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Coral Romualdo-Perez

cia3230@rit.edu

Queen Mary University of London https://orcid.org/0009-0004-0997-5004

Golam Khandaker

University of Bristol https://orcid.org/0000-0002-4935-9220

Eleanor Sanderson

University of Bristol https://orcid.org/0000-0001-5188-5775

Jennifer Y. F. Lau

Queen Mary University of London

Livia Carvalho

Queen Mary University of London https://orcid.org/0000-0001-8862-0148

Article

Keywords:

Posted Date: November 19th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11165048/v1

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Additional Declarations: Yes Funding sources are fully detailed within the manuscript. For full disclosure, LAC has received funding and consultancy fees from MINDLIFE and consultancy fees from King Faisal Specialist Hospital & Research Centre; GMK has received royalties from the Cambridge University Press for the Textbook of Immunopsychiatry, and consultancy fees from the Neuroimmune Foundation and the Danish Research Fund (DFF). LAC and GMK have no other conflict of interest to declare. All other authors report no financial relationships with commercial interests. This work was conducted as part of the MSc in Genomic Medicine at Queen Mary University of London by the first author.

Genetic liability to loneliness, inflammatory pathways, and severe mental illness risk: a Mendelian randomization study

Coral I. Romualdo-Perez, BSc[1], Golam M. Khandaker, PhD[3-6], Eleanor Sanderson, PhD[3-4], Jennifer YF Lau, PhD[2], and Livia A Carvalho, PhD[1#]

Author Affiliations

1. Translational Pharmacology Lab, William Harvey Research Institute, Charterhouse Square, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, London, UK.

2. Youth Resilience Unit, Wolfson Institute of Population Health, Queen Mary University of London, London, UK.

3. MRC Integrative Epidemiology Unit, University of Bristol, Bristol, UK

4. Population Health Sciences, Bristol Medical School, University of Bristol, Bristol, UK

5. Centre for Academic Mental Health, Population Health Sciences, University of Bristol, Bristol, UK

6. NIHR Bristol Biomedical Research Centre, University Hospitals Bristol and Weston NHS Foundation Trust, Bristol, UK

#Corresponding authors:

Dr. Livia A. Carvalho
Clinical Pharmacology
John Vane Science Centre,
Queen Mary University of London,
Charterhouse Square,
London EC1M 6BQ UK
Tel:+44 (0) 7725000710
l.carvalho@qmul.ac.uk

Ms. Coral Romualdo-Perez
William Harvey Research Institute
Queen Mary University of London,
Charterhouse Square,
London EC1M 6BQ UK
Tel:+1 (225) 5727067
cia3230@rit.edu

Word count: 4,302

Abstract: 240

Number of Tables/Figures: 6

Abstract

Loneliness is a psychosocial stressor associated with elevated risk of severe mental illness (SMI), including major depressive disorder (MDD), schizophrenia (SCZ), and bipolar disorder (BD). Loneliness is theorized to become biologically embedded partly via inflammation-related mechanisms, yet its causal relationship with SMI and the role of inflammatory signaling remain unclear. We investigated whether loneliness increases risk for SMI partly through inflammatory pathways using univariable Mendelian randomization (UVMR) and multivariable MR (MVMR). We integrated genome-wide association study (GWAS) summary statistics for loneliness and SMI with genetic instruments for inflammatory markers. MVMR models estimated the direct effect of loneliness after accounting for inflammatory markers using eQTLs and pQTLs for interleukin-1 receptor antagonist (IL-1RA), interleukin-6 (IL-6), IL-6 receptor (IL-6R), tumor necrosis factor alpha (TNF-α), and TNF receptors (TNF-R1/2). Bidirectional MR examined potential reverse causal pathways between inflammation, SMI, and loneliness. MR provided evidence consistent with a causal effect of genetic liability to loneliness on SCZ and MDD. Results were also consistent with potential, partial mediatory roles for IL-1RA, IL-6Rα, and TNF-R2 in the causal effects of loneliness on SCZ and MDD. No significant causal effects of loneliness on BD were identified. Bidirectional MR suggested evidence of reverse causation between SCZ and loneliness. Together, these findings support a causal risk-increasing effect of loneliness on SCZ and MDD that persists after adjusting for inflammatory markers, implicating inflammation as a plausible mechanistic link between loneliness and SMI and highlighting potential opportunities for prevention and targeted intervention.

1. Introduction

Loneliness is a chronic psychosocial stressor and an urgent global health issue. Chronic loneliness is associated with cognitive decline [1], decreased quality-adjusted life

years [2], and an elevated mortality risk comparable to smoking or obesity [3, 4]. The increasing prevalence of loneliness across demographic groups, especially among socioeconomically disadvantaged populations, is heightening public health concerns [5, 6]. Additionally, current evidence demonstrates that loneliness is a heritable, transdiagnostic marker for poor mental health outcomes [7, 8], with established associations with mental disorders such as schizophrenia (SCZ) [9] and major depressive disorder (MDD) [10, 11].

Mounting evidence implicates inflammatory and immune dysfunction in both loneliness and severe mental illness (SMI). Loneliness has been associated with elevated interleukin-6 (IL-6) levels across adulthood [12], while meta-analyses identify increased IL-6 and IL-1 receptor antagonist (IL-1RA) as predictive markers for MDD [13] and SCZ [14], with broader inflammatory activation observed across mood disorders [15, 16]. Both chronic and acute stress further amplify systemic inflammation [17, 18], supporting a biological pathway linking loneliness to psychiatric risk via immune dysregulation; however, whether this reflects causality, reverse causation, or confounding remains unclear. Gene expression – an intermediate layer between genes and traits – varies across tissues and is influenced by expression quantitative trait loci (eQTLs), enabling tissue-specific evaluation of genetic effects and linking risk variants for the comorbidity of social isolation and SMI to underlying pathology.

To better understand how social stressors are biologically embedded in SMI risk, we tested whether inflammation is a potential, partial mediatory pathway linking loneliness with SMI outcomes. The Social Signal Transduction Theory of SMI [19] conceptualizes social stressors, such as loneliness, as activators of inflammatory pathways, yet no prior study to date has jointly modeled loneliness and inflammatory markers within a causal framework. Prior MR analyses have identified an association between loneliness and both depression [10] and schizophrenia [20]; however, these studies primarily assessed the relationship between

loneliness and SMI outcomes directly. Further, while inflammatory markers suggest causal and therapeutic potential [21, 22], studies examining whether inflammation mediates the causal effect between psychosocial stress and psychiatric risk remain limited, despite their potential to identify mechanistic pathways linking loneliness, SMI, and treatment targets.

To address this gap, we used Mendelian randomization (MR), which leverages genetic variants as instrumental variables to estimate causal effects while reducing confounding and reverse causation [23], alongside multivariable MR (MVMR) to estimate direct effects of correlated exposures [24]. We hypothesized that inflammation is a potential partial mediator in the association between loneliness and SMI; first testing the causal effect of genetic liability to loneliness on SCZ, MDD, and BD using MR, followed by MVMR to estimate the direct effect of loneliness after accounting for inflammatory markers as potential partial mediators [25], using eQTL and pQTL data, and conducting bidirectional analyses to assess reverse causal effects. These insights may inform diversity and inclusion policies by clarifying why SMI is more prevalent in populations facing chronic loneliness, why it frequently co-occurs with mental health conditions, and why it often recurs. This work may also suggest new opportunities for preventing and treating SMI by targeting inflammation.

2. Methods

2.1. Study Design

This study employed a two-sample, summary-data Mendelian randomization (MR) design to investigate whether loneliness affects the risk of severe mental illness (SMI) through inflammatory signaling. All data used in this study were publicly available, de-identified summary statistics from previously published studies with relevant ethical approval and participant consent; therefore, no additional ethical approval or written informed consent was required for this Mendelian randomization analysis. MR assumes (i) the genetic instruments are associated with the exposure (relevance), (ii) the instruments are not associated with

exposure–outcome confounders (independence), and (iii) the instruments affect the outcome only through the exposure (exclusion restriction) [27].

We applied both univariable MR (UVMR) and multivariable MR (MVMR) [24, 27] (Fig. 1), where UVMR estimated total effects and MVMR jointly modeled loneliness and inflammatory markers to estimate mutually adjusted direct effects and evaluate inflammatory markers as potential pathways for partial mediation of the loneliness–SMI association.

Analyses incorporated genetic instruments for loneliness and cis-instruments for inflammatory markers, alongside pairwise bidirectional UVMR and MVMR analyses across loneliness, inflammatory markers, and SMI, using publicly available GWAS and QTL summary statistics from predominantly European ancestry cohorts (Fig. 2 and Table S1).

2.2. Data Sources

Genetic instruments for loneliness were obtained from a GWAS by Day, Ong, and Perry (2018) in 452,302 UK Biobank participants of European ancestry; see Fig. 2. The loneliness phenotype was defined using responses to the question, "Do you often feel lonely?" Participants answering "Yes" were cases (80,134), and those answering "No" were controls (364,890).

Blood eQTL summary statistics for seven inflammatory marker genes – interleukin-1 beta (IL-1β), interleukin-1 receptor antagonist (IL-1RA), interleukin-6 (IL-6), interleukin-6 receptor (IL-6R), tumor necrosis factor alpha (TNF-α), TNF receptor 1 (TNF-R1), and TNF receptor 2 (TNF-R2) – were extracted from eQTL Gen Phase 1 (n = 31,684) [30]. Blood pQTL summary statistic (n = 21,758) for IL-1RA, IL-6, IL-6Rα, TNF-R1, and TNF-R2 were obtained from Folkersen et al. (2020). We analyzed blood eQTL and plasma pQTL datasets separately to account for platform- and measurement-specific differences.

Outcome GWAS were restricted to European ancestry samples to minimize population stratification (Fig. 2). To reduce bias from sample overlap with the UK Biobank, psychiatric

outcomes were sourced from non-UK Biobank Psychiatric Genomics Consortium datasets: schizophrenia (SCZ; CLOZUK; 40,675 cases and 64,643 controls) [32], major depressive disorder (MDD; 135,458 cases and 344,901 controls) [33], bipolar disorder (BD; 41,917 cases and 371,549 controls) [34]. For replication, we used two independent plasma proteomic resources from Ferkingstad et al., 2021 (n = 35,559) and UK Biobank Pharma Proteomics Project (n ≈ 54,000) [36] and a cerebrospinal fluid (CSF) proteomic dataset from Western et al., 2024 (n = 3,506). Where required, we used UCSC liftOver to convert GRCh38 coordinates to GRCh37 [38, 39] and assess consistency of effect direction, effect size, and instrument strength across datasets.

2.3. Instrument Selection and Harmonization

For loneliness, inflammatory marker QTLs, and psychiatric outcomes, we selected genome-wide significant SNPs ($p < 5\times10^{-8}$) and performed LD clumping ($r^2 < 0.001$) using the European 1000 Genomes reference panel [40] via OpenGWAS [41]. Inflammatory marker instruments were restricted to cis variants (±500 kb), with additional conditionally independent SNPs identified using GCTA-COJO where available [42]. Data were harmonized to the same effect allele using TwoSampleMR (v0.6.29) [43], and proxy SNPs ($r^2 \geq 0.8$) were identified using LdlinkR (v1.4.0) when needed [44]. Instrument strength was assessed using mean F-statistics (UVMR) and conditional F-statistics (MVMR), with $F > 10$ indicating strong instruments.

2.4. Univariable Mendelian Randomization Analyses

We used inverse-variance weighted (IVW) MR as the primary estimator and the Wald ratio for single-SNP instruments. In a bidirectional framework, we tested total effects between loneliness, inflammatory markers, and SMI outcomes (SCZ, MDD, BD), including all pairwise directions. Robustness assessments (≥3 SNPs) included MR-Egger, weighted median, and weighted mode. Initial analyses used full instrument sets and were repeated after excluding

variants contributing to heterogeneity or pleiotropy, and these adjusted instrument sets were used for primary interpretation unless otherwise indicated. Heterogeneity and pleiotropy were assessed using Cochran's Q and the MR-Egger intercept, respectively, with MR-PRESSO used to detect and correct pleiotropic outliers. MR Steiger filtering was applied to limit reverse causation, and leave-one-out and single-SNP analyses identified influential variants. For loneliness instruments (N = 13), sensitivity analyses removed 5 variants for SCZ (including 2 overlapping between Steiger and MR-PRESSO), and 1 and 2 variants for MDD and BD, respectively, identified through MR-PRESSO (Tables S2-S3).

2.5. Multivariable Mendelian Randomization Analyses

We applied Multivariable Mendelian randomization (MVMR) [24] to estimate the direct effects of loneliness and inflammatory markers on SMI outcomes, accounting for shared genetic architecture [27, 44], using instruments for loneliness and cis inflammatory variants in a combined model. Directionality was further assessed using bidirectional models incorporating SMI instruments with cis inflammatory instruments and loneliness as the outcome. Analyses were conducted in R (multivariable MR package v0.4) using multivariable IVW regression as the primary estimator, with conditional F-statistics for instrument strength [44], multivariable MR-Egger for pleiotropy [45-46], and Q-statistics for residual heterogeneity [24]. As with UVMR, corresponding adjusted instrument sets were carried forward into MVMR, with full-instrument models retained for comparison.

All analyses used a two-sample framework assuming independent samples. For binary traits used as exposures (loneliness, MDD, SCZ, BD), estimates (beta, OR, 95% CI) were scaled to reflect a one-standard deviation increase in genetic liability using $SD = \sqrt{p(1-p)}$, where p was the case proportion in the source GWAS, while QTL exposures were retained in their original 1-SD scale. Results are reported as beta coefficients, standard errors, and p-

values, with only statistically significant findings carried forward to colocalization analyses (Fig. 1).

MVMR analyses were interpreted as conditional direct effects rather than formal mediation estimates. While indirect effects can be estimated using a product-of-coefficients approach, we did not calculate the indirect effects or proportions mediated because the primary loneliness exposure and SMI outcomes were binary. For binary exposures, MR can be used to test causal effects, but caution is warranted when interpreting effect estimates as measures of causal effect magnitude [24]; additionally, for binary outcomes, non-collapsibility of odds ratios limits the reliable calculation of direct and indirect effects [24]. Therefore, we evaluated inflammatory markers as potential pathways for partial mediation without quantifying indirect effects.

2.6. Colocalization Analyses

For exposure–outcome pairs with significant MR and MVMR estimates, we used Bayesian colocalization to assess whether significant MR-supported exposure-outcome associations reflected shared causal variants [47, 48], extracting ±500 kb (and ±250 kb sensitivity) regions around loneliness lead SNPs, SCZ loci, and inflammation genes with significant effects. Analyses were conducted using coloc (v5.1.0) with priors $p1 = p2 = 1\times10^{-4}$ and $p12 = 1\times10^{-5}$, defining evidence of colocalization as $PP.H4 \geq 0.80$ and sweeping sensitivity analyses across p12 (10^{-8}–10^{-2}). Results were interpreted cautiously due to reliance on detectable regional signals, as limited power can hinder distinction between shared (H4) and distinct (H3) variants [49, 50].

Claude (Anthropic; Claude Opus 4) was used for language and editorial assistance during manuscript preparation. All content was reviewed and approved by the authors.

3. Results

3.1. Univariable MR: Is loneliness likely causal to severe mental illness?

To confirm directionality, we first assessed whether genetic liability to loneliness had a causal effect on SMI through UVMR. Loneliness showed evidence of a potential risk-increasing causal effect on SCZ (IVW $p < 0.05$); supported by other MR estimates, and MDD (IVW $p < 0.05$), supported by all other MR methods except MR-Egger (Figs. 3-4). Potential horizontal pleiotropy was identified in both analyses through MR-PRESSO ($p < 0.05$), with no other outlier indices (Table S2). No significant effects were observed for loneliness on BD (Figs. 3-4).

Initial analyses using the complete loneliness instrument list, which indicated heterogeneity and pleiotropy, showed a significant causal effect but with conflicting beta directions observed between IVW and MR-Egger (Tables S2-S3). Further, sensitivity assessments revealed significant heterogeneity (Cochran's Q, $p < 0.01$) and horizontal pleiotropy (MR-Egger intercept, $p < 0.01$; MR-PRESSO, outlier test $p < 0.01$), with several variants identified as outliers (Table S2). We found that although the MR-PRESSO distortion test was non-significant for both MDD and SCZ (Table S4), the identification of outlier SNPs (outlier $p < 0.05$) indicated that key instruments may violate MR assumptions of (ii) independence and (iii) exclusion restriction due to pleiotropic instruments.

3.2. Univariable MR: Does loneliness causally influence immune dysregulation?

Next, we assessed whether loneliness had a causal effect on circulating inflammatory marker levels. UVMR analyses indicated a potential positive causal effect of loneliness on IL-6Rα_{pQTL}, TNF-R1$_{pQTL}$, and TNF-R2$_{pQTL}$ (Fig. 3). These effects were not observed in additional analyses using inflammatory marker pQTLs from plasma and CSF. Sensitivity assessments showed no evidence of heterogeneity or pleiotropy (Table S3), aside from loneliness to TNF-R2$_{pQTL}$ via MR-PRESSO ($p = 0.039$; no outliers). No significant results were observed for loneliness on IL-1RA$_{pQTL}$ or IL-6$_{pQTL}$ across all estimates. Analyses assessing the total effects of

loneliness on cis-eQTLs for inflammatory markers could not be performed due to a lack of instrumental overlap.

3.3. Univariable MR: Is immune dysregulation causally associated with loneliness or severe mental illness?

Following, we assessed whether cis-QTL instruments for inflammatory markers had a significant effect on loneliness or SMI. This showed that higher genetically proxied circulating IL-1RA$_{pQTL}$ levels had a potentially causal negative effect on loneliness, but this was not replicated with cis-pQTL instruments obtained from validation datasets (Fig. 3; Table S2). Sensitivity assessments could not be performed for this model due to only one instrument being available (Table S3). No other significant effects were observed for IL-6Rα$_{pQTL}$ and TNF-R2$_{pQTL}$ on loneliness.

Assessment of total effects of inflammation on SMI showed that higher genetically proxied circulating IL-6Rα$_{pQTL}$ levels had a positive causal effect on SCZ, with no evidence of heterogeneity or pleiotropy (Table S3) and replication in validation datasets (Table S2). No other significant effects (IVW $p < 0.05$) were identified for IL-1RA$_{pQTL}$, IL-6Rα$_{pQTL}$, and TNF-R2$_{pQTL}$ on MDD or BD; assessment of the presence of heterogeneity and pleiotropy could not be performed for markers with a single SNP available (Table S3). No cis-instruments were available for IL-6$_{pQTL}$ or TNF-R1$_{pQTL}$. Among the cis-eQTL analyses, higher genetically proxied TNF-R1 expression had a significant, negative causal effect on SCZ, while no other significant effects were observed for any of the cis-eQTLs (Wald ratio $p > 0.05$) on loneliness or SMI outcomes (Table S2).

3.4. Univariable MR: Does severe mental illness causally influence loneliness or immune dysregulation?

We further assessed whether the causal effects identified above were bidirectional. A significant positive causal effect from SCZ to loneliness (IVW $p < 0.01$) was identified.

However, initial analyses did not meet MR assumptions due to significant heterogeneity (Cochran's Q, $p < 0.05$), directional pleiotropy (MR-Egger $p < 0.005$), and horizontal pleiotropy (MR-PRESSO $p < 0.05$), with several SNPs identified as outliers (Table S2-S3). Following removal of identified outliers, the positive causal effect of SCZ on loneliness remained significant; however, evidence of directional (MR-Egger $p < 0.01$) and horizontal pleiotropy (MR-PRESSO $p < 0.01$; no outliers) persisted, with no further outliers identified. No significant causal effects of MDD or BD on loneliness were identified.

Further analyses assessed whether SMI had causal effects on circulating inflammatory marker levels. Within these results, no significant effects were observed for SCZ or MDD on IL-1RA$_{pQTL}$, IL-6$_{pQTL}$, IL-6Rα_{pQTL}, TNF-R1$_{pQTL}$, or TNF-R2$_{pQTL}$ (Table S2). A potentially negative causal effect of BD on circulating TNF-R1 levels was identified, with validation in the CSF dataset; potential horizontal pleiotropy was identified through MR-PRESSO ($p < 0.05$) with no significant outliers (Table S3).

3.5. Multivariable MR: Does loneliness causally influence severe mental illness after accounting for immune dysregulation?

We assessed whether the causal effect of loneliness on SMI persisted after accounting for inflammation. A risk-increasing potential direct causal effect of loneliness on SCZ remained after adjusting for IL-1RA$_{pQTL}$, IL-6Rα_{pQTL}, and TNF-R2$_{pQTL}$ (Fig. 5). We could not reject the null hypothesis of no heterogeneity (Cochran's Q, $p > 0.05$). Similar direct effects of loneliness on MDD were observed after adjusting for IL-1RA$_{pQTL}$, IL-6Rα_{pQTL}, and TNF-R2$_{pQTL}$. The aforementioned inflammatory pathways, both for SCZ and MDD, were further validated in secondary inflammatory marker pQTLs from plasma, showing a consistent direct effect of loneliness on SCZ and MDD (Table S5). Initial analyses using the complete loneliness set, which suggested the presence of heterogeneity and pleiotropy, were only significant for MDD (Tables S5-S6). As no cis-instruments were available for IL-6$_{pQTL}$ and TNF-R1$_{pQTL}$, these

inflammatory markers could not be incorporated into the analyses. No significant results were observed for BD (Fig. 5).

3.6. Multivariable MR Results: Does severe mental illness causally influence loneliness after accounting for immune dysregulation?

Next, we assessed bidirectionality by testing whether SMI had a direct causal effect on loneliness after accounting for inflammation. Evidence of a potential risk-increasing direct effect of SCZ on loneliness (Fig. 6) was observed after adjusting for IL-1RA$_{pQTL}$, IL-6Rα_{pQTL}, and TNF-R2$_{pQTL}$. However, there was significant heterogeneity in all models (Table S6). For MDD, no direct effect on loneliness was observed after adjusting for IL-6Rα_{pQTL}; the other models with IL-1RA and TNF-R2 were not estimable due to a lack of sufficient instruments (SNPs $\leq$ 2; Table S5). No significant effects were observed utilizing instruments for BD and cis-pQTLs on loneliness.

3.7. Colocalization: Is there a shared causal variant between loneliness, severe mental illness, and immune dysregulation?

Finally, we performed colocalization to assess whether there were shared causal variants. Colocalization evaluates whether neither trait is associated with a variant in the region (H0), only trait 1 (H1) or trait 2 (H2) is associated, both traits are associated with distinct causal variants (H3), or both traits share the same causal variant (H4) [47]. We first assessed the loneliness-associated loci to determine whether there were any shared causal variants between loneliness, SCZ, MDD, and inflammatory markers (IL-1RA, IL-6Rα, TNF-R2). For SCZ, loneliness-led analyses favored loneliness-only (H1) or distinct variants (H3), with two loci supporting H3 (PP.H3 = 0.85–0.88; Table S7) and no changes across sensitivity analyses (Table S8). SCZ-led analyses similarly favored SCZ-only models (PP.H2 > 0.80), with two loci supporting H3 (PP.H3 ≈ 0.99) and one supporting colocalization (PP.H4 ≈ 0.95; Table S7);

these findings were unchanged in sensitivity analyses (Table S8), while ±250 kb analyses supported H1/H2.

For MDD, loneliness-led analyses primarily favored H1, with one locus (rs13291079) showing mixed support (PP.H1 ≈ 0.23 and PP.H4 ≈ 0.65) and increased support for shared variants observed in sensitivity analyses for this locus (PP.H4 ≈ 0.98; Table S7). MDD-led analyses similarly identified one colocalized locus (rs76025409; PP.H4 ≈ 0.94), with remaining loci favoring MDD-only models (H2; Table S7) and no changes across sensitivity or ±250 kb analyses (Tables S7-S8).

Next, we assessed inflammation-led loci, which predominantly favored pQTL-only models (H1) across IL-1RA, IL-6, IL-6R, TNF-R1, and TNF-R2 [28, 32, 33] (Tables S9-S10), with limited evidence of colocalization except IL-1RA (PP.H4 = 0.85; 0.81 in sensitivity analyses). Inflammation–SCZ analyses primarily supported H1, with H3 support within IL-6R (Table S9), while inflammation–MDD analyses consistently favored H1 with no changes in sensitivity or ±250 kb analyses. Overall, these findings predominantly support distinct genetic signals across loneliness, inflammatory markers, and SMI, with locus-specific evidence for SCZ and MDD, but limited evidence of shared causal variants within inflammatory loci.

4. Discussion

4.1. Summary of Main Findings

Across our Mendelian randomization analyses, we observed genetic evidence supporting an effect of loneliness on severe mental illness (SMI), with inflammatory markers representing a potential pathway for partial mediation. Findings were consistent for schizophrenia (SCZ) and major depressive disorder (MDD), for which loneliness showed total effects and direct effects that persisted after accounting for circulating IL-1RA, IL-6Rα, and TNF-R2 in MVMR models, albeit MVMR alone is not sufficient to establish mediation. Bidirectional analyses also supported an effect of SCZ on loneliness, although persistent

heterogeneity and pleiotropy warrant cautious interpretation. Evidence for bipolar disorder (BD) was more limited, with a potential negative effect of BD on TNF-R1 without other robust associations.

Colocalization analyses predominantly supported distinct causal variants between loneliness, inflammatory markers, and SMI. Locus-specific evidence of potential shared causal variants was observed for MDD, whereas inflammatory loci largely favored pQTL-only models. In unison, these findings support genetic relationships between loneliness and SCZ/MDD, with marker-specific evidence supporting IL-1RA, IL-6Rα, and TNF-R2 as candidate pathways that may contribute differently across disorders; however, these pathways warrant further investigation to determine whether they act as partial inflammatory mediators linking loneliness to SMI.

4.2. Schizophrenia: Immune Pathways Linking Loneliness to Psychosis

Our findings provide genetic evidence supporting an effect of loneliness on SCZ risk, consistent with previous MR evidence supporting a causal effect between loneliness and SCZ [20], with our findings extending this work by identifying several inflammatory pathways that possibly contribute to this effect. Loneliness retained a direct effect after adjusting for IL-1RA, with limited evidence of pleiotropy or heterogeneity; a potential mediatory contribution of IL-1RA remains possible and aligns with evidence that elevated IL-1RA levels may reflect chronic immune activation or compensatory anti-inflammatory signaling in SCZ [51–53]. A strong pattern was also identified for IL-6Rα circulating protein levels, aligning with prior MR studies implicating the IL-6 signaling pathway in SCZ [54], and evidence that soluble IL-6R trans-signaling drives pro-inflammatory responses linked to neuroinflammation, stress reactivity, and impaired neurogenesis [55–56].

The direct effect of loneliness on SCZ also persisted after adjusting for circulating TNF-R2 levels, with TNF-R2 implicated in neuroprotection [57] and SCZ severity [58–59].

Replication across independent datasets for IL-1RA, IL-6Rα, and TNF-R2 supported the consistency of these findings. However, the predominance of distinct rather than shared causal variants in colocalization analyses limits mechanistic interpretations.

4.3. MDD: Immune Pathways Linking Loneliness to Depression

Our analyses provide genetic evidence supporting an effect of loneliness on MDD risk, in line with prior work linking loneliness to depression via social stress pathways [10]. Loneliness adjusted for IL-1RA levels retained a direct causal effect with limited heterogeneity and pleiotropy, aligning with observational and genetic evidence implicating IL-1RA in depression [60–62]. IL-6Rα showed a similar pattern, with replication across plasma and cerebrospinal fluid datasets, and prior evidence linking soluble IL-6R [63] and IL-6 signaling to increased depression risk [64]. TNF-R2 showed comparable effects, while previous animal models have shown that a TNF-R1/2 deletion induces antidepressant-like responses [65], with elevated TNF receptor levels also observed in SMI, including depression [59].

Colocalization with sensitivity analyses identified a possible, shared causal variant (rs13291079) between loneliness and MDD; this variant lies within an intron of PHF2 [66–69] and has been shown to act as a co-activator with NF-κB in macrophages, promoting pro-inflammatory responses [70]. However, most loneliness–MDD and inflammation–MDD loci did not support shared causal variants, limiting inference of a common inflammatory mechanism. Together, these findings support a causal effect of loneliness on MDD, with potential evidence for IL-1RA, IL-6Rα, and TNF-R2 as partial inflammatory mediators of this effect.

4.4 BD: Limited Genetic Evidence for Inflammatory Involvement

Further, evidence for BD was limited. A single MR analysis suggested a potential negative effect of BD on TNF-R1 with replication in the CSF dataset, contrasting with previous reports linking BD with increased TNF-R1 levels [58, 71]. The broader pattern of null results

may reflect reduced power and etiological heterogeneity within BD, including subtype differences (e.g., higher SNP-based heritability in BD I compared with BD II) [72, 73] alongside complex polygenic architecture [74]. Future work using larger, stratified, and multi-ancestry GWAS, together with improved inflammatory QTL instruments, will be needed to clarify whether loneliness and inflammatory signaling play distinct roles in BD pathophysiology.

4.5. Limitations

Our study had several strengths, including the novel evaluation of inflammation as a potential mediatory pathway linking loneliness and severe mental illness. We further incorporated multiple independent QTL datasets across plasma and CSF to enhance interpretability and assess the consistency of our findings. Despite the strengths, several limitations remain. First, residual heterogeneity and pleiotropy cannot be fully excluded, and limited statistical power—particularly for loneliness and cis-QTL exposures with sparse instruments or F-statistics < 10—may introduce weak instrument bias and inflate causal effect estimates, warranting careful interpretation. Additionally, loneliness was defined using a single binary self-report item, which may not capture the multidimensional nature or severity of loneliness. Some markers (e.g., IL-6_{pQTL} and TNF-$R1_{pQTL}$) lacked sufficient instruments for MR/MVMR, while protein data for TNF-α and IL-1β were unavailable. Consequently, findings involving IL-6Rα should not be generalized to circulating IL-6 levels or IL-6 signaling more broadly.

Further, MVMR estimates conditional direct effects and does not, by itself, formally establish mediation. Although variation was observed between total and direct effect estimates, we did not calculate indirect effects or proportions mediated because the binary exposure and outcomes limit the reliable decomposition of causal effects into direct and indirect effects [24]. Consequently, inflammatory markers were interpreted as potential contributors to partial

mediation rather than as quantified mediators. These interpretations are further limited by the possibility of the effects observed in MVMR arising from shared genetic architecture and undetectable pleiotropic effects, and a lack of colocalization support for shared causal variants across loneliness, inflammatory markers, and SMI further limits our interpretation. In addition, access to the most recent comprehensive GWAS summary statistics for loneliness was limited due to data-access requirements. Social traits such as loneliness may also remain vulnerable to confounding from population structure and dynastic effects [75], and restriction to European-ancestry cohorts limits generalizability.

4.6. Future Directions

Future work should examine loneliness–inflammation effects at the symptom or dimensional level, incorporate trans-ancestry analyses, and leverage larger GWAS of social traits alongside expanded, tissue-specific pQTL resources to improve instrument strength. Complementary causal mediation approaches, longitudinal designs, and molecular studies will also be important for determining whether the inflammatory markers prioritized here have mediating roles, reflect a shared biological basis, or represent independent consequences of loneliness and psychiatric risk. If validated by complementary approaches, these findings may inform prevention and intervention strategies targeting both social isolation and inflammation within individuals.

4.7 Conclusions

In summary, our findings provide genetic evidence supporting a causal effect of loneliness on SCZ and MDD, with inflammatory pathways—particularly IL-1RA, IL-6R, and TNF pathways—as candidates that may contribute to these effects. Our usage of MVMR showed that the effects of loneliness persisted after accounting for the aforementioned inflammatory markers, supporting further investigation of these markers as potential contributors to partial mediation. Colocalization primarily supported distinct genetic signals,

limiting our inference of a shared inflammatory mechanism. Evidence for BD was comparatively limited across all analyses.

Our usage of MVMR enabled the estimation of conditional direct effects, while enabling the evaluation of inflammatory markers that may contribute to disorder-specific vulnerability. Together, these results support a potential model in which loneliness may become biologically embedded through immune mechanisms, contributing to disorder-specific vulnerability, but determination of inflammatory mediation warrants further study. If validated in future studies, these findings may inform prevention and intervention strategies targeting both social and biological determinants of severe mental illness.

5. Declarations

5.1. Disclosures of Interest

LAC has received funding and consultancy fees from MINDLIFE. LAC and GMK have no conflict of interest to declare with regard to the content of this manuscript. For full disclosure, LAC has received consultancy fees from MINDLIFE and King Faisal Specialist Hospital & Research Centre; GMK has received royalties from the Cambridge University Press for the Textbook of Immunopsychiatry, and consultancy fees from the Neuroimmune Foundation and the Danish Research Fund (DFF). All other authors report no financial relationships with commercial interests. During the preparation of this work, the author(s) used Claude (Anthropic, claude.ai, model: Claude Opus 4, accessed January–March 2026), which assisted in the language and flow of the manuscript; the author(s) reviewed and edited the content as needed and take full responsibility for the article contents.

5.2. Funding

LAC is supported by the Wellcome Trust (226777/Z/22/Z), Barts Charity (G001414), and the UKRI Social Health Hub of the Mental Health Platform (MR/Z503514/1). JL is supported by the UKRI Social Health Hub of the Mental Health Platform (MR/Z503514/1).

GMK is supported by the UK Medical Research Council (MRC; MC_UU_00032/6), which contributes to the MRC Integrative Epidemiology Unit at the University of Bristol, and by the Wellcome Trust (201486/Z/16/Z and 201486/B/16/Z), the MRC (MR/W014416/1, MR/S157675/1, MR/Z50354X/1, and MR/Z503745/1), and the National Institute for Health and Care Research Bristol Biomedical Research Centre (NIHR 203315). ES is supported by UKRI (UKRI0077) and the European Union (101073237; ESSGN). The views expressed in this publication are those of the authors and do not necessarily reflect those of the European Union, MSCA Horizon Europe, ESSGN, NIHR, or the Department of Health and Social Care.

5.3 Data and Analytical Code Availability

All data used in this study is publicly available. Summary statistics for perceived social isolation (PSI; loneliness/social isolation traits) were obtained from Day et al. (UK Biobank) via the NHGRI-EBI GWAS Catalog [76] under accession number (https://www.ebi.ac.uk/gwas/studies/GCST006923). Expression summary data was obtained from Võsa et al. via eQTL Gen Phase 1. Plasma protein pQTL summary data were taken from Folkersen et al. via GWAS catalog (IL-1RA GCST90012004; IL-6 GCST90012005; IL-6Rα GCST90012025; TNF-R1 GCST90012015; TNF-R2 GCST90012026). Proteomic validation datasets for Ferkingstad et al. were accessed via the deCODE public summary-data portal (https://www.decode.com/summarydata), the UK Biobank Pharma Proteomics Project (UKB-PPP) pQTL data were obtained from the Sun et al. repository (http://ukb-ppp.gwas.eu), and the Western et al. CSF data were obtained from GWAS Catalog (IL-6 GCST90426090; IL-6Rα GCST90425952; TNF-R1 GCST90425410; TNF-R2 GCST90427361). Summary statistics used for severe mental illness (SMI) endpoints were accessed through the Psychiatric Genomics Consortium (PGC) and are publicly available from the PGC downloads portal under the relevant disorder workgroups. Analytical code, study-derived outputs, and result tables are provided in the Supplementary Data and through Zenodo (10.5281/zenodo.18473530).

5.4. Author contributions

LAC: Conceptualisation, Methodology, Writing – Original Draft, Reviewing & Editing

CRP: Conceptualisation, Methodology, Formal Analysis, Writing – Original Draft, Reviewing & Editing

GK: Methodology, Writing – Reviewing & Editing

ES: Methodology, Writing – Reviewing & Editing

JL: Reviewing & Editing

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Figure legends

Fig. 1. Conceptual framework for Mendelian randomization analyses of loneliness, inflammatory markers, and severe mental illness. Diagram illustrating the hypothesized causal effects tested using univariable and multivariable Mendelian randomization (MR). Genetic variants serve as instrumental variables for loneliness (GWAS) and inflammatory marker levels (eQTLs and pQTLs). Univariable MR (UVMR) evaluates the effect of loneliness and inflammatory markers on severe mental illness (schizophrenia, major depressive disorder, and bipolar disorder) as well as the bidirectional relationship between loneliness and inflammation. Multivariable MR (MVMR) estimates the conditional direct effects while accounting for inflammation as a potential, partial mediator.

GWAS: genome-wide association study; eQTL: Expression Quantitative Trait Loci; pQTL: protein quantitative trait loci.

Fig. 2. Flow analysis. Data sources, instrument selection strategy, and statistical analysis pipeline for Mendelian randomization.

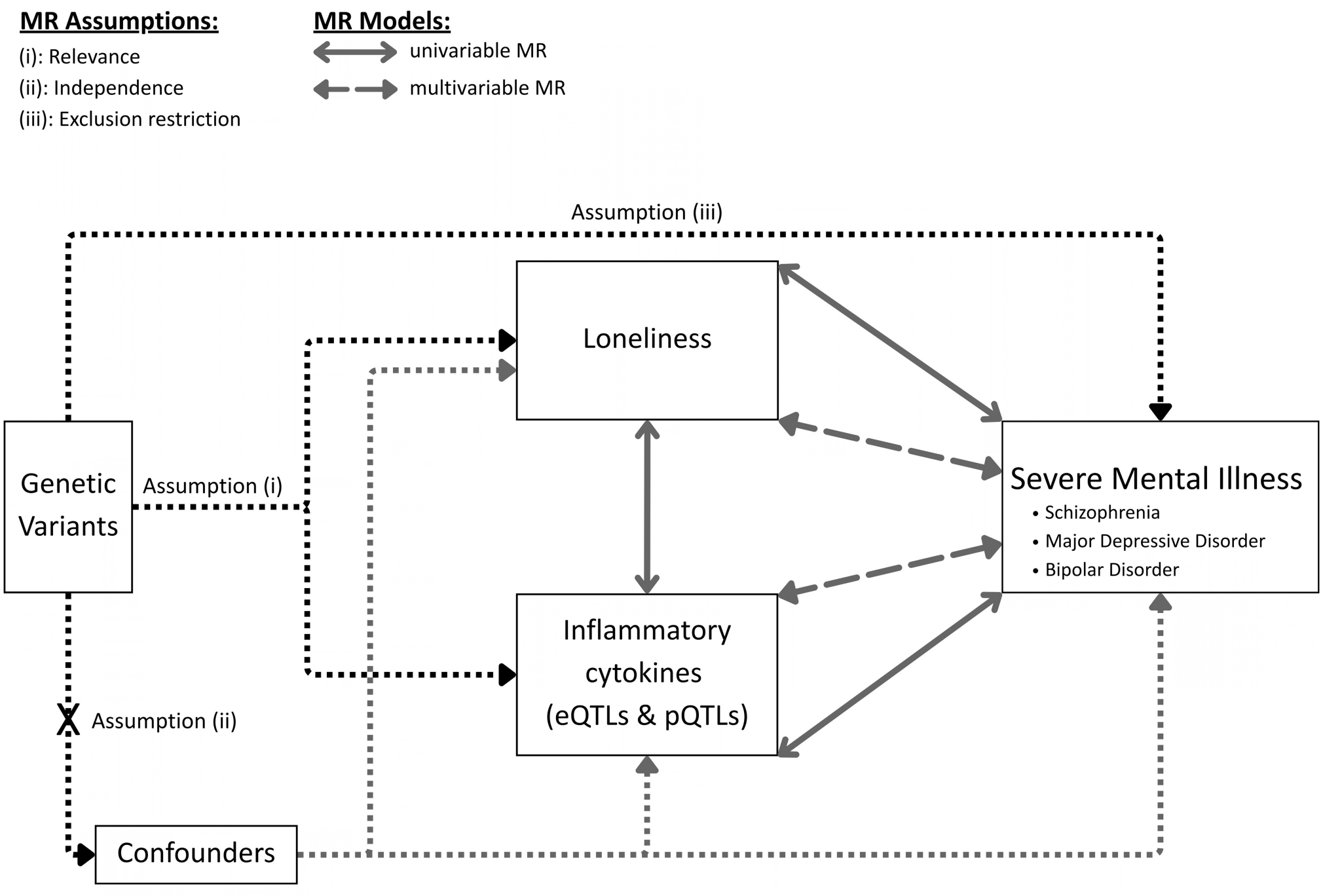
GWAS: genome-wide association study; MR: Mendelian randomization; QTL: quantitative trait loci; SMI: severe mental illness.

Fig. 3. Univariable MR estimates of loneliness instruments and inflammatory markers on severe mental illness. Estimates assess the total effects of loneliness and inflammatory marker pQTLs on schizophrenia (SCZ), major depressive disorder (MDD), and bipolar disorder (BD). (.) = significant results not validated. (*) = significant results validated in one dataset. (**) = significant results validated in two datasets. (***) = significant results validated in three datasets. Plots show odds ratios (ORs) with 95% CIs per 1-SD increase in the exposure.

Fig. 4. Scatterplot of MR estimates for loneliness to severe mental illness outcomes using instruments retained after sensitivity assessments. Panel A: schizophrenia. Panel B: major depressive disorder. Panel C: bipolar disorder.

Fig. 5. Multivariable MR estimates of loneliness instruments and inflammatory markers on severe mental illness. Estimates assess the direct effects of loneliness and inflammatory marker pQTLs on schizophrenia (SCZ), major depressive disorder (MDD), and bipolar disorder (BD). (.) = significant results not validated. (*) = significant results validated in one dataset. (**) = significant results validated in two datasets. (***) = significant results validated in three datasets. Plots show odds ratios (ORs) with 95% CIs per 1-SD increase in the exposure.

Fig. 6. Multivariable MR estimates of severe mental illness instruments and inflammatory markers on loneliness. Estimates assess the direct effects of severe mental illness (SCZ, MDD, and BD) and inflammatory marker pQTLs on loneliness. Estimates of MDD and IL-1RA and TNF-R2 to loneliness were not estimable due to insufficient instruments. (.) = significant results not validated. Plots show odds ratios (ORs) with 95% CIs per 1-SD increase in the exposure.


MR Assumptions:
(i): Relevance
(ii): Independence
(iii): Exclusion restriction
MR Models:
univariable MR
multivariable MR
Assumption (iii)
Loneliness
Genetic Variants
Assumption (i)
Severe Mental Illness
• Schizophrenia
• Major Depressive Disorder
• Bipolar Disorder
Inflammatory cytokines (eQTLs & pQTLs)
Assumption (ii)
Confounders

Social Stressor Genetic Instruments

Loneliness
445,024 EU individuals (UKB)
(Cases = 80,134 cases); (Controls = 364,890)
Day, Ong, and Perry (2018)

GWAS Instrument Identification
- From multiple genomic locations
- $p < 5 \times 10^{-8}$
- $r^2 < 0.001$
- F-stat > 10

Inflammatory response

Inflammatory Mediators

Cytokines pQTLs
21,758 EU individuals
(non-UKB)
Folkersen et al. (2020)

Cytokine eQTLs
31,684 EU individuals
(non-UKB)
Võsa et al. (2021)

QTL Instrument Identification
- $p < 5 \times 10^{-8}$
- $r^2 < 0.001$
- F-stat > 10
- CIS variants (500kb±)

Mediated pathway to SMI

Outcomes

Bipolar Disorder (BD)
413,466 EU individuals
(Cases = 41,917)
(Controls = 371,549)
(non-UKB)
Mullins et al. (2021)

Major Depressive Disorder (MDD)
480,359 EU individuals
(Cases = 135,458)
(Controls = 344,901)
(non-UKB)
Wray et al. (2018)

Schizophrenia (SCZ)
105,318 EU individuals
(Cases = 40,675)
(Controls = 64,643)
(non-UKB)
Pardiñas et al. (2018)

Statistical Analyses

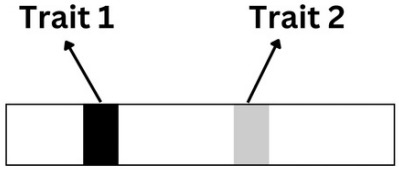
Mendelian Randomization
- Inverse Variance Weighted
- MR-EGGER
- Wald ratio

Sensitivity Analyses
- MR-PRESSO
- Single SNP Analysis
- Cochran's Q Statistic
- Egger-intercept
- Leave-one-out analysis
- Steiger filtering

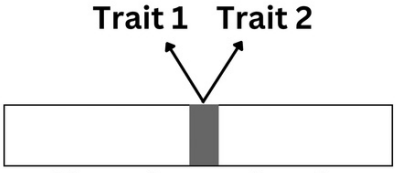
Colocalization Analyses

Trait 1 = Loneliness
Trait 2 = Inflammatory Cytokine

Coloc
- CIS (500kb±) per cytokine
- $p1 = p2 = 1 \times 10^{-4}$, $p12 = 1 \times 10^{-5}$
- PP.H4 ≥ 0.80 (evidence of colocalization)

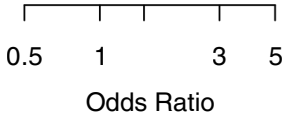


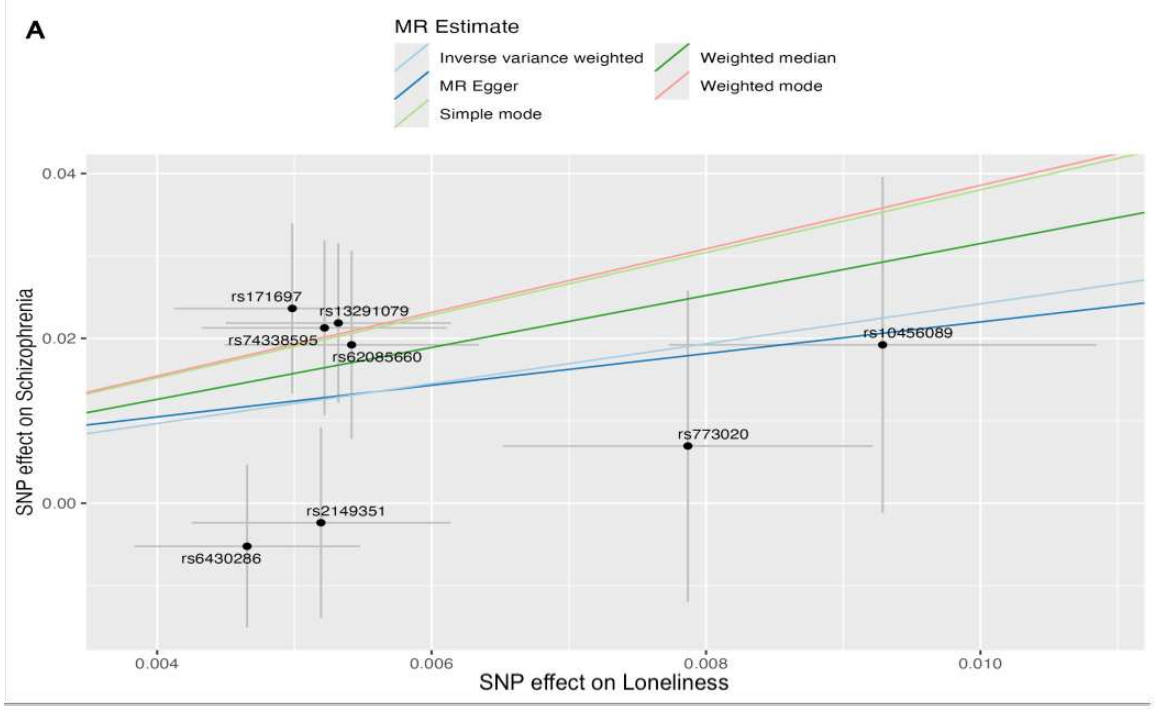
Distinct causal variants

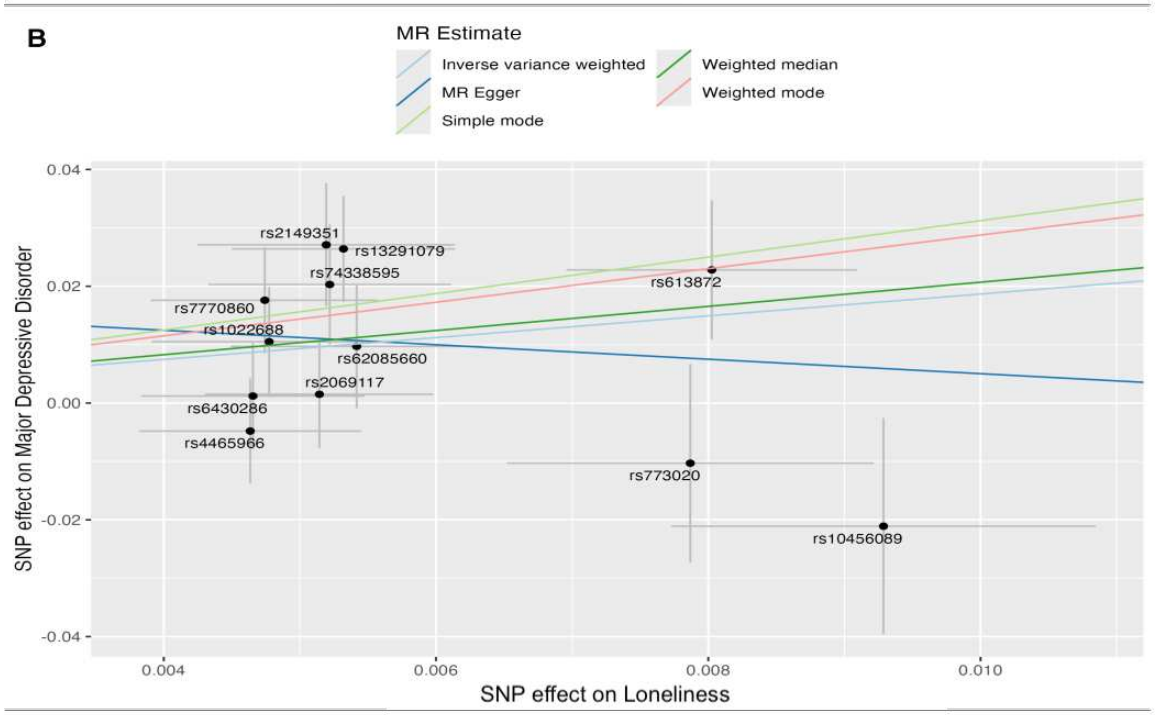


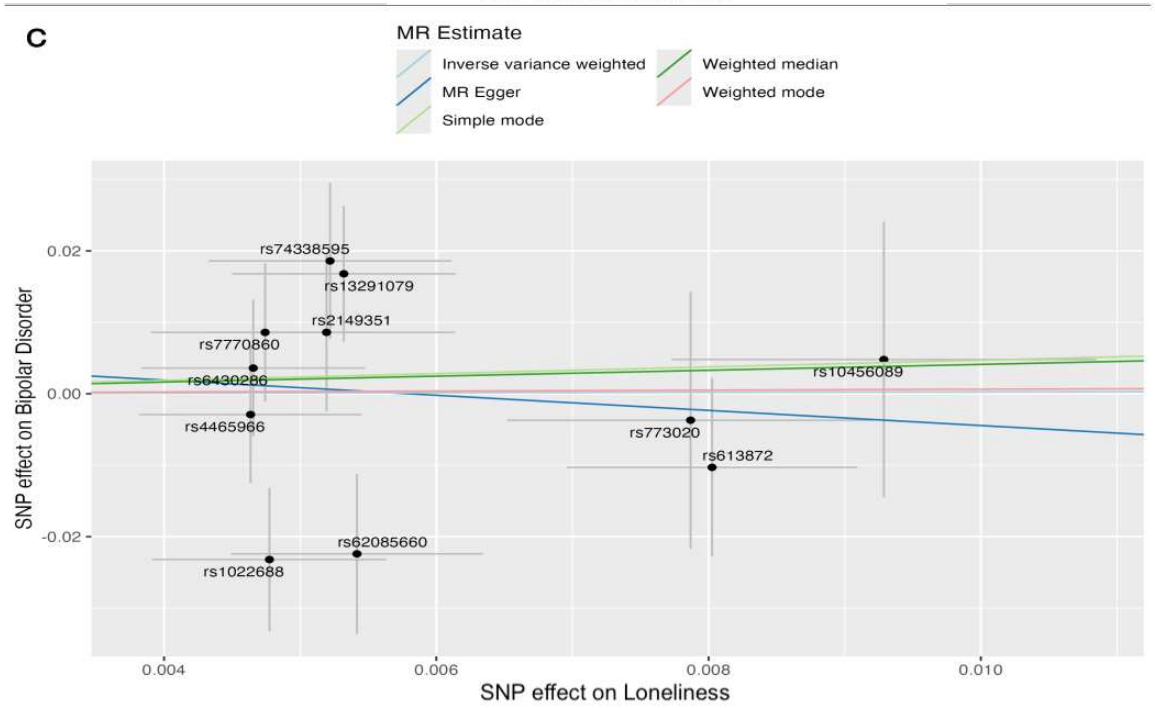
Shared causal variant
PP.H4 ≥ 0.80

Exposure	Outcome	Method	No.SNPs	F−stat	P−value	Estimate [95% CI]
Loneliness	SCZ	IVW	8	34.5	0.0023	2.50 [1.40, 4.53]
Loneliness	MDD	IVW	12	36	0.0082	2.05 [1.20, 3.50]
Loneliness	BD	IVW	11	35.8	0.97	1.01 [0.55, 1.85]
Loneliness	IL−1RA pQTL	IVW	13	35.8	0.63	1.16 [0.63, 2.14]
Loneliness	IL−6 pQTL	IVW	13	35.8	0.16	1.57 [0.84, 2.94]
Loneliness	IL−6Ra pQTL	IVW	13	35.8	0.038	1.56 [1.02, 2.38]
Loneliness	TNF−R1 pQTL	IVW	13	35.8	0.041	1.65 [1.02, 2.67]
Loneliness	TNF−R2 pQTL	IVW	13	35.8	0.021	1.67 [1.08, 2.58]
IL−1RA pQTL, cis	Loneliness	Wald ratio	1	31	0.011	0.97 [0.94, 0.99]
IL−1RA pQTL, cis	SCZ	Wald ratio	1	31	0.24	0.82 [0.59, 1.14]
IL−1RA pQTL, cis	MDD	Wald ratio	1	31	0.45	0.89 [0.66, 1.20]
IL−1RA pQTL, cis	BD	Wald ratio	1	31	0.33	0.86 [0.62, 1.17]
IL−6Ra pQTL, cis	Loneliness	IVW	2	9630	0.88	1.00 [1.00, 1.00]
IL−6Ra pQTL, cis	SCZ	IVW	2	9630	0.004	1.03 [1.01, 1.05]
IL−6Ra pQTL, cis	MDD	IVW	2	9630	0.54	1.01 [0.97, 1.06]
IL−6Ra pQTL, cis	BD	IVW	2	9630	0.69	1.00 [0.99, 1.02]
TNF−R2 pQTL, cis	Loneliness	Wald ratio	1	179	0.8	1.00 [0.99, 1.01]
TNF−R2 pQTL, cis	SCZ	Wald ratio	1	179	0.22	1.09 [0.95, 1.25]
TNF−R2 pQTL, cis	MDD	Wald ratio	1	179	0.28	1.08 [0.94, 1.23]
TNF−R2 pQTL, cis	BD	Wald ratio	1	179	0.79	1.02 [0.89, 1.16]

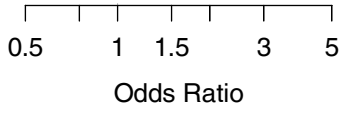



A
MR Estimate
Inverse variance weighted
MR Egger
Simple mode
Weighted median
Weighted mode
SNP effect on Schizophrenia
SNP effect on Loneliness
rs171697
rs13291079
rs74338595
rs62085660
rs10456089
rs773020
rs2149351
rs6430286
0.04
0.02
0.00
0.004
0.006
0.008
0.010

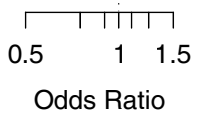

B
MR Estimate
Inverse variance weighted
MR Egger
Simple mode
Weighted median
Weighted mode
SNP effect on Major Depressive Disorder
SNP effect on Loneliness
rs2149351
rs13291079
rs74338595
rs613872
rs7770860
rs1022688
rs62085660
rs2069117
rs6430286
rs4465966
rs773020
rs10456089
0.04
0.02
0.00
-0.02
-0.04
0.004
0.006
0.008
0.010


C
MR Estimate
Inverse variance weighted
MR Egger
Simple mode
Weighted median
Weighted mode
SNP effect on Bipolar Disorder
SNP effect on Loneliness
rs74338595
rs13291079
rs2149351
rs7770860
rs6430286
rs4465966
rs10456089
rs773020
rs613872
rs62085660
rs1022688
0.02
0.00
-0.02
0.004
0.006
0.008
0.010

Exposure	Outcome	Adjusted for	No.SNPs	SMI_F_stat	IVW−Pvalue		Estimate [95% CI]
Loneliness	SCZ	IL−1RA pQTL	9	29.23	0.018	**	2.58 [1.41, 4.72]
Loneliness	SCZ	IL−6Ra pQTL	10	28.01	0.012	**	2.52 [1.45, 4.41]
Loneliness	SCZ	TNF−R2 pQTL	9	30.42	0.021	**	2.33 [1.33, 4.07]
Loneliness	MDD	IL−1RA pQTL	13	29.42	0.022	**	2.01 [1.21, 3.36]
Loneliness	MDD	IL−6Ra pQTL	14	31.1	0.024	***	2.12 [1.20, 3.76]
Loneliness	MDD	TNF−R2 pQTL	13	32.96	0.029	***	1.97 [1.15, 3.36]
Loneliness	BD	IL−1RA pQTL	12	28.15	0.98	·	0.99 [0.56, 1.77]
Loneliness	BD	IL−6Ra pQTL	13	30.61	0.92	·	1.03 [0.57, 1.85]
Loneliness	BD	TNF−R2 pQTL	12	32.6	1	·	1.00 [0.54, 1.84]



Exposure	Outcome	Adjusted for	No.SNPs	SMI_F_stat	IVW−Pvalue	Estimate [95% CI]
SCZ	Loneliness	IL−1RA pQTL	101	20.8	0.0033	1.00 [1.00, 1.00]
SCZ	Loneliness	IL−6Ra pQTL	102	43	0.0046	1.00 [1.00, 1.00]
SCZ	Loneliness	TNF−R2 pQTL	101	43.5	0.0049	1.00 [1.00, 1.00]
MDD	Loneliness	IL−6Ra pQTL	3	14.54	0.63	1.01 [0.99, 1.03]
BD	Loneliness	IL−1RA pQTL	42	28.93	0.44	1.00 [1.00, 1.01]
BD	Loneliness	IL−6Ra pQTL	43	37.62	0.43	1.00 [1.00, 1.01]
BD	Loneliness	TNF−R2 pQTL	42	37.9	0.46	1.00 [1.00, 1.01]



Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- RomualdoPerezLonelinessMRSupplementaryMaterials.xlsx