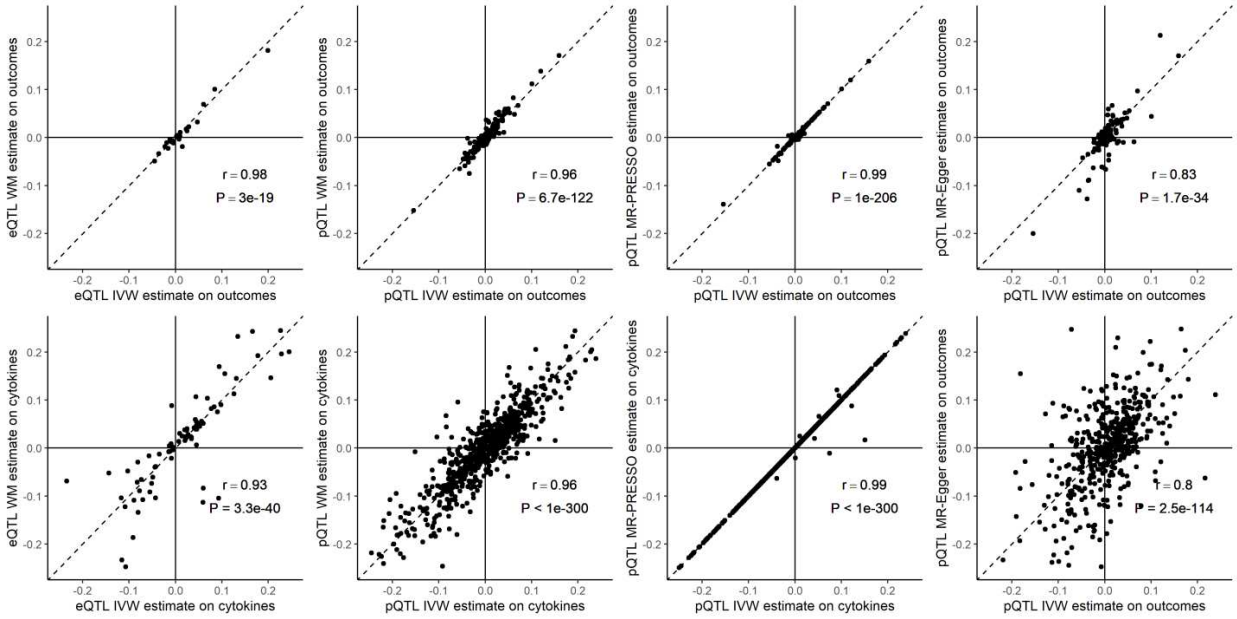
Supplementary Figure 6. Mendelian Randomization (MR) results (point estimates and their 95% confidence intervals) for the effect of genetically predicted circulating cytokine levels on cardiometabolic phenotypes considered as outcomes.

The x-axis is in standard deviation scale (for quantitative outcomes) or on a log-odds-ratio scale (for binary outcomes). The effect size estimates are per 1-standard-deviation increase in the exposure. The results are plotted only for effects with strong evidence for causality (see Supplementary Methods). pQTL: protein quantitative trait loci; eQTL: expression quantitative trait loci. The abbreviations for cytokines are given in Supplementary Table 1.



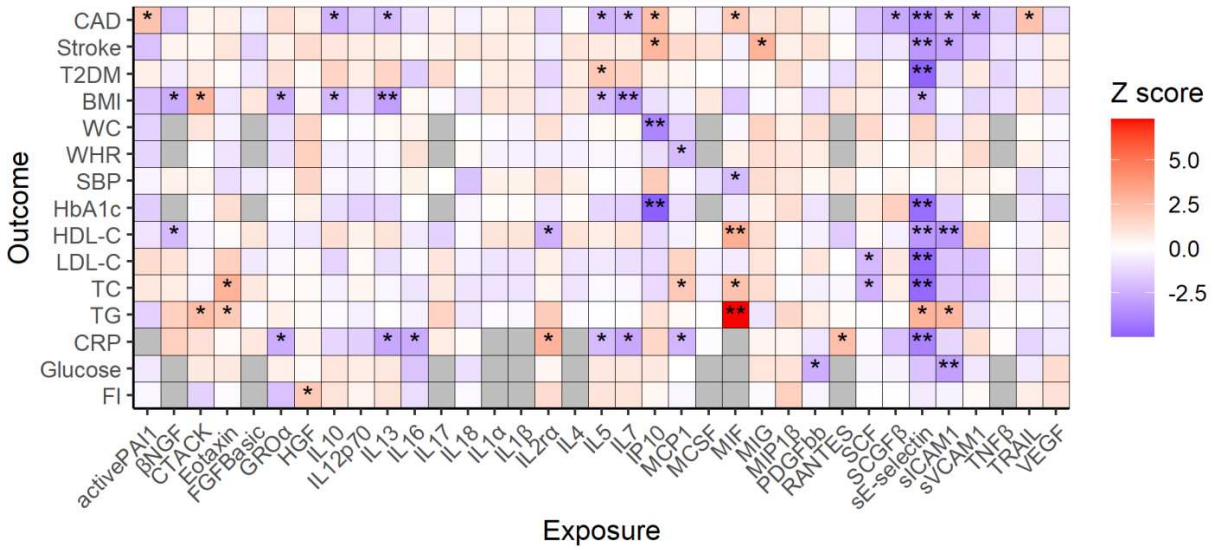
Supplementary Figure 7. Scatter plot comparing Mendelian randomization (MR) estimates for the effects of genetically predicted cytokine levels on cardiometabolic phenotypes considered as outcomes when using the two different instrument selection criteria.

The correlation between the MR estimates was quantified using Pearson's coefficient. x-axis: MR effect estimates using *cis*-protein quantitative trait loci instrument selection; y-axis: MR effect estimates using *cis*-expression quantitative trait loci instrument selection. The dashed line is the line of equality, y=x. The blue line is the Deming regression line and the shaded area its 95% confidence band. r: correlation coefficient.



Supplementary Figure 8. Scatter plots comparing Mendelian randomization (MR) estimates for the effects of genetically predicted cytokine levels on circulating cytokine levels and cardiometabolic phenotypes considered as outcomes when using different MR methods.

The correlation between the MR estimates was quantified using Pearson's correlation coefficient. IVW = inverse-variance weighted method; WM = weighted median method; eQTL = expression quantitative trait loci; pQTL = protein quantitative trait loci. r: correlation coefficient.



Supplementary Figure 9. Mendelian randomization estimates for the effects of genetically predicted cytokine levels on cardiometabolic traits using genome-wide selection for the instruments.

Associations with P < 0.05 are denoted with a single asterisk, and associations with P<0.0011 (0.05/number of cytokines) are denoted with a double asterisk. CAD: coronary artery disease; T2DM: type 2 diabetes mellitus; BMI: body-mass index; WC: waist circumference; WHR: waist-hip-ratio; SBP: systolic blood pressure; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; TC: total cholesterol; TG: triglycerides; CRP: C-reactive protein; FI: fasting insulin. The abbreviations for the cytokines are given in Supplementary Table 1.

Supplementary Figures 10a-t. Colocalization plots for circulating cytokine levels and cardiometabolic traits considered as outcomes.

Cytokine-outcome pairs with both Mendelian randomization evidence (P<0.0033) and colocalization evidence (PP_{shared} + $PP_{distinct}$ > 0.5 and PP_{shared} /(PP_{shared} + $PP_{distinct}$) > 0.5; panels a-s) for causality, or only Mendelian randomization evidence for coronary artery disease risk (panel t) are plotted within ±500kb of the coding gene of the exposure cytokine. pQTL=protein quantitative trait loci. R^2 = linkage disequilibrium correlation based on the 1000Genomes European reference panel. PP = posterior probability. Available at: https://doi.org/10.5281/zenodo.7215468.

Supplementary Table 1. Cytokines and their data sources for the genome-wide association study.

NFBC1966 = Northern Finland Birth Cohort 1966; YFS = Young Finns Study; FINRISK = FINRISK Study. *The total sample size with full genomic and cytokine data after quality control.

		Sample size			Total sample size*
Cytokine	Abbreviation	NFBC1966	FINRISK	YFS	
Active plasminogen activator inhibitor-1	activePAI1	5199			5199
Beta nerve growth factor	βNGF		1620	1950	3531
Cutaneous T-cell attracting chemokine (CCL27)	CTACK		1651	2019	3631
Eotaxin (CCL11)	Eotaxin		6186	2011	8153
Basic fibroblast growth factor	FGFBasic		5592	2017	7565
Granulocyte colony-stimulating factor	GCSF		1544	2018	7904
Growth regulated oncogene-alpha (CXCL1)	GROα		1541	2003	3505
Hepatocyte growth factor	HGF		6317	2019	8292
Interferon-gamma	IFNγ		5726	2019	7701
Interleukin-10	IL10		5708	2016	7681
Interleukin-12p70	IL12p70		6295	2019	8270
Interleukin-13	IL13		1577	2019	3557
Interleukin-16	IL16		1663	1858	3483
Interleukin-17	IL17	5071	5785	2019	12831
Interleukin-18	IL18		1656	2019	3636
Interleukin-1-alpha	IL1α	5014			5014
Interleukin-1-beta	IL1β	5067	1330	2018	8376
Interleukin-1 receptor antagonist	IL1ra	4957	1658	2019	8595
Interleukin-2	IL2		1498	2016	3475
Interleukin-2 receptor, alpha subunit	IL2rα		1704	2012	3677
Interleukin-4	IL4	5059	6149	2019	13183
Interleukin-5	IL5		1386	2017	3364
Interleukin-6	IL6	5063	6215	2018	13252
Interleukin-7	IL7		1429	2019	3409
Interleukin-8 (CXCL8)	IL8	5071	1546	2019	8597

Interleukin-9	IL9		1656	2017	3634
Interferon gamma-induced protein 10 (CXCL10)	IP10	5072	1705	2019	8757
Monocyte chemotactic protein-1 (CCL2)	MCP1	5072	6318	2019	13365
Monocyte specific chemokine 3 (CCL7)	MCP3		843	256	843
Macrophage colony-stimulating factor	MCSF		1632	866	840
Macrophage migration inhibitory factor (glycosylation-inhibiting factor)	MIF		1516	2017	3494
Monokine induced by interferon-gamma (CXCL9)	MIG		1705	2019	3685
Macrophage inflammatory protein-1a (CCL3)	MIP1α		1542	2019	3522
Macrophage inflammatory protein-1b (CCL4)	MIP1β		6268	2019	8243
Platelet derived growth factor BB	PDGFbb		6318	2019	8293
Regulated on Activation, Normal T Cell Expressed and Secreted (CCL5)	RANTES		1585	1869	3421
Soluble CD40 ligand	sCD40L	5067			5067
Stem cell factor	SCF		6316	2018	8290
Stem cell growth factor beta	SCGFβ		1704	2017	3682
Stromal cell-derived factor-1 alpha (CXCL12)	SDF1α		6003	1826	5998
soluble E-selectin	sE-selectin	5199			5199
soluble intercellular adhesion molecule-1	sICAM1	5199			5199
soluble vascular cell adhesion molecule 1	sVCAM1	5199			5199
Tumor necrosis factor-alpha	TNFα	5068	1474	2019	8522
Tumor necrosis factor-beta	TNFβ		1450	116	1559
TNF-related apoptosis inducing ligand	TRAIL		6218	2012	8186
Vascular endothelial growth factor	VEGF	5037	5143	2019	12155

Supplementary Table 2. Sources for genetic association estimates with cardiometabolic traits.

Trait	Sample size	Population ancestry	Reference
Coronary artery disease	60,801 cases 123,504 controls	Multi-ancestry	Nikpay et al. 2015
Stroke	40,585 cases 406,111 controls	European	Malik et al. 2015
Type 2 diabetes	74,124 cases 824,006 controls	European	Mahajan et al. 2018
Body mass index	806,834	European	Pulit et al. 2019
Waist circumference	210,088	European	Shungin et al. 2015
Waist-hip-ratio	210,088	European	Shungin et al. 2015
Systolic blood pressure	318,419	European	Carter et al. 2019
High-density lipoprotein cholesterol	1,320,016	European	Graham et al. 2021
Low-density lipoprotein cholesterol	1,320,016	European	Graham et al. 2021
Total cholesterol	1,320,016	European	Graham et al. 2021
Triglycerides	1,320,016	European	Graham et al. 2021
C-reactive protein[1]	343,524	European	Neale lab 2020
Glucose	46,186	European	Dupuis et al. 2010
Fasting insulin	38,238	European	Dupuis et al. 2010
Glycated hemoglobin	123,665	European	Wheeler et al. 2017
Lifetime smoking[2]	462,690	European	Wootton et al. 2019

[1]CRP is a biomarker for systemic inflammation and for this reason was considered only as an outcome trait rather than an exposure. [2]Smoking is robustly associated with cardiometabolic outcomes, but it is largely a behavioural trait and therefore was considered only as an exposure trait.

Supplementary Table 3. Cytokine coding genes, data sources and the number of instruments with two different criteria.

Chr: chromosome; GWAS: genome-wide association study; pQTL: protein quantitative trait loci; eQTL: expression quantitative trait loci. INTERVAL study: ref. [24]; SCALLOP study: ref. [25]. *Interleukin-12p70 has two coding genes.

Cytokine	Abbreviation	Gene	Chr	Start position (hg19)	End position (hg19)	Source	GWAS sample size	Number of *cis*-pQTL instruments	Number of *cis*-eQTL instruments
Active plasminogen activator inhibitor-1	activePAI1	SERPINE1	7	100770370	100782547	Current GWAS	5199	1	0
Beta nerve growth factor	βNGF	NGF	1	115828537	115880857	Current GWAS	3531	0	0
Cutaneous T-cell attracting chemokine (CCL27)	CTACK	CCL27	9	34661893	34662689	Current GWAS	3631	6	2
Eotaxin (CCL11)	Eotaxin	CCL11	17	32612687	32615199	Current GWAS+INTERVAL	11454	2	1
Basic fibroblast growth factor	FGFBasic	FGF2	4	123747863	123819390	Current GWAS	7565	0	1
Granulocyte colony-stimulating factor	GCSF	CSF3	17	38171614	38174066	Current GWAS	7904	0	0
Growth regulated oncogene-alpha (CXCL1)	GROα	CXCL1	4	74735109	74737019	Current GWAS+INTERVAL	6806	26	1
Hepatocyte growth factor	HGF	HGF	7	81331444	81399452	Current GWAS+SCALLOP	25205	1	0
Interferon-gamma	IFNγ	IFNG	12	68548550	68553521	Current GWAS	7701	0	0
Interleukin-10	IL10	IL10	1	206940948	206945839	Current GWAS	7681	0	0
Interleukin-12p70	IL12p70	IL12A*	3	159706623	159713806	Current GWAS	8270	1	0
		IL12B*	5	158741791	158757481			0	0
Interleukin-13	IL13	IL13	5	131993865	131996801	Current GWAS	3557	0	0
Interleukin-16	IL16	IL16	15	81517640	81605104	Current GWAS+SCALLOP	22678	1	0
Interleukin-17	IL17	IL17A	6	52051185	52055436	Current GWAS	12831	0	0
Interleukin-18	IL18	IL18	11	112013974	112034840	Current GWAS+SCALLOP	22831	7	2
Interleukin-1-alpha	IL1α	IL1A	2	113531492	113542971	Current GWAS	5014	0	1
Interleukin-1-beta	IL1β	IL1B	2	113587337	113594356	Current GWAS	8376	0	0
Interleukin-1 receptor antagonist	IL1ra	IL1RN	2	113885138	113891593	SCALLOP	19059	24	2
Interleukin-2	IL2	IL2	4	123372626	123377650	Current GWAS	3475	0	0

Interleukin-2 receptor, alpha subunit	IL2rα	IL2RA	10	6052657	6104333	Current GWAS	3677	12	4
Interleukin-4	IL4	IL4	5	132009678	132018370	Current GWAS	13183	0	0
Interleukin-5	IL5	IL5	5	131877136	131879214	Current GWAS	3364	0	0
Interleukin-6	IL6	IL6	7	22766766	22771621	SCALLOP	14244	0	0
Interleukin-7	IL7	IL7	8	79645007	79717758	Current GWAS	3409	1	0
Interleukin-8 (CXCL8)	IL8	IL8	4	74606223	74609433	SCALLOP	16924	1	2
Interleukin-9	IL9	IL9	5	135227935	135231516	Current GWAS	3634	0	0
Interferon gamma-induced protein 10 (CXCL10)	IP10	CXCL10	4	76942269	76944689	Current GWAS	8757	4	1
Monocyte chemotactic protein-1 (CCL2)	MCP1	CCL2	17	32582296	32584220	Current GWAS+SCALLOP	35100	5	2
Monocyte specific chemokine 3 (CCL7)	MCP3	CCL7	17	32597235	32599261	INTERVAL	3301	14	0
Macrophage colony-stimulating factor	MCSF	CSF1	1	110453233	110473616	SCALLOP	16935	12	2
Macrophage migration inhibitory factor (glycosylation-inhibiting factor)	MIF	MIF	22	24236565	24237409	Current GWAS	3494	2	1
Monokine induced by interferon-gamma (CXCL9)	MIG	CXCL9	4	76922623	76928641	Current GWAS	3685	2	2
Macrophage inflammatory protein-1a (CCL3)	MIP1α	CCL3	17	34415603	34417506	SCALLOP	19060	35	1
Macrophage inflammatory protein-1b (CCL4)	MIP1β	CCL4	17	34431220	34433014	Current GWAS+SCALLOP	25175	39	2
Platelet derived growth factor BB	PDGFbb	PDGFB	22	39619685	39640957	SCALLOP	19205	1	0
Regulated on Activation, Normal T Cell Expressed and Secreted (CCL5)	RANTES	CCL5	17	34198496	34207377	Current GWAS	3421	1	1
Soluble CD40 ligand	sCD40L	CD40LG	X	135730336	135742549	SCALLOP	19190	0	0
Stem cell factor	SCF	KITLG	12	88886570	88974250	SCALLOP	19206	2	0
Stem cell growth factor beta	SCGFβ	CLEC11A	19	51226605	51228981	Current GWAS+INTERVAL	6983	4	1

Stromal cell-derived factor-1 alpha (CXCL12)	SDF1α	CXCL12	10	44872510	44880545	Current GWAS	5998	0	0
soluble E-selectin	sE-selectin	SELE	1	169691781	169703220	Current GWAS+SCALLOP	26504	5	0
soluble intercellular adhesion molecule-1	sICAM1	ICAM1	19	10381517	10397291	Current GWAS	5199	26	1
soluble vascular cell adhesion molecule-1	sVCAM1	VCAM1	1	101185196	101204601	Current GWAS	5199	1	1
Tumor necrosis factor-alpha	TNFα	TNF	6	31543344	31546112	Current GWAS	8522	2	0
Tumor necrosis factor-beta	TNFβ	LTA	6	31539876	31542100	INTERVAL	1559	0	0
TNF-related apoptosis inducing ligand	TRAIL	TNFSF10	3	172223298	172241297	Current GWAS+SCALLOP	24135	14	4
Vascular endothelial growth factor	VEGF	VEGFA	6	43737946	43754223	Current GWAS+SCALLOP	29080	34	1

Supplementary Table 4. Variants used as instrumental variables for cardiometabolic traits and cytokines using genome-wide selection.

Chr = chromosome; Pos = position; EA = effect allele; NEA = non-effect allele; EAF = effect allele frequency; BETA = effect size estimate; SE = standard error; P = p-value; R2 = variance explained; F = F-statistic. Available at: https://doi.org/10.5281/zenodo.7215468.

Supplementary Table 5. Table comparing Mendelian randomization (MR) estimates for the effects of genetically predicted cardiometabolic traits on circulating cytokine levels using different MR methods.

N_SNPs = number of instrumental variables; CIL = 95% confidence interval, lower limit; CIU = 95% confidence interval, upper limit; IVW = inverse-variance weighted method; WM = weighted median method. Available at: https://doi.org/10.5281/zenodo.7215468.

Supplementary Table 6. Variants used as instrumental variables for cytokines selected by *cis*-protein quantitative trait loci instrument selection.

Chr = chromosome; Pos = position; EA = effect allele; NEA = non-effect allele; EAF = effect allele frequency; SE = standard error; P = p-value; F = F-statistic. Available at: https://doi.org/10.5281/zenodo.7215468.

Supplementary Table 7. Variants used as instrumental variables for cytokines selected by *cis*-expression quantitative trait loci instrument selection.

Chr = chromosome; Pos = position; EA = effect allele; NEA = non-effect allele; EAF = effect allele frequency; SE = standard error; P = p-value; F = F-statistic. Available at: https://doi.org/10.5281/zenodo.7215468.

Supplementary Table 8. Table comparing Mendelian randomization (MR) estimates for the effects of genetically predicted cytokine levels on other circulating cytokine levels using different MR methods.

N_SNPs = number of instrumental variables; CIL = 95% confidence interval, lower limit; CIU = 95% confidence interval, upper limit; IVW = inverse-variance weighted method; WM = weighted median method; eQTL = expression quantitative trait loci; pQTL = protein quantitative trait loci. Available at: https://doi.org/10.5281/zenodo.7215468.

Supplementary Table 9. Colocalization results for the genetic associations of circulating cytokine levels within ±500kb of the coding gene of the exposure cytokine.

Only cytokine-cytokine pairs with MR-evidence for causality (P<0.0011) are reported. PP = posterior probability. Available at: https://doi.org/10.5281/zenodo.7215468.

Supplementary Table 10. Table comparing Mendelian randomization (MR) estimates for the effects of genetically predicted cytokine levels on cardiometabolic phenotypes considered as outcomes using different MR methods.

N_SNPs = number of instrumental variables; CIL = 95% confidence interval, lower limit; CIU = 95% confidence interval, upper limit; IVW = inverse-variance weighted method; WM = weighted median method; eQTL = expression quantitative trait loci; pQTL = protein quantitative trait loci. Available at: https://doi.org/10.5281/zenodo.7215468.

Supplementary Table 11. Table comparing Mendelian randomization (MR) estimates for the effects of genetically predicted circulating cytokine levels on cardiometabolic traits using genome-wide instrument selection.

N_SNPs = number of instrumental variables; CIL = 95% confidence interval, lower limit; CIU = 95% confidence interval, upper limit; IVW = inverse-variance weighted method; WM = weighted median method. Available at: https://doi.org/10.5281/zenodo.7215468.

Supplementary Table 12. Colocalization results for the genetic associations of circulating cytokine levels and cardiometabolic phenotypes considered as outcomes within ±500kb of the coding gene of the cytokine.

Cytokine-outcome pairs with nominal MR-evidence for causality (P<0.05) are reported. PP = posterior probability. Available at: https://doi.org/10.5281/zenodo.7215468.