Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.
eMethods. Detailed Methodology

Datasets of summary association results

The datasets of summary genetic associations datasets (shown in eTables 1 and 2) used in this work as described below.

- Circulating C reactive protein (CRP)

Two sets of CRP-associated SNPs were used. One included 18 independent SNPs identified in a GWAS in ≤82,725 European ancestry individuals.\(^1\) SNP-CRP linear regression coefficients (changes in ln-transformed circulating CRP levels) and standard errors were obtained assuming additive genetic effects and adjusting for sex, age, recruitment site (if necessary) and relatedness (for family studies). Given that a statistical criterion was used to select these 18 instruments, they are hereafter referred to as the liberal set.

The second set included four variants in the CRP gene, which explain 98% of the genetic variation in this locus in European ancestry populations and have been shown to regulate CRP expression levels without changing protein sequence.\(^2\) SNP-CRP linear regression coefficients (changes in ln-transformed circulating CRP levels) and standard errors for these variants were obtained from the CRP Coronary Heart Disease Genetics Collaboration in a sample mostly of European ancestry. The analyses were adjusted for ancestry to minimize residual confounding due to population stratification.\(^3\) These four instruments are hereafter referred to as conservative because they are located in the CRP gene region and their selection incorporated biological criteria. Therefore, we considered this approach less likely to be biased by horizontal pleiotropy. These variants are in partial linkage disequilibrium with one another (eTable 3).

- Interleukin-1 receptor antagonist (IL-1Ra)
Two SNPs located upstream of the *IL1RN* gene were selected as IL-1Ra instruments. They map to two independent loci identified in a GWAS in 4,443 European ancestry individuals. C-allele carriers have higher levels of circulating IL-1Ra, an endogenous inhibitor of IL-1 downstream effects, mimicking the action of the drug Anakinra.

SNP-IL-1Ra associations were estimated in standard deviation units of ln(IL-1Ra) levels in the Cardiovascular Health Study (n=3,081). These were converted to ln(IL-1Ra) units by dividing the estimates by 0.54 (the standard deviation of ln(IL-1Ra) levels in the same study).

- Interleukin-6 receptor (IL-6R)

A single missense SNP (Asp358Ala) in the *IL6R* gene was selected as the IL-6R instrument. Binding of IL-6 to its membrane-bound receptor, IL-6R, is necessary for triggering classical IL-6 effects on hepatocytes and some leukocytes. The Asp358Ala SNP increases cleavage of membrane-bound IL-6R cleavage and blockade of IL-6 classical cell signaling. Therefore, downstream effects of IL-6 are attenuated in Ala-allele carriers, despite increased levels of IL-6 and soluble IL-6R (sIL-6R). IL6R is a target for drugs like tocilizumab, a monoclonal antibody used to reduce systemic and articular inflammation in patients with rheumatoid arthritis. A large scale Mendelian randomization study showed that this genetic variant was not associated with a wide range of biomarkers, except for those that are widely known downstream consequences of IL-6 (i.e. CRP and fibrinogen). In addition the effects of this genetic variant were consistent with the effects of tocilizumab.

SNP-sIL6R associations were estimated in 1,645 individuals included in a large collaborative MR study. These estimates were presented in percentage differences, which were converted to ln-transformed units.

- Schizophrenia
SNP-schizophrenia ln(odds ratio) and standard errors were downloaded from the Psychiatric Genomics Consortium website (http://www.med.unc.edu/pgc/downloads). Logistic regression assuming an additive genetic effect and adjusting for ancestry-informative principal components were performed. Analyses included 34,241 cases and 45,604 ancestry-matched controls (most of European ancestry), as well as three family-based studies of 1,235 European ancestry trios.\textsuperscript{12}

**Testing for influential genetic variants**

To identify potentially influential instruments in the liberal set of CRP instruments, two tests of influence (based on studentized residuals or Cook’s distance) were applied separately for IVW or MR-Egger regression.\textsuperscript{38,39} P-values for the studentized residuals test were obtained from a Student’s t-distribution with degrees of freedom equal to $L-2$ (for IVW) or $L-3$ (for MR-Egger regression), with $L$ being the number of genetic instruments. The F distribution with joint degrees of freedom equal to (1, $L-1$) (for IVW) or (1, $L-2$) (for MR-Egger regression) was used for the Cook’s distance test. We then applied three different statistical significance criteria to classify SNPs as potentially influential: $P<0.01$, $P<0.05$ or $P<0.1$ in at least one of the influence tests.
Mediation analysis

The expected effect assuming full mediation ($\beta_E$) can be estimated as $\hat{\beta}_E = \hat{\beta}_{X,M} \times \hat{\beta}_{M,Y}$, where $\hat{\beta}_{X,M}$ is the causal effect estimate of the exposure on the mediator, and $\hat{\beta}_{M,Y}$ is the causal effect estimate of the mediator on the outcome. The proportion of the effect of the exposure on the outcome that is mediated by the mediator ($\beta_P$) can then be estimated as $\hat{\beta}_P = 1 - (\hat{\beta}_{X,Y} - \hat{\beta}_E) / \hat{\beta}_{X,Y}$, where $\hat{\beta}_{X,Y}$ is the causal effect estimate of the exposure on the outcome. Standard errors for $\hat{\beta}_E$ and $\hat{\beta}_P$ were estimated using parametric bootstrap, so that in each bootstrap iteration each SNP-phenotype association was re-sampled from $N(\hat{\beta}_{a,j}, \sigma_{a,j}^2)$, where $\hat{\beta}_{a,j}$ is the point estimate of the effect of the $j$th variant on the $a$th phenotype, and $\sigma_{a,j}$ is its corresponding standard error. These re-sampled summary statistics are then used to calculate $\hat{\beta}_E$ and $\hat{\beta}_P$, and this process was repeated 10,000 times, generating an empirical distribution of those statistics. Confidence intervals were then derived using the normal approximation method, using the absolute median deviation from the median (corrected for normal asymptotic consistency) of the empirical distribution as the standard error.
eReferences

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**eTable 1. SNP Biomarker and SNP Schizophrenia Associations (per Effect Allele) of the Instruments of Inflammatory Biomarkers Before Data Harmonization.**

| SNP set       | SNP       | SNP-biomarker | SNP-schizophrenia |
|---------------|-----------|---------------|-------------------|
|               |           | EA | OA | ln(levels) | SE | EA | OA | ln(OR) | SE |
| CRP liberal   | rs2794520 | C  | T  | 0.1600     | 0.0060 | T  | C  | 0.0220 | 0.0110 |
| CRP liberal   | rs4420638 | A  | G  | 0.2360     | 0.0090 | A  | G  | -0.0036 | 0.0146 |
| CRP liberal   | rs1183910 | G  | A  | 0.1490     | 0.0060 | A  | G  | 0.0278 | 0.0112 |
| CRP liberal   | rs4420065 | C  | T  | 0.0900     | 0.0050 | T  | C  | 0.0224 | 0.0110 |
| CRP liberal   | rs4129267 | C  | T  | 0.0790     | 0.0050 | T  | C  | 0.0257 | 0.0108 |
| CRP liberal   | rs1260326 | T  | C  | 0.0720     | 0.0050 | T  | C  | -0.0061 | 0.0108 |
| CRP liberal   | rs12239046| C  | T  | 0.0470     | 0.0060 | T  | C  | 0.0034 | 0.0110 |
| CRP liberal   | rs6734238 | G  | A  | 0.0500     | 0.0060 | A  | G  | 0.0027 | 0.0110 |
| CRP liberal   | rs9987289 | G  | A  | 0.0690     | 0.0110 | A  | G  | 0.0832 | 0.0188 |
| CRP liberal   | rs10745954| A  | G  | 0.0390     | 0.0060 | A  | G  | -0.0251 | 0.0106 |
| CRP liberal   | rs1800961 | C  | T  | 0.0880     | 0.0150 | T  | C  | -0.0307 | 0.0300 |
| CRP liberal   | rs340029  | T  | C  | 0.0320     | 0.0060 | T  | C  | 0.0043 | 0.0112 |
| CRP liberal   | rs10521222| C  | T  | 0.1040     | 0.0150 | T  | C  | 0.0091 | 0.0325 |
| CRP liberal   | rs12037222| A  | G  | 0.0450     | 0.0070 | A  | G  | -0.0095 | 0.0128 |
| CRP liberal   | rs13233571| C  | T  | 0.0540     | 0.0090 | T  | C  | -0.0131 | 0.0167 |
| CRP liberal   | rs2847281 | A  | G  | 0.0310     | 0.0060 | A  | G  | 0.0113 | 0.0108 |
| CRP liberal   | rs6901250 | A  | G  | 0.0350     | 0.0060 | A  | G  | -0.0133 | 0.0113 |
| CRP liberal   | rs4705952 | G  | A  | 0.0420     | 0.0070 | A  | G  | 0.0033 | 0.0121 |
| CRP conservative | rs3093077 | C  | A  | 0.2100     | 0.0179 | A  | C  | 0.0083 | 0.0211 |
| CRP conservative | rs1205  | C  | T  | 0.1800     | 0.0102 | T  | C  | 0.0203 | 0.0110 |
| CRP conservative | rs1130864| A  | G  | 0.1300     | 0.0077 | A  | G  | -0.0145 | 0.0116 |
| CRP conservative | rs1800947| C  | G  | 0.2600     | 0.0153 | C  | G  | -0.0381 | 0.0231 |
| IL-1Ra        | rs1542176 | C  | T  | 0.3333     | 0.0472 | T  | C  | -0.0099 | 0.0105 |
| IL-1Ra        | rs6743376 | C  | A  | 0.4630     | 0.0472 | A  | C  | 0.0142 | 0.0111 |
| IL-6R         | rs2228145 | C  | A  | 0.2949     | 0.0148 | A  | C  | -0.0251 | 0.0108 |

SNP: single nucleotide polymorphism. CRP: C reactive protein. IL-1Ra: Interleukin-1 receptor antagonist. Interleukin-6 receptor. EA: effect allele. OA: other allele. OR: odds ratio.
**eTable 2.** SNP Biomarker and SNP Schizophrenia Associations (per Effect Allele) of the Instruments of Inflammatory Biomarkers After Data Harmonization

| SNP set       | SNP       | SNP-biomarker | SNP-schizophrenia |
|---------------|-----------|---------------|-------------------|
|               | EA        | OA            | ln(levels) | SE | EA     | OA     | ln(OR) | SE    |
| CRP liberal   | rs2794520 | C T           | 0.1600     | 0.0060 | C T    | -0.0220 | 0.0110 |
| CRP liberal   | rs4420638 | A G           | 0.2360     | 0.0090 | A G    | -0.0086 | 0.0146 |
| CRP liberal   | rs1183910 | G A           | 0.1490     | 0.0060 | G A    | -0.0278 | 0.0112 |
| CRP liberal   | rs4420065 | C T           | 0.0900     | 0.0050 | C T    | -0.0224 | 0.0110 |
| CRP liberal   | rs4129267 | C T           | 0.0790     | 0.0050 | C T    | -0.0257 | 0.0108 |
| CRP liberal   | rs1260326 | T C           | 0.0720     | 0.0050 | T C    | -0.0061 | 0.0108 |
| CRP liberal   | rs12239046| C T           | 0.0470     | 0.0060 | C T    | -0.0034 | 0.0110 |
| CRP liberal   | rs6734238 | G A           | 0.0500     | 0.0060 | G A    | -0.0027 | 0.0110 |
| CRP liberal   | rs9987289 | G A           | 0.0690     | 0.0110 | G A    | -0.0832 | 0.0188 |
| CRP liberal   | rs10745954| A G           | 0.0390     | 0.0060 | A G    | -0.0251 | 0.0106 |
| CRP liberal   | rs1800961 | C T           | 0.0880     | 0.0150 | C T    | 0.0307  | 0.0300 |
| CRP liberal   | rs340029  | T C           | 0.0320     | 0.0060 | T C    | 0.0043  | 0.0112 |
| CRP liberal   | rs10521222| C T           | 0.1040     | 0.0150 | C T    | -0.0091 | 0.0325 |
| CRP liberal   | rs12037222| A G           | 0.0450     | 0.0070 | A G    | -0.0095 | 0.0128 |
| CRP liberal   | rs13233571| C T           | 0.0540     | 0.0090 | C T    | 0.0131  | 0.0167 |
| CRP liberal   | rs2847281 | A G           | 0.0310     | 0.0060 | A G    | 0.0113  | 0.0108 |
| CRP liberal   | rs6901250 | A G           | 0.0350     | 0.0060 | A G    | -0.0133 | 0.0113 |
| CRP liberal   | rs4705952 | G A           | 0.0420     | 0.0070 | G A    | -0.0033 | 0.0121 |
| CRP conservative | rs3093077 | C A           | 0.2100     | 0.0179 | C A    | -0.0083 | 0.0211 |
| CRP conservative | rs1205 | C T           | 0.1800     | 0.0102 | C T    | -0.0203 | 0.0110 |
| CRP conservative | rs1130864 | A G           | 0.1300     | 0.0077 | A G    | -0.0145 | 0.0116 |
| IL-1Ra        | rs1542176 | C T           | 0.3333     | 0.0472 | C T    | 0.0099  | 0.0105 |
| IL-1Ra        | rs6743376 | C A           | 0.4630     | 0.0472 | C A    | -0.0142 | 0.0111 |
| IL-6R         | rs2228145 | C A           | 0.2949     | 0.0148 | C A    | 0.0251  | 0.0108 |

SNP: single nucleotide polymorphism. CRP: C reactive protein. IL-1Ra: Interleukin-1 receptor antagonist. Interleukin-6 receptor. EA: effect allele. OA: other allele. OR: odds ratio.
**eTable 3.** Pairwise Pearson Correlation Coefficients\(^a\) Among the Four CRP Genetic Instruments in the Conservative Set (Data From Phase III of the 1000 Genomes Project, Restricting to European Populations)

|        | rs1130864 | rs1205 | rs1800947 | rs3093077 |
|--------|-----------|--------|-----------|-----------|
| rs1130864 | 1.000     | 0.453  | 0.133     | -0.185    |
| rs1205   | 0.453     | 1.000  | 0.326     | 0.196     |
| rs1800947 | 0.133     | 0.326  | 1.000     | 0.088     |
| rs3093077 | -0.185    | 0.196  | 0.088     | 1.000     |

CRP: C reactive protein.
\(^a\)The \(r^2\) metric of linkage disequilibrium can be obtained by squaring the correlation coefficients.
**eTable 4.** Heterogeneity Statistics (Cochran’s Q Statistic and Associated P-Value) Associated With the Odds Ratio of Schizophrenia per Two-Fold Increments in CRP Levels Using the Liberal Set of 18 CRP-Associated Variants in a Leave-1-Out Approach.

| Excluded SNP | Q statistic | P   |
|--------------|-------------|-----|
| rs10521222   | 31.9        | 0.01|
| rs10745954   | 28.5        | 0.03|
| rs1183910    | 31.6        | 0.01|
| rs12037222   | 31.9        | 0.01|
| rs12239046   | 31.8        | 0.01|
| rs1260326    | 31.8        | 0.01|
| rs13233571   | 30.4        | 0.02|
| rs1800961    | 29.8        | 0.02|
| rs2794520    | 31.9        | 0.01|
| rs2847281    | 29.8        | 0.02|
| rs340029     | 31.3        | 0.01|
| rs4129267    | 30.1        | 0.02|
| rs4420065    | 31.1        | 0.01|
| rs4420638    | 29.0        | 0.02|
| rs4705952    | 31.9        | 0.01|
| rs6734238    | 31.8        | 0.01|
| rs6901250    | 31.4        | 0.01|
| rs9987289a   | 16.7        | 0.41|

SNP: single nucleotide polymorphism. CRP: C reactive protein.

*This variant was classified as potentially influential both in IVW and MR-Egger.