Altered IL-6 signalling and risk of tuberculosis: a multi-ancestry mendelian randomisation study

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Summary

Background The role of IL-6 responses in human tuberculosis risk is unknown. IL-6 signalling inhibitors, such as tocilizumab, are thought to increase the risk of progression to tuberculosis, and screening for latent *Mycobacterium tuberculosis* infection before using these drugs is widely recommended. We used single nucleotide polymorphisms (SNPs) in and near the IL-6 receptor gene (*IL6R*), including the non-synonymous variant, rs2228145, for which the C allele contributes to reduced classic (*cis*) IL-6 signalling activity, to test the hypothesis that altered IL-6 signalling is causally associated with the risk of developing tuberculosis.

Methods We performed a meta-analysis of genome-wide association studies (GWAS) published in English from database inception to Jan 1, 2024. GWAS were identified from the European Bioinformatics Institute, MRC Integrative Epidemiology Unit catalogues, and MEDLINE, selecting publicly available studies for which tuberculosis was an outcome and that included the *IL6R* rs2228145 SNP. Using each study's population-level summary statistics, effect estimates were extracted for each additional copy of the C allele of rs2228145. We used these estimates to perform multi-ancestry, two-sample mendelian randomisation analyses to estimate the causal effect of reduced IL-6 signalling on tuberculosis. Our primary analyses used rs2228145-C as a genetic instrument, weighted on C-reactive protein (CRP) reduction as a measure of the effect on IL-6 signalling. We also took an alternative, ancestry-specific, multiple SNP approach using IL-6 receptor plasma protein as an exposure. Additionally, we compared the effects of rs2228145 in tuberculosis with those in critical COVID-19, rheumatoid arthritis, Crohn's disease, and coronary artery disease using the summary statistics extracted from GWAS.

Findings 17 GWAS were included, collating data for 19 302 individuals with tuberculosis (cases) and 1 019 821 population controls across multiple ancestries. For each additional rs2228145-C allele, the odds of tuberculosis reduced (odds ratio [OR] 0·94 [95% CI 0·92–0·97]; p=6·8×10^{-6}). Multi-ancestry mendelian randomisation analyses supported these findings, with decreased odds of tuberculosis associated with readouts of reduced IL-6 signalling (0·52 [0·39–0·69] for each natural log CRP decrease; p=6·8×10^{-6}), with weak evidence of heterogeneity (I^2=0·315; p=0·11). Ancestry-specific, multiple SNP mendelian randomisation using increase in IL-6 receptor plasma protein as an exposure revealed a similar reduced risk of tuberculosis (OR 0·94 [95% CI 0·93–0·96]; p=2·4×10^{-10}). The protective effects on tuberculosis seen with rs2228145-C were similar in size and direction to those observed in critical COVID-19 (0·66 [0·50–0·86]), Crohn's disease (0·57 [0·44–0·74]), and rheumatoid arthritis (0·45 [0·36–0·58]), all of which benefit from the therapeutic effects of IL-6 antagonism.

Interpretation Our findings propose a causal relationship between reduced IL-6 signalling and lower risk of tuberculosis, akin to the effect seen in other IL-6 mediated diseases. This study suggests that IL-6 antagonists do not increase the risk of tuberculosis but rather should be investigated as therapeutic adjuncts in its treatment.

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Introduction

Up to a quarter of the world's population shows evidence of *Mycobacterium tuberculosis* exposure, but only a small proportion develop symptomatic tuberculosis, translating to approximately 10·6 million new cases and 1·3 million deaths worldwide in 2022.[1] Immune responses to *M tuberculosis* infection can determine clinical outcomes, as shown by elevated tuberculosis risk in people with HIV co-infection, genetic deficiencies of IFN signalling, and those receiving biologics that attenuate TNF activity.[2] The cytokine IL-6 is universally observed in immune responses to *M tuberculosis* infection, but its role in the natural history of tuberculosis remains unclear.[2]

IL-6 can modulate T-cell differentiation and B-cell antibody production. IL-6 can also regulate stromal cell production of cytokines, chemokines, and extracellular matrix proteases.[3] IL-6 is pivotal to the pathophysiology of several inflammatory diseases, including COVID-19, rheumatoid

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Research in context

Evidence before this study

IL-6 cytokine responses are a universal feature of *Mycobacterium tuberculosis* infections, but whether they play a pivotal role in individuals developing tuberculosis is not known. Filling this knowledge gap will address two questions. First, do IL-6 antagonist drugs, such as tocilizumab, confer a risk of tuberculosis development in individuals with asymptomatic *M tuberculosis* infection? Second, could modulation of the IL-6 pathway be harnessed to improve treatment of established tuberculosis?

Our study sought to use human genetic data to establish whether IL-6 signalling activity is predicted to be causally associated with the risk of tuberculosis. We searched PubMed for English-language research articles published from database inception to Oct 1, 2023, using terms "interleukin 6", "tuberculosis", "human" and "genetic". This search yielded 391 studies, but only three of these studies related to tuberculosis risk and genetic variation in the IL-6 or IL-6 receptor genes, and each included only a single ancestry. To our knowledge, no study has performed multi-ancestry meta-analyses or mendelian randomisation using multiple single nucleotide polymorphisms to assess a causal relationship between IL-6 signalling and tuberculosis risk.

Added value of this study

Currently, IL-6 responses are assumed to be crucial in protecting from tuberculosis. However, our findings challenge this view. We performed mendelian randomisation in 17 multi-ancestry

genome-wide association studies to show that lower IL-6 signalling is likely to be causally associated with protection from tuberculosis. Crucially, the effect size observed between lower IL-6 activity and tuberculosis risk was similar to that observed in other conditions (critical COVID-19, Crohn's disease, and rheumatoid arthritis), in which IL-6 antagonists are used to treat established disease, indicating that similar approaches could have therapeutic benefit in tuberculosis.

Implications of all the available evidence

Many chronic inflammatory conditions benefit therapeutically from IL-6 antagonists. Current assumptions that these drugs increase tuberculosis risk mean that patients are routinely screened and treated for possible asymptomatic *M tuberculosis* infection. This approach delays the receipt of IL-6 antagonist therapy and introduces the risk of adverse effects from antibiotics that target *M tuberculosis*. Our findings suggest treating asymptomatic *M tuberculosis* infection before the receipt of IL-6 antagonists could be unnecessary.

Additionally, because IL-6 antagonists are used to treat established inflammatory diseases, our findings indicate that tuberculosis could be considered in the same way. This approach would support early clinical studies exploring therapeutic benefit of IL-6 pathway antagonists, such as tocilizumab, as adjuncts to antibiotics in the treatment of tuberculosis.

arthritis, and Crohn's disease, exemplified by therapeutic benefit of IL-6 antagonism by tocilizumab in these contexts.[4–6] In tuberculosis, IL-6 promotes Th1 responses but is not protective in mouse models.[7,8] Longer term follow-up of IL-6 antagonist use has not identified an elevated tuberculosis risk,[9] but these drugs are considered to predispose to tuberculosis by many clinical guidelines and regulators, recommending the screening and treatment for latent *M tuberculosis* infection before their use.[10] By contrast, increased blood IL-6 activity is associated with more severe pulmonary tuberculosis and post-treatment lung impairment,[11–14] and elevated IL-6 responses are observed in people with tuberculosis compared with healthy individuals from ex-vivo stimulated monocytes and at the site of in-vivo standardised mycobacterial antigen challenge, accompanied by greater recruitment of Th17 cells and neutrophils, which both have the potential to drive tissue pathology.[15]

IL-6 exerts biological effects through binding the IL-6 receptor, which exists in both membrane-bound and soluble forms.[3] Genetic variants in *IL6R,* coding for the IL-6 receptor, associate with altered IL-6 signalling. The minor allele (C) of one variant, rs2228145 (also known as Asp358Ala), has a frequency of approximately 10% in African populations and 40% in European populations,[16] and is associated with alternative splicing of IL-6 receptors and increased proteolytic cleavage by ADAM17 of

membrane-bound IL-6 receptors, leading to an increase in soluble IL-6 receptors, and alone accounting for approximately 40% of the variance in plasma levels. The net effect of these changes is lower expression of membrane-bound, surface IL-6 receptor and attenuated downstream classic (*cis*) IL-6 signalling activity following IL-6 ligation, coupled with lower baseline circulating C-reactive protein (CRP) levels.[16–18]

Mendelian randomisation analyses simulate a natural experiment through random inheritance of single nucleotide polymorphism (SNP) alleles and establish causal inference of this genetic variation on outcome through its effect on an exposure. In IL-6 biology, *IL6R* SNP alleles serve as instrumental variables, and measures of IL-6 signalling include baseline CRP levels. rs2228145-C is associated with reduced odds of developing rheumatoid arthritis and Crohn's disease.[19] In mendelian randomisation studies, rs2228145-C mimics (phenocopies) the therapeutic effect of pharmacological IL-6 inhibition in cardiovascular disease and development of critical COVID-19, suggesting a benefit for IL-6 antagonism in these conditions.[20] These findings were subsequently supported by multiple randomised trials.[4–6,21] Therefore, across multiple disease groups, variation in rs2228145, and in *IL6R* more generally, matches high-grade clinical evidence for the effectiveness of therapeutic IL-6 inhibition.

Establishing a non-redundant, functional role for IL-6 in tuberculosis could establish whether universal tuberculosis screening in the use of tocilizumab is indicated, and whether host-directed therapy strategies involving the IL-6 pathway could have adjunctive therapeutic benefit in tuberculosis. In this study, we used multiple SNPs in *cis IL6R* as instrumental variables in mendelian randomisation analyses in human populations across different genetic ancestries to test the hypothesis that IL-6 signalling is causally associated with the risk of developing tuberculosis.

Methods

Search strategy and selection criteria

We performed a meta-analysis of genome-wide association studies (GWAS) assessing host genetic susceptibility to tuberculosis. We used GWAS summary statistics in two-sample mendelian randomisation analyses to estimate the causal effect of reduced IL-6 signalling on tuberculosis.

We screened the European Bioinformatics Institute, the MRC Integrative Epidemiology Unit GWAS catalogues, and the MEDLINE database using the terms "tuberculosis" AND "GWAS" OR "Genome wide association study". Searches were performed by two authors (FH and TP) and conflicts were resolved with a third author (GP). Our inclusion criteria were: case–control GWAS published in English from Jan 1, 2000, to Jan 1, 2024; publicly available summary statistics; inclusion of the rs2228145 SNP; and use of tuberculosis as an outcome, accepting the definition of tuberculosis used in each included study (table 1).

For all included studies, we reviewed the papers they cited and, using Google Scholar, the papers that cited them. When multiple GWAS on the same population were available (eg, UK Biobank), the most recent study was used. Further details, including exclusion criteria, are available in the appendix (p 2).

Data analysis

For all GWAS, we extracted effect estimates, standard errors, and allele frequencies for the rs2228145 SNP and for SNPs within 300 kilobases of *IL6R* and within 300 kilobases of *CRP*. Mendelian randomisation estimates were generated by the Wald ratio and were meta-analysed using an inverse variance weighted (IVW) approach. Between-study heterogeneity was assessed using I^2. We report both fixed-effects and random-effects analyses across cohorts. There was no systematic assessment of the risk of bias because all studies used a standard GWAS systematic approach.

We considered the genetic background of the exposure and outcome datasets, because ancestries could vary by allele frequency, linkage disequilibrium patterns, effect sizes at individual SNPs, and interactions with the environment or other genetic variants.[35] These variables can contribute to substantial bias in estimates and can also shroud ancestry-specific effects. For rs2228145, previous work has established similar effect sizes on IL-6 signalling across all tested ancestries,[36] so we calculated mendelian randomisation estimates using the effect of rs2228145 on CRP using exposure data generated in GWAS performed across multiple ancestries, terming these analyses multi-ancestry mendelian randomisation. By contrast, we could not be certain *cis CRP* or *cis IL6R* SNPs affect CRP levels or plasma IL-6 receptor protein levels, respectively, to the same degree in different ancestries. Therefore, we identified SNPs and generated their exposure estimates separately for different ancestry groups, as defined by the closest reference population in the 1000 Genomes Project: European, African, South Asian, and East Asian.[37] We restricted mendelian randomisation analyses to calculating the effect of these ancestry-specific SNPs on outcomes in GWAS grouped by the same ancestral category.

In our primary analyses, we performed mendelian randomisation on the odds of tuberculosis using the rs2228145 SNP, weighted by the effect of this SNP on log CRP, which is produced by hepatocytes in response to IL-6. Pharmacological blockade of IL-6 receptors leads to dramatic reductions in CRP.[38] Therefore, CRP is commonly used as a marker of IL-6 signalling in genetic studies to quantify the effect of *IL6R* variants. However, this approach cannot distinguish between CRP as a marker of IL-6 signalling or as a direct causal agent. To exclude the possibility that CRP had a direct causal effect, we undertook multi-ancestry, two-sample, mendelian randomisation analyses using SNPs *cis* to *CRP* that are associated with CRP levels via the Pan UK Biobank, using ancestry-specific exposure in GWAS and identifying cis independent SNPs by correlations based on genotype allele counts, using a threshold for inclusion of $p < 5 \times 10^{-8}$ and $r^2 > 0 \cdot 1$.[39,40] Because these genetic variants alter CRP levels by a mechanism independent of IL-6 signalling, a null effect excludes CRP as causal. We also extracted outcome in GWAS for conditions in which IL-6 signalling is associated with disease outcome (critical COVID-19, rheumatoid arthritis, Crohn's disease, and coronary artery disease),[4–6,21] and performed mendelian randomisation to compare the predicted causal effect size of IL-6 signalling on these conditions.[38,41–43]

In secondary analyses we tested IL-6 receptor concentrations in plasma as an alternative measure of IL-6 signalling. Functional and genetic studies have shown variants at *IL6R* that associate with higher concentrations of plasma IL-6 receptors alongside lower CRP concentrations and reduced IL-6 signalling.[16,44] Multi-ancestry GWAS of *IL6R* allow identification of variants in addition to rs2228145. To ensure these additional SNPs affected IL-6 signalling, we selected SNPs that affected both IL-6 receptor protein and CRP levels, using Pearson's correlation analyses to ensure an inverse relationship between these measures. Ancestry-specific *IL6R* variants were identified as for *cis CRP* analyses, with results on the scale of change in normalised protein expression of the IL-6 receptor in plasma. Given the difference in scales and units for CRP and IL-6 receptor analyses, their effect size is not directly

	Country	Tuberculosis case definition	Ancestry	GWAS tuberculosis cases; GWAS population controls	HIV status of tuberculosis cases; HIV status of population controls
Studies from the International Tuberculosis Host Genetics Consortium meta-analysis[22]					
Wellcome Trust Case Control Consortium (2007)[23]	The Gambia	Acid-fast staining and culturing of *M tuberculosis* from sputum samples	African	1316; 1382	Negative; negative
Thye et al (2010)[24]	Ghana	Acid-fast staining and culturing of *M tuberculosis* from sputum samples	African	1359; 1952	Negative; negative
Daya et al (2014)[25]	South Africa	Acid-fast staining and culturing of *M tuberculosis* from sputum samples	African	19; 577	Negative; negative
Schurz et al (2019)[26]	South Africa	Acid-fast staining and culturing of *M tuberculosis* from sputum samples	African	410; 405	Negative; negative
Unpublished (from Schurz et al [2024][22])	China	Acid-fast staining and culturing of *M tuberculosis* from sputum samples	East Asian	483; 587	NA; NA
Unpublished (from Schurz et al [2024][22])	China	Acid-fast staining and culturing of *M tuberculosis* from sputum samples	East Asian	1290; 1145	NA; NA
Qi et al (2017)[27]	China	Acid-fast staining and culturing of *M tuberculosis* from sputum samples	East Asian	972; 1537	NA; NA
Mahasirimongkol et al (2012)[28]	Japan	Acid-fast staining and culturing of *M tuberculosis* from sputum samples	East Asian	751; 3199	NA; NA
Mahasirimongkol et al (2012)[28]	Thailand	Acid-fast staining and culturing of *M tuberculosis* from sputum samples	East Asian	433; 295	Negative; negative
Unpublished (from Schultz et al [2024][22])	Estonia	Biobank tuberculosis cases	European	239; 7047	Negative; negative
Unpublished (from Schultz et al [2024][22])	Germany	NA	European	586; 333	NA; NA
Curtis et al (2015)[29]	Russia	Acid-fast staining and culturing of *M tuberculosis* from sputum samples	European	5914; 6022	Negative; NA
Additional data sources not included in the International Tuberculosis Host Genetics Consortium meta-analysis					
UK Biobank[30]	UK	Self-report of tuberculosis	European	2046; 418 427	NA; NA
FinnGen[31]	Finland	ICD A15 (respiratory-confirmed tuberculosis)	European	401; 321 302	NA; NA
Biobank Japan[32]	Japan	ICD A15–16 (respiratory tuberculosis)	East Asian	549; 211 904	NA; NA
East London Genes & Health[33]	UK	ICD A15 (respiratory-confirmed tuberculosis)	South Asian	1701; 42 487	NA; NA
Zheng et al (2018)[34]	China	Microbiological and clinical diagnosis	East Asian	833; 1220	Negative; NA

GWAS=genome-wide association studies. *M tuberculosis*=mycobacterium tuberculosis. NA=not available.

Table 1: Populations included from studies and datasets, tuberculosis case definitions, and HIV status of case and control populations

comparable, unlike the direction and statistical strength of their effect.

Sensitivity analyses included the use of both single and multiple SNPs in studies that had microbiological confirmation of tuberculosis, alternative mendelian randomisation approaches (mendelian randomisation-Egger and weighted median), and leave-one-out analyses to ensure results were robust to removal of rs2228145.[45] Further details on mendelian randomisation approaches and assumptions are available in the appendix (p 3).

Analyses were done with R (version 4.0.3) using the TwoSampleMR, meta, and tidyverse packages.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

The largest included study was a multi-ancestry, GWAS meta-analysis by the International Tuberculosis Host Genetics Consortium that comprised 12 GWAS across diverse populations, extracting associations from each
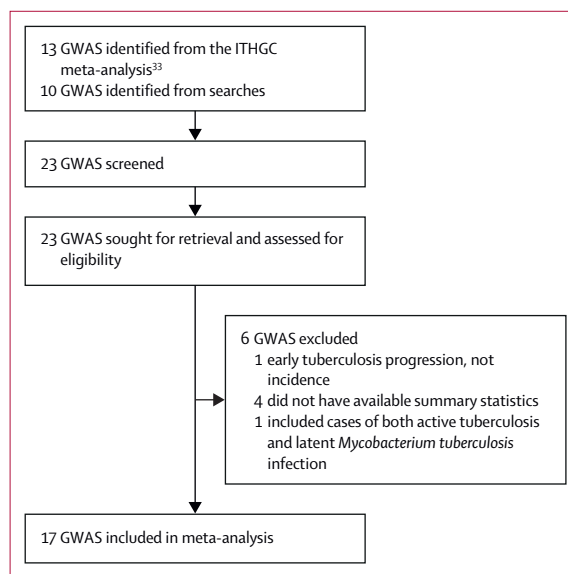

Figure 1: Study selection
GWAS=genome-wide association studies. ITHGC=International Tuberculosis Host Genetics Consortium.

study, including the summary statistics, demographics, tuberculosis case definitions, and methodology (figure 1).[22] Our searches also identified five further relevant studies with publicly available summary statistics: four cohort studies (UK Biobank,[30] FinnGen,[31] East London Genes & Health,[33] and Biobank Japan[32]) and one case–control study from China not included in the meta-analysis by the International Tuberculosis Host Genetics Consortium,[22] for which we subsequently obtained summary statistics (figure 1; table 1).[34] Three GWAS were excluded because summary statistics were not available,[46–48] and three more were excluded because case definitions were not limited to tuberculosis.[49–51]

We initially focused on the major genetic determinant of IL-6 activity, rs2228145, using the available GWAS and the definitions from each study to identify tuberculosis cases and controls (table 1). A meta-analysis across all 17 GWAS, comprising 19 032 individuals with tuberculosis (cases) and 1 019 821 individuals in population control groups showed the C allele of rs2228145 was associated with decreased risk of tuberculosis, with a summary odds ratio (OR) of 0·94 (95% CI 0·92–0·97; p=6·8 × 10^{-6}) per each additional C allele in a fixed-effects meta-analysis (table 2). There was weak evidence of heterogeneity across studies (I^2=0·315; p=0·11). Random-effects meta-analysis had similar point estimates but wider CIs than the fixed-effects meta-analysis (OR 0·95 [95% CI 0·92–0·98]; p=0·0017).

To quantify the predicted causal effect of altered IL-6 signalling activity on tuberculosis risk, we performed mendelian randomisation using the rs2228145 SNP. Results were weighted on the CRP reduction associated with this SNP in an independent GWAS,[40] so that ORs lower than one represent reduced tuberculosis risk with lower IL-6 signalling. This approach revealed a predicted causal effect of reduced IL-6 signalling on tuberculosis with an OR of 0·52 (95% CI 0·39–0·69; p=6·8 × 10^{-6}) for each natural log CRP decrease (figure 2).

Given our use of CRP as a marker for IL-6 signalling, we sought to exclude a direct effect of CRP itself on the association with tuberculosis. We identified ancestry-specific variantsto the *cis CRP* gene associated with CRP levels,[44] yielding instruments containing 19 independent SNPs in African, 13 in east Asian, 32 in south Asian, and 41 in European ancestry populations (appendix p 11). We used these to perform mendelian randomisation on each tuberculosis GWAS, matching the ancestry of the instrument to that of the outcome dataset. This analysis showed that, contrasting with the effect of *IL6R* rs2228145 SNP, there was no significant effect of *CRP* variants on tuberculosis case status (OR per SD decrease in CRP 0·91 [95% CI 0·81–1·03]; p=0·13 in fixed-effects meta-analysis; appendix p 7).

To extrapolate the clinical relevance of IL-6 signalling in tuberculosis, we compared the predicted causal effect sizes on tuberculosis risk with those for other clinical conditions in which therapeutic attenuation of IL-6 signalling is associated with reduced risk of disease or is used for

|	Country	OR (95% CI)	SE	C allele frequency	p value
Wellcome Trust Case Control Consortium (2007)[23]	The Gambia	1·23 (1·0–1·51)	0·1032	0·09	0·045
Thye et al (2010)[24]	Ghana	1·08 (0·91–1·28)	0·0876	0·09	0·37
Daya et al (2014)[25]	South Africa	0·99 (0·63–1·57)	0·2342	0·22	0·97
Schurz et al (2019)[26]	South Africa	0·92 (0·69–1·23)	0·147	0·16	0·56
Unpublished (from Schurz et al [2024])[22]	China	0·93 (0·72–1·2)	0·1306	0·42	0·57
Unpublished (from Schurz et al [2024])[22]	China	0·96 (0·85–1·08)	0·0599	0·42	0·49
Qi et al (2017)[27]	China	0·86 (0·77–0·97)	0·0606	0·41	0·016
Zheng et al (2018)[34]	China	1·01 (0·88–1·16)	0·069	NA	0·87
Biobank Japan[32]	Japan	0·91 (0·8–1·02)	0·0617	0·39	0·11
Mahasirimongkol et al (2012)[28]	Japan	0·92 (0·81–1·04)	0·062	0·60	0·17
Mahasirimongkol et al (2012)[28]	Thailand	1·00 (0·92–1·09)	0·0439	0·77	0·99
East London Genes & Health[33]	UK	0·93 (0·86–1·0)	0·0396	0·29	0·06
Unpublished (from Schurz et al [2024])[22]	Estonia	1·17 (0·97–1·42)	0·098	0·33	0·11
FinnGen[31]	Finland	0·87 (0·73–1·03)	0·0875	0·30	0·12
Unpublished (from Schurz et al [2024])[22]	Germany	1·01 (0·82–1·23)	0·1041	0·38	0·96
Curtis et al (2015)[29]	Russia	0·91 (0·86–0·96)	0·0287	0·33	0·0007
UK Biobank[30]	UK	0·92 (0·86–0·98)	0·0319	0·39	0·0069
Meta-analysis (fixed-effects model)	··	0·94 (0·92–0·97)	0·0137	··	6·8 × 10^{-6}
Meta-analysis (random-effects model)	··	0·95 (0·92–0·98)	0·0172	··	0·0017

GWAS=genome-wide association study. NA=not available. OR=odds ratio. SNP=single nucleotide polymorphism.

Table 2: Associations of the rs2228145-C SNP in each GWAS and meta-analyses using fixed-effects or random-effects models

treatment.[4–6,21] These analyses showed similar effect estimates between tuberculosis and all these conditions, with reduced IL-6 signalling associated with lower risk of all diseases, and larger point estimates seen for tuberculosis than those for the effect on critical COVID-19, Crohn's disease, and coronary artery disease (figure 3).

To validate the relationship between IL-6 and tuberculosis beyond a single SNP, we identified independent *IL6R* SNPs that associated with IL-6 receptor plasma protein levels in a large, multi-ancestry GWAS.[44] We focused on SNPs with effect estimates on IL-6 receptor that inversely correlate with those for CRP (r=–0·74; p=4·0 × 10^{-13}; appendix pp 8, 14), supporting their relevance in IL-6 signalling. We then identified ancestry-specific SNPs (40 in African, 17 in east Asian, 51 in south Asian, and 61 in European ancestry populations) as instruments and performed mendelian randomisation on tuberculosis outcome matched to each GWAS ancestry. In this analysis, increasing IL-6 receptor plasma protein was predicted to be protective for tuberculosis (summary OR 0·94 per SD change in IL-6 receptor plasma protein [95% CI 0·93–0·96]; p=2·4 × 10^{-10}) using a fixed-effects model (figure 4; appendix p 15). There was evidence of moderate heterogeneity (I^2=0·51) across the GWAS. The OR from a random effects model was 0·95 (95% CI 0·92–0·98; p=0·0011).

We performed subgroup analyses in studies that had microbiological confirmation of tuberculosis, showing
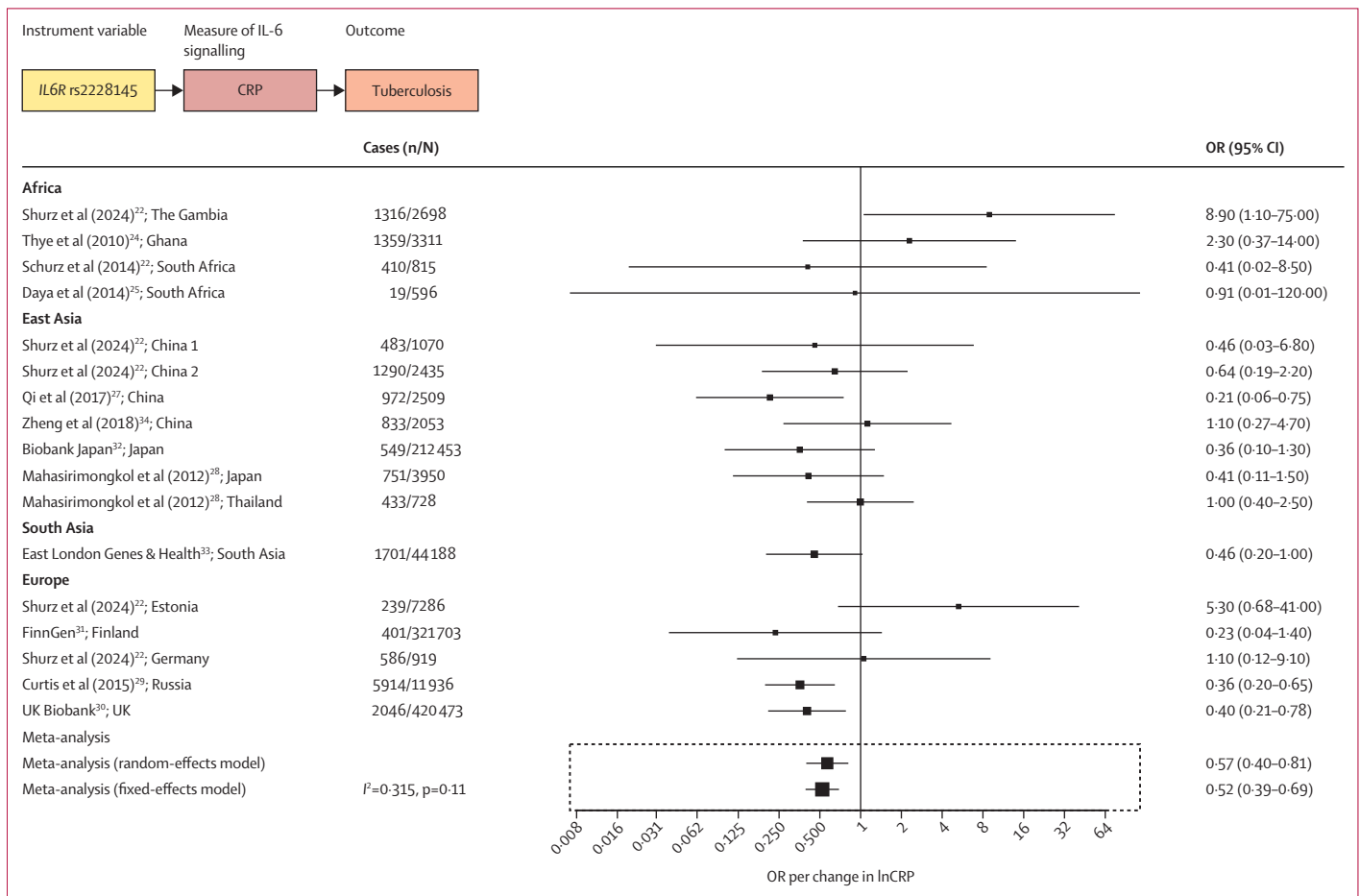
Figure 2: Predicted causal effect of altered IL-6 signalling activity on tuberculosis risk using mendelian randomisation analyses at *IL6R* rs2228145 alone
ORs for the effect of reduced IL-6 signalling on tuberculosis weighted on the scale of natural log (ln) CRP decrease. ORs less than 1 indicate lower risk of tuberculosis. Mendelian randomisation estimates were generated by the Wald ratio, were meta-analysed using an inverse variance weighted approach, and use rs2228145 as a single instrumental variable. Study participants included are depicted as the number of tuberculosis cases (n) over the total number of cases and controls (N) in each study. CRP=C-reactive protein. OR=odds ratio.
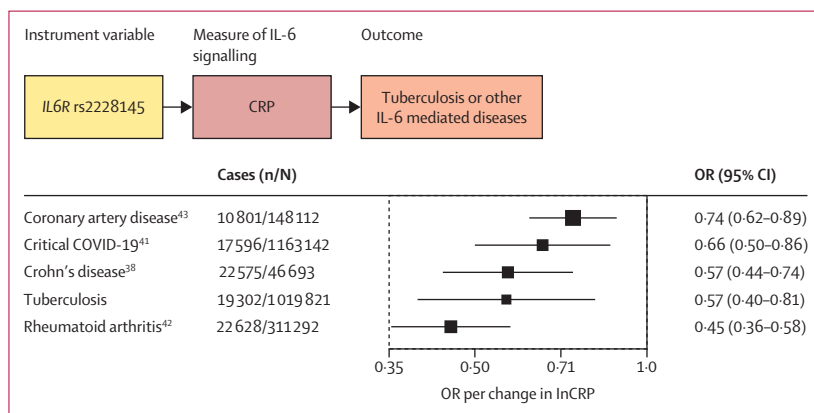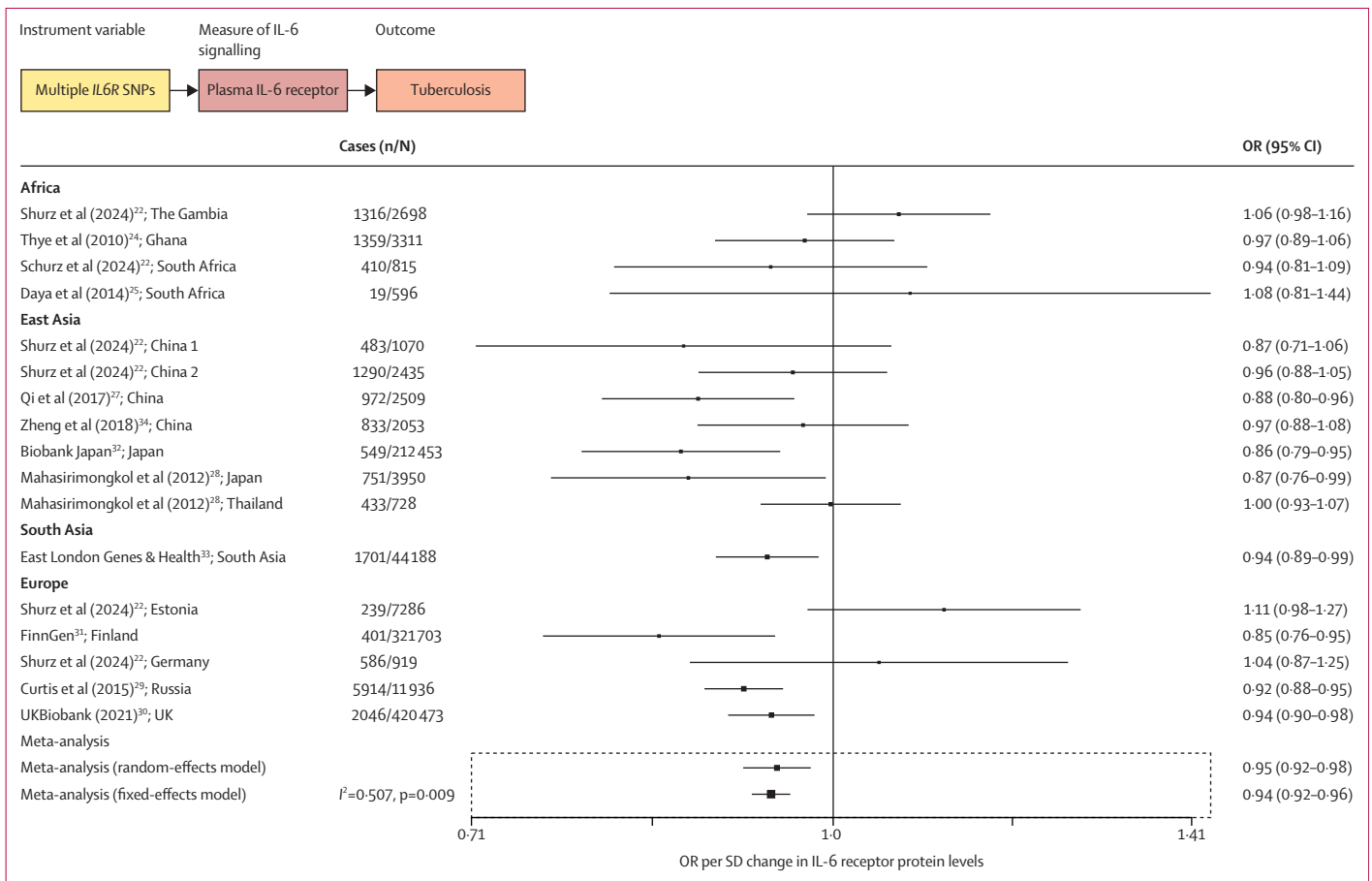

Figure 3: Comparison of mendelian randomisation effect estimates at *IL6R* rs2228145 in tuberculosis and other conditions in which IL-6 signalling is associated with disease risk
ORs for the effect of reduced IL-6 signalling on diseases are shown, weighted on the scale of natural log (ln) CRP decrease. ORs less than 1 indicate lower risk of disease. Estimates for tuberculosis were derived from fixed-effects meta-analysis across studies included in figure 1. Effect estimates for all other conditions were extracted directly from genome-wide association study summary statistics. Mendelian randomisation estimates were generated by the Wald ratio and used rs2228145 as a single instrumental variable. Study participants included are depicted as the number of disease cases (n) over the total number of cases and controls (N) in each study. CRP=C-reactive protein. OR=odds ratio.

similar effect estimates in both single and multiple SNP analyses (appendix p 9). We validated our ancestry-specific mendelian randomisation analyses using different meta-analytic approaches (mendelian randomisation-Egger and weighted median), generating similar results to those using IVW (appendix p 19). To exclude the possibility that rs2228145 was the sole driver of the causal association with tuberculosis, we performed leave-one-out analyses excluding the rs2228145 SNP. This yielded similar effect sizes (OR 0·93 [95% CI 0·91–0·96]; p=7·0 × 10^{-7}) to that with all SNPs, and exclusion of any other SNP also did not affect the association observed with tuberculosis risk (appendix p 10).

Discussion

To assess the role of the IL-6 pathway in human *M tuberculosis* infection, we performed a meta-analysis of the association between genetic variation at the *IL6R* locus and odds of tuberculosis comprising 19 302 individuals with tuberculosis and 1 019 821 population controls across 17 GWAS in African, south Asian, east Asian, and European ancestries. We found the C allele of the *IL6R* SNP

Instrument variable	Measure of IL-6 signalling	Outcome
Multiple *IL6R* SNPs	Plasma IL-6 receptor	Tuberculosis

	Cases (n/N)		OR (95% CI)
Africa			
Shurz et al (2024)[22]; The Gambia	1316/2698		1·06 (0·98–1·16)
Thye et al (2010)[24]; Ghana	1359/3311		0·97 (0·89–1·06)
Schurz et al (2024)[22]; South Africa	410/815		0·94 (0·81–1·09)
Daya et al (2014)[25]; South Africa	19/596		1·08 (0·81–1·44)
East Asia			
Shurz et al (2024)[22]; China 1	483/1070		0·87 (0·71–1·06)
Shurz et al (2024)[22]; China 2	1290/2435		0·96 (0·88–1·05)
Qi et al (2017)[27]; China	972/2509		0·88 (0·80–0·96)
Zheng et al (2018)[34]; China	833/2053		0·97 (0·88–1·08)
Biobank Japan[32]; Japan	549/212 453		0·86 (0·79–0·95)
Mahasirimongkol et al (2012)[28]; Japan	751/3950		0·87 (0·76–0·99)
Mahasirimongkol et al (2012)[28]; Thailand	433/728		1·00 (0·93–1·07)
South Asia			
East London Genes & Health[33]; South Asia	1701/44 188		0·94 (0·89–0·99)
Europe			
Shurz et al (2024)[22]; Estonia	239/7286		1·11 (0·98–1·27)
FinnGen[31]; Finland	401/321 703		0·85 (0·76–0·95)
Shurz et al (2024)[22]; Germany	586/919		1·04 (0·87–1·25)
Curtis et al (2015)[29]; Russia	5914/11 936		0·92 (0·88–0·95)
UKBiobank (2021)[30]; UK	2046/420 473		0·94 (0·90–0·98)
Meta-analysis			
Meta-analysis (random-effects model)			0·95 (0·92–0·98)
Meta-analysis (fixed-effects model)	I^2=0·507, p=0·009		0·94 (0·92–0·96)

0·71   1·0   1·41

OR per SD change in IL-6 receptor protein levels

Figure 4: **Predicted causal effect of reduced IL-6 signalling activity on tuberculosis risk using ancestry-specific, multiple *IL6R* SNPs**
ORs for the effect of reduced IL-6 signalling on tuberculosis weighted on the scale of SD change in increased IL-6 receptor plasma protein. ORs less than 1 indicate lower risk of tuberculosis. Mendelian randomisation estimates were generated by the Wald ratio and meta-analysed using an inverse variance weighted approach. Study participants included are depicted as the number of tuberculosis cases (n) over the total number of cases and controls (N) in each study. OR=odds ratio. SNP=single nucleotide polymorphism.

rs2228145, which phenocopies the effect of IL-6 antagonists such as tocilizumab, to be associated with lower odds of tuberculosis. Mendelian randomisation using both this single and other neighbouring, functional *IL6R* SNPs support an overarching conclusion that reduced classic IL-6 signalling is predicted to be causally associated with lower odds of tuberculosis, similar to the protective effect in other IL-6 mediated diseases.

Our interpretation of mendelian randomisation analyses necessitated assuming the *cis IL6R* SNPs represent a proxy for decreased IL-6 activity. rs2228145-C promotes cleavage of cell surface IL-6 receptors and reduces classic IL-6 signalling, lowering baseline CRP levels and phenocopying pharmacological IL-6 antagonism.[16–18,21,52] For other *IL6R* SNPs, we used the inverse relationship between CRP and IL-6 receptor plasma protein to instrument an altered homoeostasis set point that decreases classic IL-6 signalling. These analyses identified a clear predicted causal effect of reduced IL-6 signalling and lower tuberculosis risk, challenging the current view that inhibition of IL-6 activity in vivo confers a susceptibility to tuberculosis disease.

Although long term follow-up and patient registries have not identified an association between IL-6 antagonists and tuberculosis,[9] there remains uncertainty,[53] such that screening and treatment for latent *M tuberculosis* infection is still recommended before the commencement of these drugs,[10] delaying initiation of indicated biological therapy and predisposing patients to the adverse effects of the antibiotics used. In contrast to the known association with pyogenic infections, our findings indicate that IL-6 antagonists are unlikely to increase the risk of tuberculosis, and this should be considered by guideline committees monitoring infections, including by *M tuberculosis*, associated with these compounds.[10,54]

IL-6 promotes *M tuberculosis* growth and monocyte expansion following human haematopoietic stem-cell infection.[11] Furthermore, IL-6 activity is associated with more extensive tuberculosis,[11] greater radiological severity, and impaired lung function.[12,13] Tuberculosis is characterised by high baseline levels of IL-6 activity associated with greater induction of the downstream protein SOCS3 that could in turn attenuate Th1 cell responses important for

microbiological control and, potentially, promote immunopathology.[55] IL-6 responses can also drive tissue damage by facilitating Th17 cell differentiation, IL-17 activity, neutrophil chemotaxis, and fibroblast matrix metalloproteinase production.[3] This constellation of immune responses is elevated in patients with tuberculosis compared with patients with latent *M tuberculosis* infection or cured tuberculosis following standardised in-vivo mycobacterial antigen challenge.[15] On the premise that tuberculosis is a manifestation of immunopathology, one unifying hypothesis could be that attenuated IL-6 signalling protects from clinically apparent symptomatic tuberculosis by limiting IL-6 mediated tissue immunopathology in subclinical *M tuberculosis* infection.[56]

The major strength of our study is the functional nature of the *IL6R* SNPs on IL-6 signalling[16–18] and the well established association between variation at *IL6R* in mendelian randomisation studies and clinical outcomes of IL-6 inhibition,[6,20,21,52] further supporting the hypothesis that the protective effect of the *IL6R* SNPs on tuberculosis is through attenuation of classic IL-6 signalling. Further strengths include the large and diverse patient populations; the use of previously validated CRP and IL-6 receptors as proxy for classic IL-6 signalling activity; demonstration that the effects observed were not mediated by CRP itself; and assurance that candidate SNP instruments were identified from independent, non-tuberculosis GWAS. For analyses using multiple *cis IL6R* SNPs, we used ancestry-specific SNPs to identify differences in linkage disequilibrium and effect sizes across ancestries. This approach might have been overly cautious given the rarity of ancestry-specific effects,[57] and the European predominance in the UK Biobank could have limited the identification of all IL-6 receptor SNPs across ancestries. Nevertheless, use of these multiple IL-6 receptor SNPs as ancestry-specific instruments on protein levels still increased the power and precision of our effect estimates.[44] Leave-one-out analyses supported that this effect was independent of any one SNP, including rs2228145, indicating the association with tuberculosis risk was through attenuated IL-6 signalling rather than solely through the effect of a single *IL6R* SNP. Furthermore, the similar association between IL-6 and tuberculosis with that seen for other IL-6 mediated inflammatory diseases, in which the *IL6R* rs2228145-C allele is protective and IL-6 antagonism is therapeutic, indicates a putative pathological role played by IL-6 in tuberculosis and highlights the translational potential of our findings.

Limitations included variable tuberculosis case definitions and potential misclassification, offset by the large sample sizes and findings robust to microbiological tuberculosis case stratification. Between BioBank Japan and the GWAS from Japan there is probably some sample overlap, but it probably involves less than 1% of all cases included and is unlikely to affect precision. Information on comorbidities such as diabetes and HIV serostatus was not available for all included GWAS populations, although most cohorts either included only individuals who were HIV seronegative or local seroprevalence was very low (eg UK Biobank, FinnGen, and BioBank Japan). We also caution against extrapolating our findings to less common tuberculosis presentations included (eg, extrapulmonary or paediatric tuberculosis). The protective effect of reduced IL-6 signalling did show some evidence of heterogeneity, with effect estimates that were smaller or reversed, or both, in some populations, especially in Africa. This variability could reflect a different natural history of tuberculosis in Africa, such as infecting *M tuberculosis* strains and population-level *M tuberculosis* exposure, correlated to, but not caused by, ancestry. Alternatively, our results reflect a genuine difference in the genetic effects of IL-6 signalling in individuals of African ancestry. However, previous analyses of IL-6 signalling in infection have not identified ancestry-specific effects,[58] and the heterogeneity in African studies, as well as in the smaller European GWAS from Estonia and Germany, could reflect either lower *IL6R* SNP allele frequency in Africa or smaller study sample sizes that reduced statistical power. Although we relate the risk of diseases to the clinical effect of tocilizumab therapy, this drug can inhibit both *cis* and *trans* IL-6 signalling, and our exposures only reflect a homoeostasis set point change in *cis* IL-6 activity, and a lack of *trans* signalling biological readouts preclude assessment of its specific role. Moreover, mendelian randomisation estimates predict the effects of a lifetime of reduced IL-6 signalling on the risk of tuberculosis, which might qualitatively differ from the effects of short-term IL-6 antagonism.[59] A tuberculosis diagnosis requires *M tuberculosis* exposure, subclinical infection, and progression to clinical disease.[56] Thus, prospective observational or intervention studies will need to complement our genetic findings to define at which point along this timeline reduced IL-6 activity could protect from developing tuberculosis disease.

We found genetic evidence for a causal, protective effect of reduced IL-6 signalling in the development of tuberculosis, an observation that should diminish concerns that IL-6 blockade enhances tuberculosis risk. Future work will need to incorporate the effect of tuberculosis epidemiology and host genetic background to assess the precise role of IL-6 in this complex host–pathogen interaction. This will include exploring a possible role for IL-6 mediated pathology and adjunctive IL-6 antagonism in tuberculosis therapy through mechanistic studies that incorporate in-vitro cellular models and in-vivo human experimental medicine approaches.

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