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Inflammatory Diseases, Inflammatory Biomarkers, and Alzheimer Disease: An Observational Analysis and Mendelian Randomization

Author(s):

Jian Huang, PhD^{1,2}; Bowen Su¹; Ville Karhunen, PhD^{1,3,4}; Dipender Gill, MD, PhD¹; Verena Zuber, PhD¹; Ari Ahola-Olli, MD, PhD^{5,6,7}; Saranya Palaniswamy, PhD^{1,3}; Juha Auvinen, MD, PhD³; Karl-Heinz Herzig, MD, PhD^{8,9}; Sirkka Keinänen-Kiukaanniemi, MD, PhD^{3,10,11}; Marko Salmi, MD, PhD¹²; Sirpa Jalkanen, MD, PhD¹²; Terho Lehtimäki, MD, PhD¹³; Veikko Salomaa, MD, PhD¹⁴; Olli T. Raitakari, MD, PhD^{15,16,17}; Paul M. Matthews, MD, DPhil^{18,19}; Paul Elliott, MBBS, PhD^{1,19,20}; Konstantinos K. Tsilidis, PhD^{1,21}; Marjo-riitta Jarvelin, MD, PhD^{1,3,10,20,22,23}; Ioanna Tzoulaki, PhD¹; Abbas Dehghan, MD, PhD¹

Corresponding Author:

Abbas Dehghan, a.dehghan@imperial.ac.uk

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Affiliation Information for All Authors: 1.Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London, London, UK; 2.Singapore Institute for Clinical Sciences (SICS), Agency for Science, Technology and Research (A*STAR), Singapore; 3.Center for Life Course Health Research, Faculty of Medicine, University of Oulu, Oulu, Finland; 4.Research Unit of Mathematical Sciences, University of Oulu, Oulu, Finland; 5.The Stanley Center for Psychiatric Research, Broad Institute of MIT and Harvard, Cambridge, MA, USA; 6.Analytical and Translational Genetics Unit, Massachusetts General Hospital, Boston, MA, USA; 7.Institute for Molecular Medicine Finland, University of Helsinki, Helsinki, Finland; 8.Research Unit of Biomedicine, Medical Research Center (MRC), University of Oulu, University Hospital, Oulu, Finland; 9.Department of Gastroenterology and Metabolism, Poznan University of Medical Sciences, Poznan, Poland; 10.Unit of Primary Care, Oulu University Hospital, Oulu, Finland; 11.Healthcare and Social Services of Selänne, Pyhäjärvi, Finland and city of Oulu, Oulu, Finland; 12.MediCity and Institute of Biomedicine, University of Turku, Turku, Finland; 13.Department of Clinical Chemistry, Fimlab Laboratories, and Finnish Cardiovascular Research Center, Tampere, Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland; 14.Finnish Institute for Health and Welfare, Helsinki, Finland; 15.Research Centre of Applied and Preventive Cardiovascular Medicine, University of Turku, Turku, Finland; 16.Department of Clinical Physiology and Nuclear Medicine, Turku University Hospital, Turku, Finland; 17.Centre for Population Health Research, University of Turku and Turku University Hospital, Turku, Finland; 18.Department of Brain Sciences, Faculty of Medicine, Imperial College London, London, UK; 19.UK Dementia Research Institute at Imperial College London, London, UK; 20.MRC Centre for Environment and Health, School of Public Health, Imperial College London, London, UK; 21.Department of Hygiene and Epidemiology, University of Ioannina Medical School, Ioannina, Greece; 22.Biocenter Oulu, University of Oulu, Oulu, Finland; 23.Department of Life Sciences, College of Health and Life Sciences, Brunel University London, London, UK;

Equal Author Contribution:

Jian Huang and Bowen Su contributed equally to this work as first authors. Ioanna Tzoulaki and Abbas Dehghan contributed equally to this work as senior authors.

Contributions:

Jian Huang: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data

Bowen Su: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data

Ville Karhunen: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data

Dipender Gill: Drafting/revision of the manuscript for content, including medical writing for content

Verena Zuber: Drafting/revision of the manuscript for content, including medical writing for content; Additional contributions: Providing statistical guidance

Ari Ahola-Olli: Drafting/revision of the manuscript for content, including medical writing for content

Saranya Palaniswamy: Drafting/revision of the manuscript for content, including medical writing for content

Juha Auvinen: Drafting/revision of the manuscript for content, including medical writing for content

Karl-Heinz Herzog: Drafting/revision of the manuscript for content, including medical writing for content

Sirkka Keinänen-Kiukaanniemi: Drafting/revision of the manuscript for content, including medical writing for content

Marko Salmi: Drafting/revision of the manuscript for content, including medical writing for content
Sirpa Jalkanen: Drafting/revision of the manuscript for content, including medical writing for content
Terho Lehtimäki: Drafting/revision of the manuscript for content, including medical writing for content
Veikko Salomaa: Drafting/revision of the manuscript for content, including medical writing for content
Olli T. Raitakari: Drafting/revision of the manuscript for content, including medical writing for content
Paul M. Matthews: Drafting/revision of the manuscript for content, including medical writing for content
Paul Elliott: Drafting/revision of the manuscript for content, including medical writing for content
Konstantinos K. Tsilidis: Drafting/revision of the manuscript for content, including medical writing for content
Marjo-riitta Jarvelin: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data
Ioanna Tzoulaki: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept or design; Analysis or interpretation of data
Abbas Dehghan: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept or design; Analysis or interpretation of data

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Abstract**Objectives**

Whether chronic autoimmune inflammatory diseases causally affect the risk of AD is controversial. We characterised the relationship between inflammatory diseases and the risk of AD and explore the role of circulating inflammatory biomarkers in the relationships between inflammatory diseases and AD.

Methods

We performed observational analyses for chronic autoimmune inflammatory diseases and risk of AD using data from 2,047,513 participants identified in the UK Clinical Practice Research Datalink (CPRD). Using data of a total of more than 1,100,000 individuals from 15 large scale genome-wide association study (GWAS) datasets, we performed two-sample Mendelian randomisation (MR) to investigate the relationships between chronic autoimmune inflammatory diseases, circulating inflammatory biomarker levels, and risk of AD.

Results

Cox regression models using CPRD data showed that overall incidence of AD was higher among patients with inflammatory bowel disease (IBD) (hazard ratio (HR)=1.17; 95%CI 1.15 to 1.19; P-value= 2.1×10^{-4}), other inflammatory polyarthropathies & systematic connective tissue disorders (OID) (HR=1.13; 95%CI 1.12 to 1.14; P-value= 8.6×10^{-5}), psoriasis (HR=1.13; 95%CI 1.10 to 1.16; P-value= 2.6×10^{-4}), rheumatoid arthritis (RA) (HR=1.08; 95%CI 1.06 to 1.11; P-value= 4.0×10^{-4}), and multiple sclerosis (MS) (HR=1.06; 95%CI 1.04 to 1.07; P-value= 2.8×10^{-4}) compared to the age (± 5 years) and sex-matched comparison groups free from all inflammatory diseases under investigation. Bidirectional MR analysis identified relationships between chronic autoimmune inflammatory diseases and circulating inflammatory biomarkers. Particularly, circulating monokine induced by gamma interferon (MIG) level was suggestively associated with a higher risk of AD (odds ratio from inverse variance weighted (OR_{IVW})=1.23; 95%CI 1.06 to 1.42; P_{IVW} =0.007), and lower risk of Crohn's disease (OR_{IVW} =0.73; 95%CI -0.62, 0.86; P_{IVW} = 1.3×10^{-4}). Colocalisation supported a common causal SNP for MIG and Crohn's disease (posterior probability=0.74) but not AD

(posterior probability=0.03). Using a two-sample MR approach, genetically predicted risks of inflammatory diseases were not associated with higher AD risk.

Conclusion

Our data suggest that the association between inflammatory diseases and risk of AD is unlikely to be causal and may be a result of confounding. In support, while inflammatory biomarkers showed evidence for causal associations with inflammatory diseases, evidence was weak that they affected both inflammatory disease and AD.

Introduction

Progressive cerebral neurodegeneration with extracellular amyloid- β plaques and intraneuronal neurofibrillary tangles are pathological features distinguishing Alzheimer's disease (AD), the most common cause of dementia. The brains of AD patients show evidence for a sustained brain innate immune response.¹ Moreover, higher levels of circulating inflammatory markers in the blood were observed in AD patients compared to that of healthy controls.² Observational studies and meta-analyses have reported a higher risk of dementia among patients with rheumatoid arthritis (RA)³, psoriasis⁴, and inflammatory bowel disease (IBD)⁵, although contradictory results also have been reported.^{6,7} Whether chronic autoimmune inflammatory diseases causally affect the risk of AD is controversial.

The observed associations between these inflammatory diseases and AD may be due to common circulating inflammatory biomarkers, modulation of which could provide opportunities for the prevention and treatment of AD. However, prior studies showing inconsistent effects of anti-inflammatory drugs on AD have cast doubt on the potential for therapeutic modulation of chronic inflammation in AD.^{8,9} In this study, we investigated the relationship between different chronic autoimmune inflammatory diseases and risks of AD/dementia using a real-world observational analysis using large-scale population-based electronic health records and an instrumental variable analysis with genetic instruments known as Mendelian randomisation (MR), which is less susceptible to confounding and

reverse causation than conventional observational analysis.¹⁰ We performed bidirectional MR to further examine the role of circulating inflammatory proteins associated with or induced by autoimmune disease in the relationships between inflammatory diseases and AD.

Identification of such inflammatory proteins could identify potential therapeutic targets for AD.

Materials and methods

Real-world observational analysis

Clinical Practice Research Datalink (CPRD)

The study cohort was selected from CPRD between 1st January 1987 and 3rd May 2018 with the primary care data linking to secondary care data from Hospital Episode Statistics (HES), mortality data from the Office of National Statistics (ONS) and small-area measures of social deprivation.¹¹

Sampling

We designed a cohort study in which exposed participants were eligible CPRD participants who were diagnosed with one of the following inflammatory diseases: 1) RA, 2) IBD, 3) multiple sclerosis (MS), 4) psoriasis, and 5) other inflammatory polyarthropathies & systematic connective tissue disorders (OID) (**eMethods in the Supplement and eTables 1–5**). Exposed participants were excluded if their dates of inflammatory disease diagnoses were missing or if their dates of inflammatory disease diagnoses were after or less than one year prior to their incident AD diagnosis. Each eligible exposed participant was matched on age

(±5 years) and sex with two non-exposed participants who had no record of these inflammatory diseases from the remaining CPRD participants.

Outcome definition

AD case was defined by the presence of one or more AD diagnosis codes from a selected list of CPRD Medcodes or International Classification of Diseases, 10th Revision (ICD10) codes in linked HES or ONS datasets (**eTable 6**). The AD diagnosis date was defined as the date of the first AD recording in the CPRD, HES or ONS dataset. Where dates of diagnoses were missing, the diagnosis records were excluded. We identified 134,952 AD cases for our analysis (**eFigure 1 in the Supplement**).

Conventional Cox regression models and propensity score analysis

Conventional Cox regression models with follow-up time as the underlying timescale were used to estimate the risk of developing AD with hazard ratios (HR) and 95% confidence intervals (CI) with the presence of inflammatory disease. Eligible exposed participants were coded as 1, while non-exposed participants were coded as 0. The time of the first record of inflammatory disease diagnosis for exposed participants and their matched non-exposed participants was considered the baseline of the cohort. The end of follow-up was defined as the date of 1) AD incidence (as defined above), 2) death, 3) practice transfer out date, 4) last data collection date of GP practice, or 5) last follow-up date from CPRD (01/05/2018), whichever occurred first (**eFigure 2 in the Supplement**).

Covariates that potentially influenced or strongly associated with the AD onset were adjusted for in Cox regression models. These included region in the UK, Index of Multiple Deprivation (IMD, a proxy of socioeconomic status linked to CPRD), body mass index (BMI, latest record up to 5 years before baseline to reduce missing values), smoking status (latest record up to 5 years before baseline), number of GP consultations (number of records before baseline) and history of major comorbidities, including cardiovascular diseases (coronary heart disease, heart failure, stroke, peripheral arterial disease) and type II diabetes. For propensity score analysis, we adjusted for confounding by rebalancing each inflammatory disease and non-exposed groups, using inverse propensity score treatment weighting (IPTW) to account for selection assignment differences between inflammatory diseases and their comparison groups.¹² For missingness of IMD, BMI and smoking information, multiple imputation with chained equations were used in the Cox regression models and propensity score weighting models to address missingness.¹³

Competing risk analysis

Competing risk analysis using IPTW and adjusting for the same set of covariates as included in the Cox regression models was used to estimate the single-world cause-specific hazards and cumulative incidence functions (CIFs), which indicate the effect of inflammatory diseases on the risk of dementia in the presence of competing death.¹⁴

Sensitivity analyses

We also performed sensitivity analyses to assess the robustness of the analyses: 1) restricting the analyses to eligible exposed participants with their first inflammatory disease diagnosis after 2004 due to the implementation of pay for performance in primary care and

improvement of CPRD recording;¹⁵ 2) restricting the analyses to participants who could be linked to HES or ONS datasets (linkage datasets) which provide additional information on inflammatory diseases, AD or death recordings; 3) using the recording of dementia diagnosis as the outcome; 4) using patients with both an AD diagnosis in CPRD and HES/ONS plus at least one dementia drug prescription in CPRD; 5) removing AD cases that developed within two years of inflammatory disease diagnosis; 6) removing AD cases that developed within three years of inflammatory disease diagnosis (**eTable 6**). See **eMethods in the Supplement** for more details.

Mendelian randomisation

Genetic associations of circulating inflammatory biomarkers

We selected circulating inflammatory biomarkers of which meta-analyses of genome-wide association study (GWAS) were available based on three Finnish cohorts, namely Northern Finland Birth Cohort 1966 (NFBC1966), the Cardiovascular Risk in Young Finns (YFS), and FINRISK.¹⁶ To increase the power of our analysis, we further incorporated the Finnish meta-analysis with summary statistics from GWAS on proteins in the INTERVAL study¹⁷ and SCALLOP Consortium¹⁸. Details of the meta-analysis are described in the **eMethods** in the Supplement **and eTable 7**.

Genetic associations of inflammatory diseases, Alzheimer's disease, and dementia

We obtained genetic associations for eight inflammatory diseases from the largest GWAS, including psoriasis, rheumatoid arthritis (RA), multiple sclerosis (MS), inflammatory bowel disease (IBD), and the two subtypes of IBD (Crohn's disease and ulcerative colitis). Case

ascertainment of inflammatory diseases was based on clinical diagnosis recorded in the hospital or self-reported records. Genetic associations of risk of late-onset AD were obtained from the GWAS meta-analysis by the International Genomics of Alzheimer's Project (IGAP).¹⁹ The discovery stage of the IGAP GWAS meta-analysis included 21,982 cases (clinically diagnosed or autopsy) and 41,944 cognitively normal controls of European ancestry.¹⁹ As a sensitivity analysis, we also used genetic associations of dementia obtained from a meta-analysis of the IGAP, GR@ACE, and UK Biobank (N=409,435 individuals of European ancestry).²⁰ See **eMethods in the Supplement and eTable 8** for more details.

Two-sample Mendelian randomisation

We performed two-sample MR to investigate three sets of associations, i.e., 1) the associations of genetic liability of inflammatory diseases with AD/dementia; 2) the associations of genetic liability of inflammatory diseases and AD with circulating inflammatory biomarker levels, and 3) the associations of genetically predicted circulating inflammatory biomarker levels with the risk of inflammatory diseases and AD. For each MR analysis, we selected genetic instruments with a P-value smaller than 5×10^{-8} with the exposure of interest. We included independent SNPs as genetic instruments when genetic associations were available for both the exposure and outcome of interest. Correlated SNPs ($r^2 > 0.001$) were excluded by keeping the one with the smallest P-value for the SNP-exposure association. To avoid weak instrument bias, we only included SNPs with an F-statistics greater than 10.¹⁰

In our primary method, we used the Wald ratio to estimate SNP-specific effects when only one instrument was available.²¹ For MR analyses with two or three instruments, we used an inverse-variance weighted (IVW) fixed-effects model for the MR effect estimates.²¹ For MR

analyses with more than three instruments, we used IVW random-effects model for the MR effect estimates.²¹ We additionally used two sensitivity methods, weighted median and MR-Egger regression, to assess the robustness and horizontal pleiotropic effects when more than two instruments were available for the analysis.²¹ We also excluded potential outlier SNPs using MR-PRESSO, which identified outliers by comparing the observed and expected residual sum of squares for each SNP when regressing the SNP-exposure association on the SNP-outcome association.²² We performed a sensitivity analysis excluding genetic instruments on chromosome 6 for the association of inflammatory diseases with AD/Dementia because of the complex linkage disequilibrium issue of the *HLA* genes. For analyses with biomarker level as the exposure, we reported the odds ratio for the disease outcome per standard deviation (SD) higher of circulating inflammatory biomarker level. For the analyses with a disease exposure, the original result output indicates the effect on an outcome per unit increase in the ln(Odds ratio) of exposure risk. We multiplied the effect by 0.693 (i.e., ln(2)) to report the effect on a continuous outcome or the odds ratio for a binary outcome per doubling in odds of the disease exposure.

We performed MR-Steiger to further explore the directionality for the biomarker-disease pairs showing a bidirectional relationship.²³ MR-Steiger infers the directionality of the association by assessing the variance explained in the exposure and outcome by the genetic instruments.²³ Additionally, we performed sensitivity MR analyses excluding SNPs that were nominally associated with the outcome ($P < 0.05$) for the biomarker-disease pairs of interest.

We performed post-hoc power analysis for the MR for the associations of genetically predicted circulating inflammatory biomarker levels with the risk of inflammatory diseases and AD.²⁴ Specifically, we approximated the proportion of variance explained by the independent genetic variants for the circulating level of an inflammatory biomarker and estimated the minimum effect detectable for each association at an 85% power.

We accounted for multiple comparisons using Bonferroni correction. Specifically, in the MR analysis for the associations of genetically predicted inflammatory diseases with AD, we accounted for multiple comparisons of six inflammatory diseases using a P-value threshold of $0.05/6=0.0083$. In the bidirectional MR analysis for circulating inflammatory biomarker levels and diseases of interest, we accounted for multiple comparisons of 533 unique associations (322 for the effects of 7 diseases on 46 circulating inflammatory biomarkers and 211 for the effects of circulating inflammatory biomarkers on the diseases) with a P-value threshold of $0.05/533=9.4\times 10^{-5}$.

Colocalization

We further performed colocalization testing for the genetic signals for AD and Crohn's disease to investigate whether the two diseases shared causal variants. Specifically, we focused on the genomic region within 50kb from the coding gene of MIG (*CXCL9*, 4:76922428-76928641) given the associations identified in the two-sample MR analyses. We also performed colocalization for MIG with AD, and MIG with Crohn's disease. Given the functional relevance between MIG and IP10 (*CXCL10*, 4:76942273-76944650), we also performed colocalization for IP10 with AD, and IP10 with Crohn's disease.

Statistical software

All analyses were performed in Stata (version 16) and R 4.1.2. The *causalCmprsk* R package was used for the competing risk analysis.¹⁴ MR analyses were performed using the *TwoSampleMR* and *MR-PRESSO* packages. Colocalization was done using the *coloc* package. All statistical tests were two-sided.

Data availability

Access to CPRD data is subject to protocol approval via CPRD's Research Data Governance (RDG) Process. GWAS data on inflammatory diseases, AD, and dementia are available for download through the corresponding publication. GWAS on proteins in the INTERVAL study and SCALLOP Consortium are available for download through the corresponding publication. Summary statistics for the Finnish meta-analysis are available on request.

Standard Protocol Approvals, Registrations, and Patient Consents

The use of CPRD data for this study was approved by the Independent Scientific Advisory Committee (ISAC) for Medicines and Healthcare products Regulatory Agency (MHRA) database research (protocol number: 20_000209). Two-sample MR analyses were performed using publicly available GWAS, written informed consent was obtained from the participants by the individual cohort being involved in the GWAS.

Results

Observational analysis (CPRD)

The CPRD cohort included a total of 6,613,198 participants who met our quality checks (**Figure 1**). We included 85,147 RA patients, 57,114 IBD patients, 20,743 patients with MS, 220,729 patients with psoriasis and 339,960 patients with OID in the analyses with a median clinical follow-up of 13 years. There were more obese patients and more patients with cardiovascular diseases and type 2 diabetes in patients diagnosed with inflammatory diseases except for MS at baseline than the non-exposed (**Table 1**).

Cox regression models with different covariates adjustment showed consistent findings for each of the disease relationships with AD. Overall incidence of AD was significantly higher among patients with IBD (HR=1.17; 95%CI 1.15, 1.19; P-value= 2.1×10^{-4}), OID (HR=1.13; 95%CI 1.12, 1.14; P-value= 8.6×10^{-5}), psoriasis (HR=1.13; 95%CI 1.10, 1.16; P-value= 2.6×10^{-4}), RA (HR=1.08; 95%CI 1.06, 1.11; P-value= 4.0×10^{-4}), and MS (HR=1.06; 95%CI 1.04, 1.07; P-value= 2.8×10^{-4}) compared to the corresponding non-exposed group (**Model 3 in Table 2**). These associations also were consistent with the analysis adjusted for propensity score. Effect sizes were similar in sensitivity analyses involving further restrictions of sampling: 1) restricting the analyses with inflammatory disease diagnosis from 2004 onwards; 2) using linkage eligible patients; 3) extending the outcome from AD to recording of any dementia diagnosis; 4) using patients with both an AD diagnosis in CPRD and HES/ONS plus at least one dementia drug prescription in CPRD; 5) removing AD cases that developed within two years of inflammatory disease diagnosis; and 6) removing AD cases that developed within three years of inflammatory disease diagnosis (**eMethods in the Supplement and eTables 9 and 10**). Similar associations were also found in sensitivity analyses using dementia as the outcome with a slightly higher HR among patients with IBD (HR=1.22, 95%CI 1.20-1.23, P-value= 1.7×10^{-5}). In the time-dependent CIF analysis, the 10-year risk of developing AD in the RA patients was 1.12% (95%CI 1.06%, 1.19%) compared with 1.07% (95%CI 1.02%, 1.15%) among the non-RA participants (**Figure 2B and eFigure 3 in the Supplement**) and 1.09% (95%CI 1.03%, 1.14%) among the MS patients compared with 1.02% among (95%CI 0.07%, 1.07%) the non-MS participants (**Figure 2D and eFigure 3 in the Supplement**). The estimated 10-year risk of developing AD was also higher in patients with IBD, psoriasis and OID compared with participants without these inflammatory diseases, whereas the 10-year risk of death was lower in patients with IBD, psoriasis or OID (**Figure 2A, C, E, F and eFigure 3 in the Supplement**). In the sensitivity analyses with

dementia as the outcome, the 10-year risk of developing dementia in patients with one of the inflammatory disease diagnoses was consistent with the findings in the analyses of AD, whereas the 10-year risk of developing dementia was higher in RA (3.76%; 95%CI: 3.67%-3.85%) and MS patients (2.45%; 95%CI: 2.37%-2.52%) (**eFigures 4 and 5 in the Supplement**).

Mendelian randomisation (Inflammatory diseases and AD/Dementia)

Using two-sample MR approach, genetically predicted liability to inflammatory diseases was not associated with a higher risk of AD or dementia (**Table 2 and eTable 11**). After accounting for multiple comparisons, each doubling in odds of genetically predicted RA was associated with a lower risk of AD ($OR_{IVW}=0.96$; 95%CI 0.93, 0.99; $P_{IVW}=0.006$) and lower risk of dementia ($OR_{IVW}=0.95$; 95%CI 0.94, 0.97; $P_{IVW}=3.8\times 10^{-8}$). However, this relationship was not sustained after excluding genetic instruments on chromosome 6 (RA→AD: $OR_{IVW}=1.02$; 95%CI 0.97, 1.08; $P_{IVW}=0.44$; RA→Dementia: $OR_{IVW}=0.99$; 95%CI 0.98, 1.01; $P_{IVW}=0.73$).

Mendelian randomisation (Circulating inflammatory biomarker and AD)

Given the well-established link between inflammation and AD,²⁵ we further performed bidirectional MR analyses for circulating inflammatory biomarker levels and the diseases of interest to identify inflammatory biomarkers that are a common cause or the consequence of inflammatory disease and AD. **Figure 3** presents the results from the Wald ratio or IVW and **eTables 12 and 13** include the sensitivity methods. After accounting for multiple comparisons, each doubling in odds of MS was associated with a lower circulating level of MCP1 (coding gene: *CCL2*; MS→MCP1: $N_{SNP}=67$; $\beta_{IVW}=-0.01$; 95%CI -0.009, -0.005;

$P_{IVW}=2.0\times 10^{-10}$). Each doubling in odds of RA was associated with a higher circulating level of MIP1a (*CCL3*; $N_{SNP}=13$; $\beta_{IVW}=0.03$; 95%CI 0.013, 0.038; $P_{IVW}=5.1\times 10^{-5}$) and MIP1b (*CCL4*; $N_{SNP}=12$; $\beta_{IVW}=0.03$; 95%CI 0.018, 0.045; $P_{IVW}=5.7\times 10^{-6}$). Each doubling in odds of psoriasis was associated with a higher circulating level of TRAIL (*TNFSF10*; $N_{SNP}=31$; $\beta_{IVW}=0.01$; 95%CI 0.004, 0.011; $P_{IVW}=6.0\times 10^{-5}$). MR estimates from the weighted median and MR-Egger regression showed consistent directions (**Figure 4**) and MR-Egger did not suggest horizontal pleiotropy. Genetically predicted AD was not associated with circulating levels of any biomarkers tested.

Among the 46 biomarkers investigated, 35 had at least one genetic instrument for MR analysis. After accounting for multiple comparisons, each SD higher circulating MIP1b (*CCL4*) level was associated with a higher risk of IBD ($N_{SNP}=4$; $OR_{IVW}=1.14$; 95%CI 1.07, 1.21; $P_{IVW}=2.4\times 10^{-5}$), but lower risk of RA ($N_{SNP}=4$; $OR_{IVW}=0.84$; 95%CI 0.79, 0.90; $P_{IVW}=9.4\times 10^{-8}$). Each SD higher circulating IL1RA (*IL1RN*) level was associated with a lower risk of RA ($N_{SNP}=4$; $OR_{IVW}=0.80$; 95%CI 0.72, 0.90; $P_{IVW}=3.3\times 10^{-5}$). MR estimates from the weighted median and MR-Egger regression showed consistent direction (**Figure 4**) and MR-Egger did not suggest horizontal pleiotropy. We identified seven more significant causal associations between circulating inflammatory biomarkers and inflammatory diseases after Bonferroni correction, however, less than three genetic instruments were available for these biomarkers. Thus, sensitivity methods were not performed. Particularly, genetically predicted circulating levels of IL6 (*IL6*) and IP10 (*CXCL10*) were associated with more than one inflammatory disease. Each SD higher circulating IL6 (*IL6*) level was associated with higher risk of MS ($N_{SNP}=2$; $OR_{IVW}=2.45$; 95%CI 2.05, 2.93; $P_{IVW}=1.3\times 10^{-22}$), but lower risk of RA ($N_{SNP}=1$; $OR_{Wald}=0.54$; 95%CI 0.43, 0.67; $P_{Wald}=1.3\times 10^{-8}$). Each SD higher circulating levels of IP10 ($N_{SNP}=1$) was associated with higher risk of psoriasis and IBD (IP10→Psoriasis: $OR_{Wald}=2.97$; 95%CI 1.74, 5.05; $P_{Wald}=6.3\times 10^{-5}$; IP10→IBD: $OR_{Wald}=1.67$;

95%CI 1.42, 1.97; $P_{\text{Wald}}=1.3\times 10^{-9}$), but lower risk of Crohn's disease and UC (IP10→Crohn: $\text{OR}_{\text{Wald}}=0.50$; 95%CI 0.38, 0.66; $P_{\text{Wald}}=5.7\times 10^{-7}$; IP10→UC: $\text{OR}_{\text{Wald}}=0.54$; 95%CI 0.41, 0.70; $P_{\text{Wald}}=5.4\times 10^{-6}$). We also found a reverse association between the circulating level of IL2ra (*IL2RA*) and the risk of MS ($N_{\text{SNP}}=1$; $\text{OR}_{\text{Wald}}=0.82$; 95%CI 0.76, 0.89; $P_{\text{Wald}}=3.2\times 10^{-6}$). The observed effect sizes for all these associations were larger than the minimum effect detectable at 85% power (**eTable 14**). However, most of the null findings in our analyses had an observed effect size smaller than the minimum detectable effect (**eTable 14**).

From the above MR analyses for circulating inflammatory biomarkers and inflammatory diseases, we found a bidirectional relationship between circulating MIP1b (*CCL4*) level and risk of RA. MR-Steiger suggested both directions were valid, however the RA→MIP1b association was less susceptible to measurement error (**eTable 15**). **eFigure 6 in the Supplement** shows that the MIP1b→RA association was driven by a single SNP ($P_{\text{rs11574435-RA}}=0.004$), and the association did not sustain after exclusion of this SNP. RA→MIP1b association remained nominally significant after excluding two SNPs nominally associated with MIP1b ($P_{\text{IVW}}=0.004$).

Genetically predicted circulating inflammatory biomarker levels were not associated with the risk of AD after accounting for multiple comparisons. Nevertheless, the top signal identified for AD (circulating MIG (*CXCL9*) level ($N_{\text{SNP}}=2$; $\text{OR}_{\text{IVW}}=1.23$; 95%CI 1.06, 1.42; $P_{\text{IVW}}=0.007$)), also was a suggestive causal biomarker for Crohn's disease ($N_{\text{SNP}}=2$; $\text{OR}_{\text{IVW}}=0.73$; 95%CI -0.62, 0.86; $P_{\text{IVW}}=1.3\times 10^{-4}$). The observed effect sizes for these associations were larger than the minimum effect detectable at 85% power (**eTable 14**).

However, colocalization did not suggest a common causal SNP for AD and Crohn's disease within the genomic region (+/-50kb from the MIG coding gene *CXCL9*) (posterior probability (PP.H4) = 0.001; **eFigure 7 in the Supplement**). A common causal SNP was also unlikely for MIG and AD (PP.H4=0.03) although possible for MIG and Crohn's disease

(PP.H4=0.74; **eFigure 8 in the Supplement**). Colocalization suggested neither a common causal SNP for IP10 (*CXCL10*) and AD (PP.H4=0.09), nor for IP10 (*CXCL10*) and Crohn's disease (PP.H4=0.09; **eFigure 9 in the Supplement**).

Discussion

In this study, we performed real-world observational analysis and two-sample MR to investigate the relationship between inflammatory diseases and AD. Consistent with previous observational studies,^{4, 5, 26} our real-world observational analysis based on CPRD data showed that inflammatory diseases were associated with a higher risk of AD. However, these associations were not supported by two-sample MR analysis, suggesting that confounding factors might be driving the observed association between inflammatory diseases and AD. In MR analysis, we found that several biomarkers are likely to be affected by inflammatory diseases. Moreover, we found evidence for a potential causal role of MIG in Crohn's disease. However, consistent with the results of the observational study, we did not find an inflammatory biomarker that could explain the association of inflammatory diseases and AD. The role of inflammation in AD progression is supported by the identification of innate immune genes in genetic studies on AD, such as *CD33* and *TREM2*,^{19, 27} and the emerging understanding that microglia, which contribute to regulation of immune response in the brain, likely is central to the pathogenesis of AD.²⁸ Chronic inflammation may drive neuroinflammatory changes and chronic activation of microglia, leading to oxidative stress and enhanced deposition of toxic proteins in AD.²⁹ Chronic inflammation also increases the risk of thromboembolic events and ischaemic stroke, contributing to the development of vascular dementia, which leads to stepwise instead of gradual cognitive decline.³⁰ However,

it is also possible that the observational associations between inflammatory diseases and AD are due to common molecular mechanisms.

Our findings for the relationships between circulating inflammatory biomarkers and AD were not entirely consistent with other recent studies with similar designs.^{31,32} Both Yeung *et al.* and Pagoni *et al.* used genetic associations of 41 biomarkers from the previous Finnish GWAS, which had adjusted for BMI.³¹⁻³³ Several studies have reported a causal effect of obesity or higher BMI on inflammatory biomarker levels,^{34,35} but BMI was not a causal factor of AD or dementia.^{36,37} Using BMI-adjusted genetic associations of biomarkers could result in collider bias in two-sample MR due to unmeasured confounding.³⁸ In our study, we updated the Finnish GWAS by including 5 additional biomarkers (activePAI, IL1a, sEselectin, sICAM, and sVCAM) and excluding BMI from the genetic model. We also took advantage of two additional GWAS to increase the sample size of 20 biomarkers (the maximum sample size was increased from 8,293 to 13,365).¹⁶

Our MR findings suggested a link between MIG and higher risk of AD, but lower risk of Crohn's disease. MIG belongs to the CXC chemokine family and is also known as chemokine (C-X-C motif) ligand 9 (CXCL9). Chemokines have been found to involve in both neuroinflammatory and neurodegenerative processes and play a role in the development of amyloid β plaques and neurofibrillary tangles, two pathological hallmarks of AD.³⁹ However, colocalization in our study only supported common causal SNP for MIG and Crohn's disease, indicating the association between MIG and AD may be confounded by linkage disequilibrium. We previously found that circulating MIG causally affects IP10 level.¹⁶ MIG (CXCL9), IP10 (CXCL10), and IP9 (CXCL11) share the same receptor, C-X-C chemokine receptor 3 (CXCR3),³⁹ but colocalization in our study did not support common causal SNP for IP10 and Crohn's disease. This may suggest a more prominent role of MIG in Crohn's disease. CXCL9 polymorphisms were found associated with Crohn's disease,

although only in paediatric patients.^{40,41} In addition, a recent study also identified a major role of MIG (*CXCL9*) in age-related chronic inflammation.⁴² Taken together, we did not find strong evidence supporting common inflammatory biomarkers affecting both risk of AD and inflammatory diseases. Our findings suggest neuroinflammatory processes that are responsible for AD may be distinct from the mechanisms underlying inflammatory diseases. Nevertheless, the role of inflammatory biomarkers not being investigated in this study warrant further exploration.

There are limitations to our study. First, the observational analysis relies on the quality of data recording in the electronic health records. Some chronic autoimmune inflammatory diseases (e.g., RA, psoriasis) could be under-recorded, confounding estimates of their contributions to the risk of AD. The use of CPRD Medcodes also may provide a poor estimate of the proportion of patients with AD, as non-specific Medcodes are often used in primary care for suspected dementia and these can be mis-applied.⁴³ In addition, the diagnosis of AD was not confirmed by cerebrospinal fluid biomarkers such as amyloid- β and tau protein. On the other hand, one systematic review assessed the validity of dementia recording in EHR reported high false-positive rates of dementia recordings.⁴⁴ However, recordings of AD diagnosis have improved in recent years⁴⁵ and we used the linkage dataset, which may provide additional patients records of AD diagnosis. Second, genetic factors explain a small proportion of the variance in the incidence of some inflammatory diseases.⁴⁶⁴⁷ Thus, a lack of association between genetically predicted inflammatory diseases and risk of AD in our MR analysis may not rule out the contribution of inflammatory diseases to AD pathophysiology. Third, genetic associations for biomarkers were based on relatively small GWAS, which may raise the issue of lack of statistical power. Nevertheless, the observed effect sizes for our findings were larger than the minimum effect detectable at 85% power. Fourth, univariate MR analyses may not represent direct effect of a specific biomarker on the

disease outcomes because effects of one biomarker may be mediated by others in the complex biomarker network. Fifth, we primarily investigated peripheral inflammatory diseases, thus our findings may not be able to inform on inflammation related to the central nervous system. In addition, circulating inflammatory biomarkers may not be relevant to neurological diseases. However, it has been reported some biomarkers can pass through blood-brain barrier, including IL1RA in our findings,⁴⁸ others can affect the integrity of blood-brain barrier, e.g., MCP1.⁴⁹ Monocytes can cross compromised blood-brain barrier and generate monocyte-derived macrophages.⁵⁰ This may further suggest the synergistic effect of multiple biomarkers. Last but not least, all our analyses were based on individuals of European ancestry, generalisation to other population requires further investigation.

Here we have integrated evidence from real-world observational analyses based on large sample size with a two-sample MR analysis, which is less susceptible to confounding and reverse causation, to investigate the associations between chronic autoimmune inflammatory diseases and risk of AD and dementia. Our findings suggested these associations were non-causal but the factors confounding the observation have yet to be unravelled. Moreover, while some circulating inflammatory biomarkers were associated with the inflammatory diseases, evidence was weak that they affected both risk of AD and inflammatory diseases.

<http://links.lww.com/WNL/C486>

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Reference

1. Kinney JW, Bemiller SM, Murtishaw AS, Leisgang AM, Salazar AM, Lamb BT. Inflammation as a central mechanism in Alzheimer's disease. *Alzheimers Dement (N Y)* 2018;4:575-590.
2. Lai KSP, Liu CS, Rau A, et al. Peripheral inflammatory markers in Alzheimer's disease: a systematic review and meta-analysis of 175 studies. *J Neurol Neurosurg Psychiatry* 2017;88:876-882.
3. Ungprasert P, Wijarnprecha K, Thongprayoon C. Rheumatoid arthritis and the risk of dementia: A systematic review and meta-analysis. *Neurology India* 2016;64:56.
4. Liu L, Chen S-t, Li H-j, et al. Association Between Psoriasis and Dementia: Current Evidence. *Frontiers in aging neuroscience* 2020;12:279.
5. Zhang B, Wang HE, Bai Y-M, et al. Inflammatory bowel disease is associated with higher dementia risk: a nationwide longitudinal study. *Gut* 2021;70:85-91.
6. Kridin K, Linder D, Shalom G, et al. Psoriasis and Dementia: A Cross-sectional Study of 121,801 Patients. *Acta Dermato-Venereologica* 2020;100.
7. Policicchio S, Ahmad AN, Powell JF, Proitsi P. Rheumatoid arthritis and risk for Alzheimer's disease: a systematic review and meta-analysis and a Mendelian Randomization study. *Scientific reports* 2017;7:1-11.
8. Benito-León J, Contador I, Vega S, Villarejo-Galende A, Bermejo-Pareja F. Non-steroidal anti-inflammatory drugs use in older adults decreases risk of Alzheimer's disease mortality. *PLOS ONE* 2019;14:e0222505.
9. Li X, Kaida-Yip F, Zabel M. NSAID Use and the Prevention of Alzheimer's Disease: A Meta-Analysis (P6.184). *Neurology* 2018;90:P6.184.
10. Davies NM, Holmes MV, Davey Smith G. Reading Mendelian randomisation studies: a guide, glossary, and checklist for clinicians. *BMJ* 2018;362:k601.
11. Herrett E, Gallagher AM, Bhaskaran K, et al. Data resource profile: clinical practice research datalink (CPRD). *International journal of epidemiology* 2015;44:827-836.
12. Austin PC. The use of propensity score methods with survival or time - to - event outcomes: reporting measures of effect similar to those used in randomized experiments. *Statistics in medicine* 2014;33:1242-1258.
13. Royston P, White IR. Multiple imputation by chained equations (MICE): implementation in Stata. *J Stat Softw* 2011;45:1-20.
14. Vakulenko-Lagun B, Magdamo C, Charpignon M-L, et al. Package 'causalCmprsk'. *Journal of the American Medical Association* 2021;276:889-897.
15. Kontopantelis E, Springate D, Reeves D, Ashcroft DM, Valderas JM, Doran T. Withdrawing performance indicators: retrospective analysis of general practice performance under UK Quality and Outcomes Framework. *Bmj* 2014;348.
16. Karhunen V, Gill D, Malik R, et al. Genetic study of circulating cytokines offers insight into the determinants, cascades and effects of systemic inflammation. *medRxiv* 2020:2020.2010.2026.20219477.
17. Sun BB, Maranville JC, Peters JE, et al. Genomic atlas of the human plasma proteome. *Nature* 2018;558:73-79.
18. Folkersen L, Gustafsson S, Wang Q, et al. Genomic and drug target evaluation of 90 cardiovascular proteins in 30,931 individuals. *Nat Metab* 2020;2:1135-1148.
19. Kunkle BW, Grenier-Boley B, Sims R, et al. Genetic meta-analysis of diagnosed Alzheimer's disease identifies new risk loci and implicates Abeta, tau, immunity and lipid processing. *Nat Genet* 2019;51:414-430.
20. de Rojas I, Moreno-Grau S, Tesi N, et al. Common variants in Alzheimer's disease and risk stratification by polygenic risk scores. *Nature Communications* 2021;12:3417.

21. Sanderson E, Glymour MM, Holmes MV, et al. Mendelian randomization. *Nature Reviews Methods Primers* 2022;2:6.
22. Verbanck M, Chen CY, Neale B, Do R. Detection of widespread horizontal pleiotropy in causal relationships inferred from Mendelian randomization between complex traits and diseases. *Nat Genet* 2018;50:693-698.
23. Hemani G, Tilling K, Davey Smith G. Orienting the causal relationship between imprecisely measured traits using GWAS summary data. *PLoS Genet* 2017;13:e1007081.
24. Burgess S. Sample size and power calculations in Mendelian randomization with a single instrumental variable and a binary outcome. *Int J Epidemiol* 2014;43:922-929.
25. McAlpine CS, Park J, Griciu A, et al. Astrocytic interleukin-3 programs microglia and limits Alzheimer's disease. *Nature* 2021.
26. Weber A, Hung Mak S, Berenbaum F, et al. Association between osteoarthritis and increased risk of dementia: a systemic review and meta-analysis. *Medicine* 2019;98.
27. Griciu A, Tanzi RE. The role of innate immune genes in Alzheimer's disease. *Curr Opin Neurol* 2021;34:228-236.
28. Hemonnot AL, Hua J, Ulmann L, Hirbec H. Microglia in Alzheimer Disease: Well-Known Targets and New Opportunities. *Front Aging Neurosci* 2019;11:233.
29. Kinney JW, Bemiller SM, Murtishaw AS, Leisgang AM, Salazar AM, Lamb BT. Inflammation as a central mechanism in Alzheimer's disease. *Alzheimer's & Dementia: Translational Research & Clinical Interventions* 2018;4:575-590.
30. Venkat P, Chopp M, Chen J. Models and mechanisms of vascular dementia. *Experimental neurology* 2015;272:97-108.
31. Yeung CHC, Schooling CM. Systemic inflammatory regulators and risk of Alzheimer's disease: a bidirectional Mendelian-randomization study. *Int J Epidemiol* 2020.
32. Pagoni P, Howe LD, Smith GD, Ben-Shlomo Y, Stergiakouli E, Anderson EL. Causal effects of circulating cytokine concentrations on risk of Alzheimer's disease: A bidirectional two-sample Mendelian randomization study. *medRxiv* 2020:2020.2011.2018.20232629.
33. Ahola-Olli AV, Wurtz P, Havulinna AS, et al. Genome-wide Association Study Identifies 27 Loci Influencing Concentrations of Circulating Cytokines and Growth Factors. *Am J Hum Genet* 2017;100:40-50.
34. Welsh P, Polisecki E, Robertson M, et al. Unraveling the directional link between adiposity and inflammation: a bidirectional Mendelian randomization approach. *J Clin Endocrinol Metab* 2010;95:93-99.
35. Zuydam NV, Wielscher M, McCarthy M, Jarvelin M-R. Increased Obesity Is Causal for Increased Inflammation—A Mendelian Randomisation Study. *Diabetes* 2018;67:217-LB.
36. Nordestgaard LT, Tybjaerg-Hansen A, Nordestgaard BG, Frikke-Schmidt R. Body Mass Index and Risk of Alzheimer's Disease: A Mendelian Randomization Study of 399,536 Individuals. *J Clin Endocrinol Metab* 2017;102:2310-2320.
37. Mukherjee S, Walter S, Kauwe JSK, et al. Genetically predicted body mass index and Alzheimer's disease-related phenotypes in three large samples: Mendelian randomization analyses. *Alzheimers Dement* 2015;11:1439-1451.
38. Hartwig FP, Tilling K, Smith GD, Lawlor DA, Borges MC. Bias in two-sample Mendelian randomization when using heritable covariable-adjusted summary associations. *bioRxiv* 2020:816363.
39. Martin E, Delarasse C. Complex role of chemokine mediators in animal models of Alzheimer's Disease. *Biomedical Journal* 2018;41:34-40.
40. Schroepf S, Kappler R, Brand S, et al. Strong overexpression of CXCR3 axis components in childhood inflammatory bowel disease. *Inflamm Bowel Dis* 2010;16:1882-1890.

41. Lacher M, Kappler R, Berkholtz S, Baurecht H, von Schweinitz D, Koletzko S. Association of a CXCL9 polymorphism with pediatric Crohn's disease. *Biochem Biophys Res Commun* 2007;363:701-707.
42. Sayed N, Huang Y, Nguyen K, et al. An inflammatory aging clock (iAge) based on deep learning tracks multimorbidity, immunosenescence, frailty and cardiovascular aging. *Nature Aging* 2021;1:598-615.
43. Russell P, Banerjee S, Watt J, et al. Improving the identification of people with dementia in primary care: evaluation of the impact of primary care dementia coding guidance on identified prevalence. *BMJ open* 2013;3:e004023.
44. McGuinness LA, Warren - Gash C, Moorhouse LR, Thomas SL. The validity of dementia diagnoses in routinely collected electronic health records in the United Kingdom: a systematic review. *Pharmacoepidemiology and drug safety* 2019;28:244-255.
45. Donegan K, Fox N, Black N, Livingston G, Banerjee S, Burns A. Trends in diagnosis and treatment for people with dementia in the UK from 2005 to 2015: a longitudinal retrospective cohort study. *The Lancet Public Health* 2017;2:e149-e156.
46. Patsopoulos NA. Genetics of Multiple Sclerosis: An Overview and New Directions. *Cold Spring Harb Perspect Med* 2018;8.
47. Loddo I, Romano C. Inflammatory Bowel Disease: Genetics, Epigenetics, and Pathogenesis. *Front Immunol* 2015;6:551.
48. Gutierrez EG, Banks WA, Kastin AJ. Blood-borne interleukin-1 receptor antagonist crosses the blood-brain barrier. *Journal of Neuroimmunology* 1994;55:153-160.
49. Yao Y, Tsirka SE. Monocyte chemoattractant protein-1 and the blood-brain barrier. *Cell Mol Life Sci* 2014;71:683-697.
50. Brioschi S, Zhou Y, Colonna M. Brain Parenchymal and Extraparenchymal Macrophages in Development, Homeostasis, and Disease. *J Immunol* 2020;204:294-305.

Table 1 Baseline characteristics of eligible participants included in the Clinical Practice Research Datalink (CPRD) observational analysis

| Baseline characteristics | RA | | IBD | | MS | | Psoriasis | | OID | |
|---------------------------------------|-----------------|------------------|-----------------|-----------------|-----------------|-----------------|------------------|------------------|------------------|------------------|
| | Exposed | Non-exposed | Exposed | Non-exposed | Exposed | Non-exposed | Exposed | Non-exposed | Exposed | Non-exposed |
| Number of participants | 85,147 | 170,294 | 57,114 | 114,228 | 20,743 | 41,486 | 220,729 | 441,458 | 339,960 | 679,918 |
| Age at baseline (year, median) | 58 | 58 | 48 | 48 | 44 | 44 | 48 | 48 | 63 | 63 |
| Sex (female %) | 59,472 (69.85) | 118,944 (69.85%) | 30,173 (52.83%) | 60,346 (52.83%) | 14,415 (69.49%) | 28,830 (69.49%) | 111,605 (50.56%) | 223,210 (50.56%) | 121,343 (35.69%) | 242,686 (35.69%) |
| CVD (N, %) | 26,872 (31.56%) | 26,941 (15.82%) | 12,803 (22.42%) | 18,231 (15.96%) | 3,053 (14.72%) | 6,646 (16.02%) | 48,636 (22.03%) | 69,795 (15.81%) | 130,935 (38.51%) | 100,628 (14.96%) |
| Diabetes (N, %) | 9,052 (10.63%) | 11,597 (6.81%) | 6,149 (10.77%) | 7,802 (6.83%) | 1,446 (6.97%) | 2,846 (6.86%) | 25,563 (11.58%) | 29,578 (6.7%) | 58,197 (17.12%) | 42,903 (6.31%) |
| Socio-economic status (N, %) | | | | | | | | | | |
| 1 (least deprived) | 10,204 (11.98%) | 22,479 (13.2%) | 8,084 (14.15%) | 15,055 (13.18%) | 2,927 (14.11%) | 5,472 (13.19%) | 30,239 (13.70%) | 58,140 (13.17%) | 49,342 (14.51%) | 89,206 (13.12%) |
| 2 | 10,620 (12.47%) | 21,525 (12.64%) | 7,788 (13.64%) | 14,427 (12.63%) | 2,841 (13.70%) | 5,240 (12.63%) | 28,459 (12.89%) | 55,756 (12.63%) | 47,125 (13.86%) | 85,466 (12.57%) |
| 3 | 10,714 (12.58%) | 20,469 (12.02%) | 7,184 (12.58%) | 13,730 (12.02%) | 2,695 (12.99%) | 4,991 (12.03%) | 27,316 (12.38%) | 53,063 (12.02%) | 44,202 (13.00%) | 81,454 (12.00%) |
| 4 | 9,319 (10.94%) | 17,745 (10.42%) | 5,905 (10.34%) | 11,914 (10.43%) | 2,121 (10.23%) | 4,327 (10.43%) | 22,795 (10.33%) | 46,044 (10.43%) | 34,130 (10.04%) | 71,052 (10.45%) |
| 5 (most deprived) | 8,025 (9.42%) | 14,952 (8.78%) | 4,501 (7.88%) | 10,052 (8.8%) | 1,545 (7.45%) | 3,647 (8.79%) | 18,835 (8.53%) | 38,848 (8.8%) | 26,099 (7.68%) | 60,173 (8.85%) |
| Missing | 36,265 (42.59%) | 14,952 (42.94%) | 23,652 (41.41%) | 49,061 (42.95%) | 8,614 (41.53%) | 17,814 (42.94%) | 93,085 (42.17%) | 189,650 (42.96%) | 139,062 (40.91%) | 292,638 (43.12%) |
| Smoking (N, %) | | | | | | | | | | |
| Non-smoker (%) | 38,828 (45.60%) | 72,188 (42.39%) | 27,353 (47.89%) | 48,421 (42.39%) | 9,445 (45.53%) | 17,603 (42.43%) | 92,253 (41.79%) | 187,443 (42.46%) | 166,922 (49.10%) | 286,042 (42.22%) |
| Ex-smoker (%) | 24,190 (28.41%) | 31,573 (18.54%) | 17,918 (31.37%) | 21,201 (18.56%) | 4,855 (23.41%) | 7,737 (18.65%) | 67,714 (30.68%) | 80,566 (18.25%) | 115,304 (33.92%) | 121,298 (17.84%) |
| Smoker (%) | 15,482 (18.18%) | 32,203 (18.91%) | 8,756 (15.33%) | 21,623 (18.93%) | 4,291 (20.69%) | 7,837 (18.89%) | 50,574 (22.91%) | 82,818 (18.76%) | 42,748 (12.57%) | 130,817 (19.24%) |
| Missing | 6,647 (7.81%) | 34,331 (20.16%) | 3,087 (5.40%) | 22,994 (20.13%) | 2,152 (10.37%) | 8,310 (20.03%) | 10,188 (4.62%) | 90,631 (20.53%) | 14,986 (4.41%) | 141,695 (20.84%) |
| BMI (N, %) | | | | | | | | | | |
| Underweight | 3,731 (4.38%) | 3,440 (2.02%) | 1,893 (3.31%) | 2,330 (2.04%) | 720 (3.47%) | 846 (2.04%) | 4,805 (2.18%) | 9,006 (2.04%) | 6,549 (1.93%) | 13,938 (2.05%) |
| Normal weight | 26,591 (31.23%) | 46,661 (27.4%) | 19,286 (33.77%) | 31,298 (27.4%) | 6,693 (32.27%) | 11,384 (27.44%) | 63,678 (28.85%) | 120,959 (27.4%) | 79,551 (23.40%) | 188,134 (27.53%) |
| Overweight | 23,340 (27.41%) | 43,067 (25.29%) | 17,700 (30.99%) | 28,854 (25.26%) | 4,921 (23.72%) | 10,504 (25.32%) | 70,783 (32.07%) | 110,718 (25.08%) | 115,405 (33.95%) | 168,960 (24.72%) |
| Obese | 17,648 (20.73%) | 28,081 (16.49%) | 11,100 (19.43%) | 18,870 (16.52%) | 3,531 (17.02%) | 6,862 (16.54%) | 55,910 (25.33%) | 71,693 (16.24%) | 99,782 (29.35%) | 107,767 (15.71%) |
| Missing | 13,837 (16.25%) | 49,045 (28.8%) | 7,135 (12.49%) | 32,875 (28.78%) | 4,878 (23.52%) | 11,890 (28.66%) | 25,553 (11.58%) | 129,038 (29.23%) | 38,673 (11.38%) | 201,120 (29.59%) |
| Region (N, %) | | | | | | | | | | |
| North East | 1,270 (1.49%) | 2,418 (1.42%) | 905 (1.58%) | 1,622 (1.42%) | 264 (1.27%) | 589 (1.42%) | 3,533 (1.60%) | 6,269 (1.42%) | 5,583 (1.64%) | 9,587 (1.41%) |
| North West | 9,206 (10.81%) | 17,796 (10.45%) | 6,151 (10.77%) | 11,937 (10.45%) | 2,101 (10.13%) | 4,335 (10.45%) | 25,223 (11.43%) | 46,000 (10.42%) | 34,436 (10.13%) | 71,188 (10.47%) |

| | | | | | | | | | | |
|---------------------------------------|----------------------|----------------------|----------------------|------------------------|----------------------|----------------------|-----------------------|----------------------|-----------------------|---------------|
| Yorkshire & The Humber | 3,472 (4.08%) | 6,284 (3.69%) | 2,015 (3.53%) | 4,226 (3.7%) | 853 (4.11%) | 1,531 (3.69%) | 8,469 (3.84%) | 16,290 (3.69%) | 11,910 (3.50%) | 25,225 |
| East Midlands | 3,328 (3.91%) | 6,148 (3.61%) | 2,034 (3.56%) | 4,135 (3.62%) | 757 (3.65%) | 1,502 (3.62%) | 7,821 (3.54%) | 15,981 (3.62%) | 11,135 (3.28%) | 24,749 |
| West Midlands | 7,586 (8.91%) | 14,237 (8.36%) | 4,777 (8.36%) | 9,561 (8.37%) | 1,600 (7.71%) | 3,472 (8.37%) | 18,880 (8.55%) | 36,906 (8.36%) | 32,366 (9.52%) | 56,433 |
| East of England | 7,617 (8.95%) | 15,292 (8.98%) | 5,231 (9.16%) | 10,246 (8.97%) | 2,044 (9.85%) | 3,721 (8.97%) | 19,530 (8.85%) | 39,643 (8.98%) | 29,946 (8.81%) | 61,057 |
| South West | 7,982 (9.37%) | 14,850 (8.72%) | 5,157 (9.03%) | 9,972 (8.73%) | 1,870 (9.02%) | 3,622 (8.73%) | 19,398 (8.79%) | 38,539 (8.73%) | 33,999 (10.00%) | 58,881 |
| South Central | 7,856 (9.23%) | 18,221 (10.7%) | 6,078 (10.64%) | 12,200 (10.68%) | 2,396 (11.55%) | 4,431 (10.68%) | 22,275 (10.09) | 47,236 (10.7%) | 36,667 (10.79%) | 72,615 |
| London | 8,260 (9.70%) | 22,939 (13.47%) | 6,039 (10.57%) | 15,364 (13.45%) | 2,139 (10.31%) | 5,572 (13.43%) | 23,803 (10.78) | 59,641 (13.51%) | 31,559 (9.28%) | 92,809 |
| South East Coast | 8,056 (9.46%) | 16,978 (9.97%) | 5,742 (10.02%) | 11,377 (9.96%) | 2,132 (10.28%) | 4,132 (9.96%) | 19,934 (9.03%) | 44,146 (10.00%) | 34,846 (10.25%) | 67,652 |
| Northern Ireland | 2,379 (2.79%) | 3,832 (2.25%) | 1,544 (2.70%) | 2,570 (2.25%) | 578 (2.79%) | 933 (2.25%) | 7,012 (3.18%) | 9,800 (2.22%) | 7,897 (2.32%) | 15,298 |
| Scotland | 8,638 (10.14%) | 14,373 (8.44%) | 5,946 (10.41%) | 9,652 (8.45%) | 2,317 (11.17%) | 3,506 (8.45%) | 22,283 (10.14%) | 37,082 (8.4%) | 27,357 (8.05%) | 57,657 |
| Wales | 9,497 (11.15%) | 16,910 (9.93%) | 5,513 (9.65%) | 11,366 (9.95%) | 1,692 (8.16%) | 4,128 (9.95%) | 22,468 (10.18%) | 43,881 (9.94%) | 42,259 (12.43%) | 66,700 |
| Incident dementia cases (N, %) | 6,648 (7.81%) | 9,468 (5.56%) | 3,358 (5.88%) | 366,460 (5.59%) | 1,101 (5.31%) | 2,319 (5.59%) | 11,884 (5.38%) | 20,307 (4.6%) | 27,398 (8.06%) | 37,124 |
| Incident AD cases (N, %) | 1,749 (2.13%) | 2,357 (1.38%) | 962 (1.68%) | 1,665 (1.40%) | 376 (1.76%) | 713 (1.38%) | 3,538 (1.60%) | 6,142 (1.39%) | 7,212 (2.12%) | 9,657 |

Abbreviation: Alzheimer's diseases (AD), body-mass index (BMI), cardiovascular disease (CVD), inflammatory bowel disease (IBD), multiple sclerosis (MS), other inflammatory polyarthropathies & systematic connective tissue disorders (OID), rheumatoid arthritis (RA).

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Table 2 Comparisons between the associations of inflammatory diseases with Alzheimer's disease using Cox regression models (CPRD) and using two-sample Mendelian randomisation (MR)

| Exposure | CPRD | | | | | MR analysis | | | | | | |
|-----------|--------------------|-----------|------|------------|---------|----------------|----------|------|------------|---------|-----------------------|--------------------|
| | Model ^a | N | HR | 95%CI | P-value | Number of SNPs | Method | OR | 95%CI | P-value | Heterogeneity P-value | Pleiotropy P-value |
| Crohn | | | NA | | | 84 | IVW | 1.01 | 0.99, 1.03 | 0.254 | 0.040 | NA |
| | | | | | | 84 | WM | 1.01 | 0.98, 1.03 | 0.622 | NA | NA |
| | | | | | | 84 | MR-Egger | 1.00 | 0.95, 1.05 | 0.982 | 0.035 | 0.698 |
| IBD | Model 1 | 171,342 | 1.17 | 1.15, 1.18 | 1.9E-04 | 125 | IVW | 0.98 | 0.95, 1.01 | 0.223 | 7.5E-05 | NA |
| | Model 2 | 131,823 | 1.21 | 1.19, 1.24 | 3.4E-04 | 125 | WM | 0.96 | 0.92, 1.01 | 0.162 | NA | NA |
| | Model 3 | 171,342 | 1.17 | 1.15, 1.19 | 2.1E-04 | 125 | MR-Egger | 0.94 | 0.87, 1.02 | 0.151 | 8.2E-05 | 0.300 |
| MS | Model 1 | 62,229 | 1.05 | 1.04, 1.07 | 1.4E-04 | 67 | IVW | 1.01 | 0.99, 1.04 | 0.271 | 0.350 | NA |
| | Model 2 | 40,284 | 1.06 | 1.04, 1.07 | 3.1E-04 | 67 | WM | 1.00 | 0.96, 1.04 | 0.973 | NA | NA |
| | Model 3 | 62,229 | 1.06 | 1.04, 1.07 | 2.8E-04 | 67 | MR-Egger | 0.99 | 0.95, 1.04 | 0.787 | 0.356 | 0.287 |
| Psoriasis | Model 1 | 662,187 | 1.13 | 1.09, 1.17 | 4.3E-04 | 32 | IVW | 1.00 | 0.99, 1.01 | 0.892 | 0.876 | NA |
| | Model 2 | 392,109 | 1.13 | 1.10, 1.16 | 3.9E-04 | 32 | WM | 1.00 | 0.99, 1.01 | 0.827 | NA | NA |
| | Model 3 | 662,187 | 1.13 | 1.10, 1.16 | 2.6E-04 | 32 | MR-Egger | 1.00 | 0.99, 1.01 | 0.763 | 0.868 | 0.436 |
| RA | Model 1 | 255,441 | 1.08 | 1.06, 1.10 | 4.1E-04 | 13 | IVW | 0.94 | 0.90, 0.98 | 0.006 | 0.026 | NA |
| | Model 2 | 159,650 | 1.05 | 1.04, 1.07 | 3.9E-04 | 13 | WM | 0.92 | 0.88, 0.95 | 2.4E-05 | NA | NA |
| | Model 3 | 255,441 | 1.08 | 1.06, 1.11 | 4.0E-04 | 13 | MR-Egger | 0.91 | 0.85, 0.97 | 0.015 | 0.045 | 0.216 |
| UC | | | NA | | | 56 | IVW | 1.02 | 0.99, 1.04 | 0.122 | 0.117 | NA |
| | | | | | | 56 | WM | 1.01 | 0.99, 1.05 | 0.350 | NA | NA |
| | | | | | | 56 | MR-Egger | 1.02 | 0.94, 1.11 | 0.608 | 0.100 | 0.938 |
| OID | Model 1 | 1,019,880 | 1.12 | 1.10, 1.14 | 2.7E-04 | | | | | | | |
| | Model 2 | 678,542 | 1.12 | 1.11, 1.14 | 3.1E-04 | | | | NA | | | |
| | Model 3 | 1,019,880 | 1.13 | 1.12, 1.14 | 8.6E-05 | | | | | | | |

Abbreviations: Clinical Practice Research Datalink (CPRD), confidence interval (CI), Crohn's disease (Crohn), cardiovascular diseases (CVD), general practitioner (GP), hazard ratio (HR), inflammatory bowel disease (IBD), inverse-variance weighting (IVW), Mendelian randomisation (MR), multiple sclerosis (MS), other inflammatory polyarthropathies & systematic connective tissue disorders (OID), odds ratio (OR), rheumatoid arthritis (RA), single nucleotide polymorphism (SNP), ulcerative colitis (UC), weighted median (WM)

^a Model 1 adjusted for CPRD practice, comorbidities (CVD and type II diabetes) and number of GP visits (consultation); Model 2 adjusted for CPRD practice, deprivation (socio-economic status), body mass index, smoking, comorbidities (CVD and type II diabetes) and number of GP visits (consultation); Model 3 adjusted for CPRD practice, deprivation (socio-economic status), body mass index, smoking, comorbidities (CVD and type II diabetes) and number of GP visits (consultation) with missing data imputed by multiple imputation.

Figure 1 Flowchart of inclusion and exclusion criteria of study population in the Clinical Practice Research Datalink (first registration date (FRD); transfer out date (TOD))

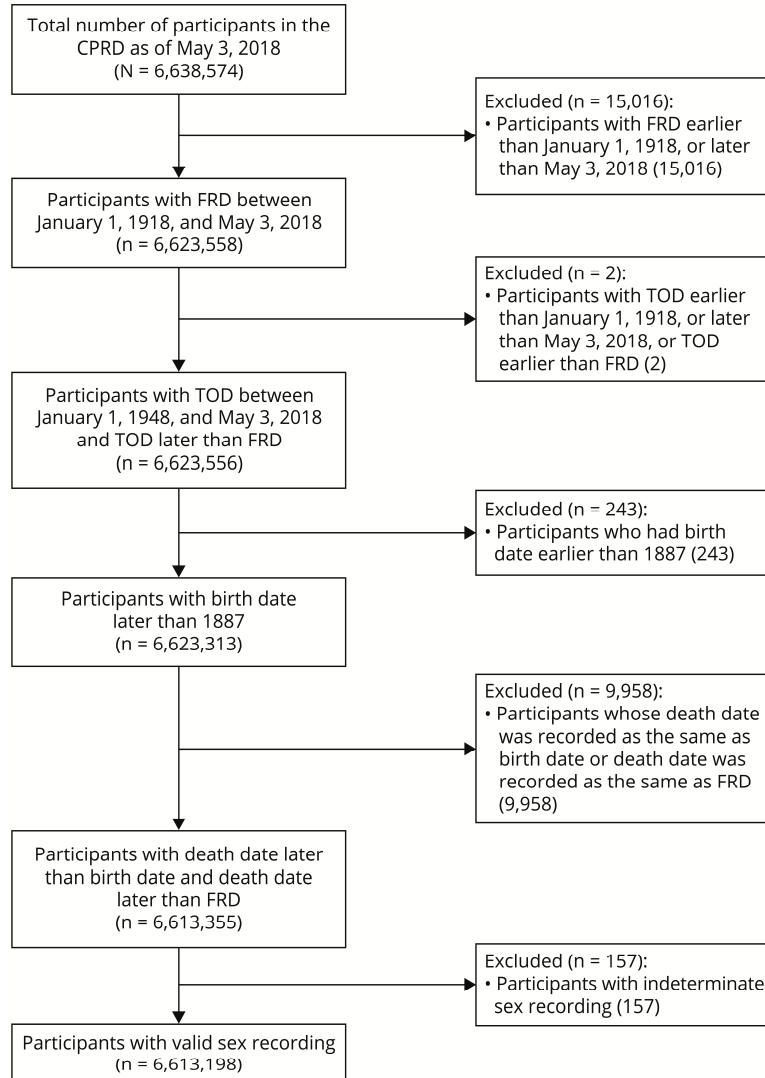


Figure 2 Cumulative incidence function (CIF) curves for dementia onset and for death using Clinical Practice Research Datalink.

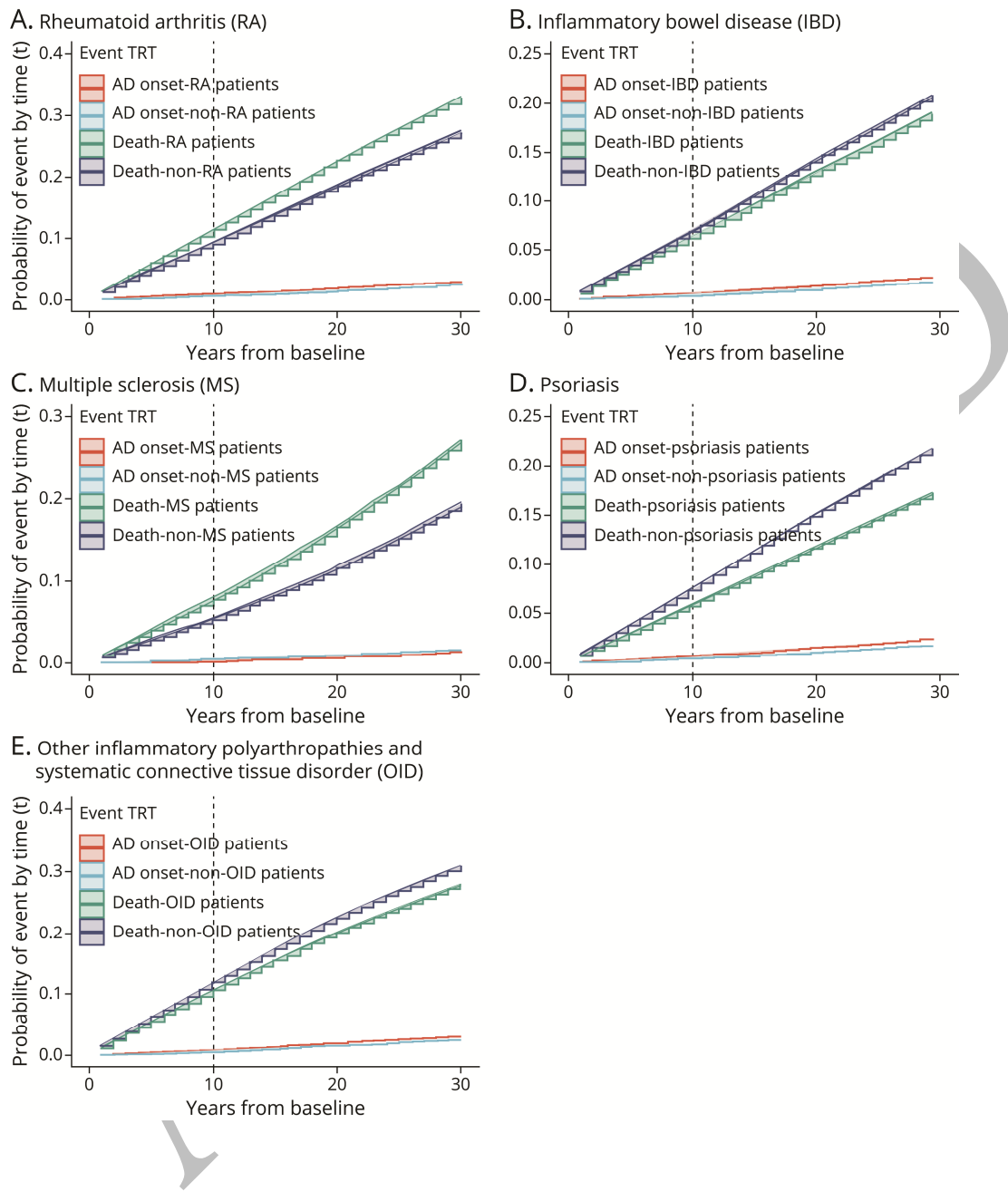


Figure 3 Bidirectional Mendelian randomisation (MR) analysis for the associations between circulating inflammatory biomarker levels and diseases of interest. MR estimates were obtained from Wald ratio method ($N_{\text{SNP}}=1$), from inverse-variance weighted (IVW) fixed-effects model (IVW-FE, $N_{\text{SNP}}=2$ or 3), or from IVW random-effects model (IVW-RE, $N_{\text{SNP}}>3$). Asterisk indicates P -value <0.05 and double asterisk indicates P -value $<0.05/533$. (Alzheimer's disease (AD), Crohn's disease (Crohn), inflammatory bowel disease (IBD), multiple sclerosis (MS), rheumatoid arthritis (RA), ulcerative colitis (UC))

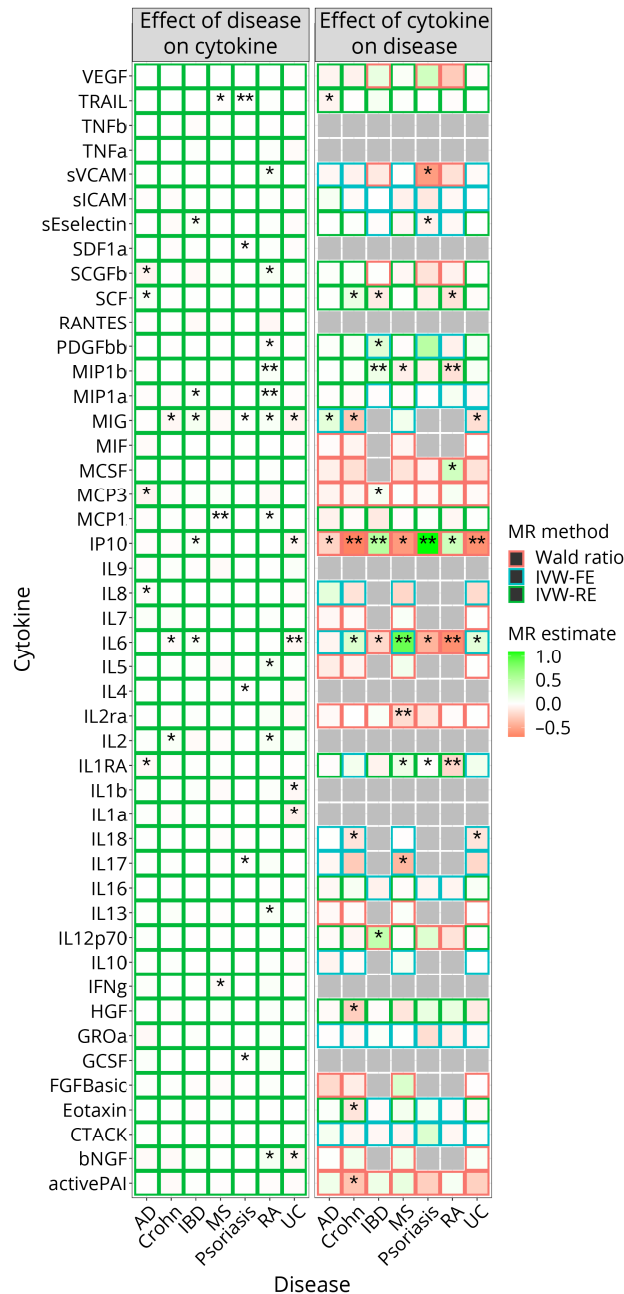
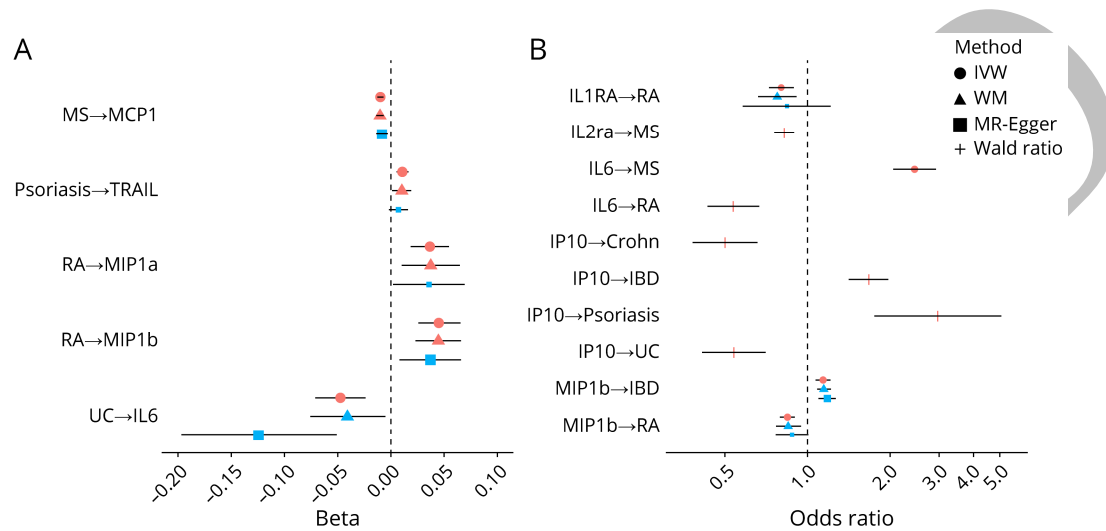


Figure 4 Bidirectional Mendelian randomisation (MR) analysis for the associations between circulating inflammatory biomarker levels and diseases of interest ($P_{\text{Wald}} < 0.05/533$ or $P_{\text{IVW}} < 0.05/533$). MR estimates were obtained from Wald ratio method ($N_{\text{SNP}}=1$), from inverse-variance weighted (IVW) fixed-effects model (IVW-FE, $N_{\text{SNP}}=2$ or 3), or from IVW random-effects model (IVW-RE, $N_{\text{SNP}} > 3$). Red symbol indicates $P < 0.05/695$, larger blue symbol indicates 95%CI does not include the null value. (Alzheimer's disease (AD), Crohn's disease (Crohn), confidence interval (CI), inflammatory bowel disease (IBD), inverse-variance weighting (IVW), multiple sclerosis (MS), rheumatoid arthritis (RA), ulcerative colitis (UC), weighted median (WM))



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