**The Potential Shared Role of Inflammation in Insulin Resistance and Schizophrenia: A Bi-Directional Two-Sample Mendelian Randomization Study**

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**Abstract**

**Background**

Insulin resistance predisposes to cardiometabolic disorders, which are commonly comorbid with schizophrenia, and are the key contributors to the significant excess mortality in schizophrenia. Mechanisms for the comorbidity remain unclear, but observational studies have implicated inflammation in both schizophrenia and cardiometabolic disorders separately. We aimed to examine whether there is genetic evidence that insulin resistance and seven related cardiometabolic traits may be causally associated with schizophrenia, and whether evidence supports inflammation as a common mechanism for cardiometabolic disorders and schizophrenia.

**Methods and Findings**

We used summary data from genome-wide association studies of mostly European adults from large consortia (Meta-Analyses of Glucose and Insulin-related traits Consortium (MAGIC) featuring up to 108,557 participants; Diabetes Genetics Replication And Meta-analysis (DIAGRAM) featuring up to 435,387 participants; Global Lipids Genetics Consortium (GLGC) featuring up to 173,082 participants; Genetic Investigation of Anthropometric Traits (GIANT) featuring up to 339,224 participants; Psychiatric Genomics Consortium (PGC) featuring up to 105,318 participants; Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) consortium featuring up to 204,402 participants). We conducted two-sample uni- and multi-variable Mendelian randomization (MR) analysis to test whether: (i) ten cardiometabolic traits (fasting insulin, high-density lipoprotein and triglycerides representing an IR phenotype, and seven related cardiometabolic traits: low-density lipoprotein, fasting plasma glucose, glycated haemoglobin, leptin, body mass index, glucose tolerance and type 2 diabetes) could be causally associated with schizophrenia; (ii) inflammation could be a shared mechanism for these phenotypes. We conducted a detailed set of sensitivity analyses to test the assumptions for a valid MR analysis. We did not find statistically significant evidence in support of a causal relationship between cardiometabolic traits and schizophrenia, or *vice versa*. However, we report that a genetically-predicted inflammation-related insulin resistance phenotype (raised fasting insulin (Inverse Variance Weighted (IVW) OR=2.76, 95% C.I, 1.08-7.11, Holm-Bonferroni corrected *p-*value (*p*)*=*0.040), raised triglycerides (IVW OR=2.86, 95% C.I., 1.23-6.66, *p­=*0.035), lower high-density lipoprotein (IVW OR=0.52, 95% C.I., 0.33-0.82; *p­=*0.030)) was associated with schizophrenia. Evidence for these associations attenuated completely in multi-variable MR analyses after adjusting for C-reactive protein (CRP), an archetypal inflammatory marker: (fasting insulin IVW OR=0.95, 95% C.I, 0.55-1.62, *p=*0.645), triglycerides (IVW OR=0.79, 95% C.I., 0.58-1.21, *p­=*0.203) and lower high-density lipoprotein (IVW OR=1.48, 95% C.I., 0.66-3.33; *p­=*0.340), suggesting that the associations could be fully explained by inflammation. One potential limitation of the study is that the full range of gene-products from the genetic variants we used as proxies for the exposures is unknown, and so we are unable to comment on potential biological mechanisms of association other than inflammation, which may also be relevant.

**Conclusions**

Our findings support a role for inflammation as a common cause for insulin resistance and schizophrenia, which may at least partly explain why the traits commonly co-occur in clinical practice. Inflammation and immune pathways may represent novel therapeutic targets for the prevention or treatment of schizophrenia and comorbid insulin resistance. Future work is needed to understand how inflammation may contribute to the risk of schizophrenia and insulin resistance.

**Author Summary**

**Why was this study done?**

* Cardiometabolic disorders such as diabetes are up to 30% more common in people with schizophrenia than in the general population, and are amongst the predominant causes of a 10-15 year shortened life-expectancy in people with schizophrenia.
* Insulin resistance, a precursor to diabetes, is sometimes detectable in young adults suffering their first episode of psychosis, which suggests that chronic lifestyle and clinical factors, such as smoking, physical inactivity and medication side effects, may not fully explain the comorbidity.
* Inflammation has been consistently associated with schizophrenia and cardiometabolic disorders, and so could be a common mechanism for schizophrenia and cardiometabolic disorders. This could help to at least in part explain why people who have schizophrenia also have higher rates of cardiometabolic disorders, over and above the commonly attributed lifestyle/clinical factors.

**What did the researchers do and find?**

* To examine whether insulin resistance and seven related cardiometabolic traits causally influence schizophrenia risk or *vice versa*, we conducted bi-directional, two-sample, uni- and multi-variable Mendelian Randomization (MR) analyses. The MR approach uses genetic variants as proxies for modifiable exposures to untangle the problems of reverse causation and unmeasured confounding.
* To test a hypothesis that inflammation may be a common mechanism for schizophrenia and cardiometabolic disorders, we also examined a subset of genetic variants which were associated with inflammation as well as the cardiometabolic trait, and used multi-variable MR as a sensitivity analysis to adjust for C-reactive protein (CRP), an archetypal inflammatory marker, as a general downstream marker of systemic inflammation.
* After correction for multiple testing, overall, there was no significant evidence in support of a causal relationship between cardiometabolic traits and schizophrenia, or *vice versa*. However, we found evidence that supports a causal relationship of an inflammation-related insulin resistance phenotype (comprising of raised fasting insulin, raised triglycerides and decreased high-density lipoprotein) with schizophrenia.
* Evidence for the association of an inflammation-related insulin resistance phenotype with schizophrenia attenuated fully in multi-variable MR analysis after adjusting for CRP, suggesting that these associations may be underpinned by inflammation.

**What do these findings mean?**

* These results suggest that cardiometabolic traits are unlikely to have a causal role in the pathogenesis of schizophrenia, or *vice versa*. However, our results suggest that inflammation is related to the risk of both schizophrenia and insulin resistance, which may at least partly explain why they commonly occur in clinical practice.
* Treating or preventing inflammation may be a putative therapeutic option for prevention and/or treatment of both schizophrenia and comorbid insulin resistance.
* In the future, more research is needed to understand the biological mechanisms underpinning how inflammation may increase the risk of schizophrenia and insulin resistance.

**Introduction**

Schizophrenia is a complex behavioural and cognitive syndrome characterized primarily by disruptions to perception and cognition [1]. It has a lifetime prevalence of around 0.4% [2], but carries a significant global disease burden [3]. Cardiometabolic disorders are up to 30% more common in schizophrenia than the general population [4] and are the leading contributors to premature death in these patients [5]. Their increased prevalence in schizophrenia is commonly attributed to the adverse effects of antipsychotic medications [6], or lifestyle factors such as physical inactivity and a poor diet [7], but this is unlikely to be the whole story. Whilst the aforementioned factors contribute cumulative risk over time [8], recent meta-analyses of case-control studies suggest that a phenotype of raised fasting insulin, raised triglycerides and low high-density lipoprotein cholesterol (HDL), indicative of insulin resistance (IR) [9-11], is associated with relatively young antipsychotic-naïve patients with first-episode psychosis (FEP) [12, 13], and, cross-sectionally, with psychotic symptoms in young adults [14]. Therefore, IR, which is a significant risk factor for type 2 diabetes mellitus (T2DM) and obesity, might be causally related to, or share pathophysiologic mechanisms with schizophrenia.

The majority of existing research in the field is cross-sectional, and therefore cannot confirm whether cardiometabolic disorders are a cause or consequence of illness (i.e., reverse causality). For example, one longitudinal study found no evidence for an association between IR in childhood and risk of psychosis in late adolescence [14]. Additionally, whilst previous studies have adjusted for a number of potential confounders, residual confounding, which is a limitation of both cross-sectional and longitudinal research, could still be relevant. Mendelian randomization (MR) analysis can address these limitations by using genetic variants inherited randomly at conception as unconfounded proxies of a modifiable exposure, to examine whether the exposure may have a causal effect on a disease outcome [15]. MR studies of cardiometabolic traits and schizophrenia are limited, have focused on a very limited set of cardiometabolic exposures, and have reported mixed findings [16, 17]. To our knowledge, MR studies examining associations between a wide range of cardiometabolic traits and schizophrenia are lacking. Such studies may help to identify common potentially causal risk factors and pathophysiologic mechanisms for these physical and psychiatric illnesses.

Inflammation could be pathophysiologically related to cardiometabolic disorders and schizophrenia. Higher levels of circulating inflammatory markers have been associated with both psychosis and cardiometabolic disorders, both cross-sectionally and longitudinally [18-20]. MR studies have reported potential causal associations between inflammation, particularly C-reactive protein (CRP) and interleukin-6 (IL-6), and schizophrenia [21, 22]. CRP and IL-6 are also implicated in pathogenesis of IR [23], and may exaggerate the effects of IR on psychosis-risk in young adults [14]. However, to our knowledge, no MR studies have examined whether inflammation could be pathophysiologically related to IR and schizophrenia, for example via mediating or common-causal mechanisms.

Therefore, we have conducted a study to examine evidence in support of four scenarios regarding the potential relationships between inflammation, IR and schizophrenia: a) inflammation is a common cause (confounder) between IR and schizophrenia; b) IR mediates an association between inflammation and schizophrenia; or *vice versa*: c) inflammation is a common cause (confounder) between schizophrenia and IR; d) schizophrenia mediates an association between inflammation and IR. See S1 Methods for directed acyclic graphs (DAGs) illustrating the proposed mechanisms.

First, we carried out MR analyses to test whether 10 cardiometabolic traits related to IR (fasting insulin (FI); triglycerides, high-density lipoprotein (HDL); low-density lipoprotein (LDL); fasting plasma glucose (FPG); body mass index (BMI); glucose tolerance; leptin, glycated haemoglobin (HbA1C); and type 2 diabetes mellitus (T2DM)) could be causally associated with schizophrenia. To test the direction of association, we used genetically predicted levels of cardiometabolic traits as exposures and schizophrenia as the outcome, and *vice versa*. Next, we examined whether inflammation could be a shared mechanism linking IR and schizophrenia using MR analyses including genetic variants for each cardiometabolic trait that were also associated with a marker of inflammation at genome-wide level. Finally, we used multi-variable MR (MVMR) analysis to control for genetic associations of cardiometabolic traits with CRP, an archetypal general inflammatory marker which we used as a general measure for systemic inflammation.

**Methods**

**Selection of Genetic Variants Related to Cardiometabolic Traits and Schizophrenia**

For fasting insulin, triglycerides and HDL, we used a set of 53 single nucleotide polymorphisms (SNPs) reported to be associated with all three traits, representative of an IR phenotype, from a recent meta genome-wide association study (GWAS) of 188,577 European adults which adjusted for BMI [11]. Summary statistics for genome-wide significant SNPs were obtained for six related continuous (FPG, HbA1C, LDL, BMI, leptin, glucose tolerance) and one binary (T2DM) cardiometabolic traits from recent large GWAS (S2-10 Methods). We obtained summary statistics for schizophrenia from a recent GWAS from the Psychiatric Genomics Consortium (PGC) [24] based on 40,675 cases and 64,643 European controls. The degree of sample overlap between exposure and outcome samples was likely to be low since the data were obtained from different consortia [25].

**Ethics Statement**Our study was a secondary analysis of the above publicly-available data. Informed consent was sought for all participants per the original GWAS protocols, and all ethical approvals for the GWAS were obtained by original GWAS authors.

**Statistical Analysis**The analysis plan was prospectively conceived by the authors in 2019 but was not formally deposited in a repository or database. All described analyses were planned except the MVMR sensitivity analysis including CRP (see below), which was conceived in light of the findings from the primary analysis, to further test whether inflammation may be responsible for the results. We obtained summary-level data (SNP rs number; β-coefficient or log odds ratio; standard errors or 95% confidence intervals; effect allele; other allele; *p*-value; effect allele frequency; sample size; number of cases/controls) from each GWAS. Where a specific instrument SNP was not available in the outcome dataset, we located proxy SNPs using linkage disequilibrium (LD) tagging (r2>0.8) via *LDlink* [26]. Alleles were harmonised based on matching alleles and the resulting instruments were clumped for LD to ensure independence (10,000kb pairs apart, r2<0.001). In the event of palindromic SNPs, the forward strand was inferred where possible using allele frequency information. We performed bidirectional analysis (i.e. with schizophrenia as exposure and cardiometabolic traits as outcomes) to examine direction of association. Statistical analysis was conducted using the *TwoSampleMR* package (v0.5.4) [27] for *R* [28] . Our primary MR analysis method was inverse variance weighted (IVW) regression. We also conducted weighted median and MR-Egger regression analysis (S11 Methods). For the binary outcome of schizophrenia, the estimates for continuous exposures (FI, HDL, triglycerides, LDL; FPG; BMI; HbA1C; glucose tolerance, leptin) represent log-odds ratios converted into odds ratios (ORs), representing the increase in risk of schizophrenia per standard deviation (SD) of exposure, and 95% confidence intervals (C.I.s). For binary exposures (T2DM), the estimates represent the OR for schizophrenia per unit increase in the log-odds of T2DM. For continuous cardiometabolic outcomes, β-coefficients represent the SD increase in exposure per unit increase in the log-odds of schizophrenia, with standard errors (SEs).

We performed several sensitivity analyses to check the validity of our results. Heterogeneity among SNPs included in each analysis was examined using the Cochran’s Q test. We checked for horizontal pleiotropy using the MR Egger regression intercept alongside a more recent and robust method to detect horizontal pleiotropy and outliers, ‘MR pleiotropy residual sum and outlier’ (MR-PRESSO) [29]. Using MR-PRESSO, we used the global test to examine for horizontal pleiotropy, and where evident, used the method to correct the IVW-estimate via outlier removal (S11 Methods). We examined for measurement error in SNP-exposure associations using the *I2GX* statistic [30]. This study is reported as per the Strengthening the Reporting of Mendelian randomization studies (STROBE-MR) guideline [31] (S1 Checklist) and The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [32] (S2 Checklist).

***Analysis using Inflammation-Related SNPs***

Next, we repeated MR analysis using only inflammation-related SNPs for each cardiometabolic risk factor as an instrumental variable for the outcome of schizophrenia. We did this to test the hypothesis that these SNPs may represent a mechanism involving inflammation. This could be via, for example, a common causal basis (Panel A in S1 Methods) or via vertical (mediating) pleiotropy [27] (Panel B in S1 Methods). We used *Phenoscanner v2* [33] to examine each SNP associated with each cardiometabolic risk factor, to identify SNPs that were also associated (at genome-wide level; *p*<5×10-8 to maximise specificity) with a measure of inflammation, defined as blood concentration/count of cytokines (such as chemokines, interferons, interleukins, lymphokines, or tumour necrosis factors), acute phase proteins (e.g., CRP), or immune cells (e.g., neutrophils, lymphocytes) (S12-17 Methods). No inflammation-related SNPs were identified for glucose tolerance or leptin.

Using the same method, we identified inflammation-related schizophrenia SNPs (S18 Methods) and used them as instrumental variables in MR analysis examining cardiometabolic traits as outcomes.

***Sensitivity Analysis - Adjustment for Inflammation***

As a *post-hoc* sensitivity analysis to estimate whether any associations evident above may be explained by inflammation, we carried out MVMR analysis [34, 35] using the 53 SNPs for fasting insulin, triglycerides and HDL, representative of IR an phenotype, as exposures with schizophrenia as the outcome, after conditioning on the associations of these 53 SNPs with CRP. We chose CRP because it is a widely used downstream measure of systemic inflammation, and publicly available data from large-scale GWAS for CRP are available. Summary statistics for CRP were obtained from a recent large GWAS based on 204,402 participants [36]. For CRP as an exposure in MVMR, we used all independent (10,000kb pairs apart, r2<0.001) SNPs reported to be conditionally associated with CRP (*p*<10-5) and located within the *CRP* coding region (S19 Methods).

**Correction for Multiple Testing**

Statistical significance was estimated using the Holm-Bonferroni correction method [37], correcting for the number of exposures tested at each stage of analysis.

**Results**

**MR Analyses using All Genetic Variants Associated with IR and Other Cardiometabolic Traits**

We did not find statistically significant evidence for associations between genetically-predicted levels of triglycerides and HDL with schizophrenia, since estimates were inconsistent across MR methods and did not survive correction for multiple testing (weighted median OR for triglycerides=1.25; 95% C.I., 1.04-1.50; corrected *p*=0.180); weighted median OR for HDL=0.80; 95% C.I., 0.66-0.97; corrected *p*=0.180). We also found weak evidence for an association between genetically-predicted leptin levels and schizophrenia, but the evidence did not survive correction for multiple testing (IVW OR=2.54; 95% CI, 1.02-6.31; corrected *p*=0.440). We did not find any evidence for associations of genetically-predicted levels of any other cardiometabolic risk factor and schizophrenia using any MR method (Table 1).

**Table 1: MR Analyses of Cardiometabolic Traits and Schizophrenia using All SNPs**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Risk Factor** | **SNPs, No.a** | **Method** | **Odds Ratio (95% C.I.)** | ***p*-value** | **Corrected *p*-valueb** |
| Fasting Insulin | 46 | IVW | 0.85 (0.64-1.10) | 0.219 | 1.000 |
|  |  | Weighted Median | 0.94 (0.71-1.23) | 0.631 | 1.000 |
|  |  | MR Egger | 1.63 (0.76-3.48) | 0.210 | 1.000 |
| Triglycerides | 46 | IVW | 0.94 (0.77-1.15) | 0.565 | 1.000 |
|  |  | Weighted Median | 1.25 (1.04-1.50) | 0.018 | 0.180 |
|  |  | MR Egger | 1.22 (0.90-1.66) | 0.202 | 1.000 |
| HDL | 46 | IVW | 1.06 (0.88-1.27) | 0.560 | 1.000 |
|  |  | Weighted Median | 0.80 (0.66-0.97) | 0.020 | 0.180 |
|  |  | MR Egger | 0.79 (0.59-1.08) | 0.142 | 1.000 |
| Fasting Plasma Glucose | 18 | IVW | 1.07 (0.87-1.31) | 0.522 | 1.000 |
|  |  | Weighted Median | 1.01 (0.84-1.23) | 0.887 | 1.000 |
|  |  | MR Egger | 1.13 (0.74-1.74) | 0.584 | 1.000 |
| Type 2 Diabetes Mellitus | 89 | IVW | 0.93 (0.78-1.12) | 0.470 | 1.000 |
|  |  | Weighted Median | 0.93 (0.79-1.09) | 0.375 | 1.000 |
|  |  | MR Egger | 1.03 (0.65-1.62) | 0.895 | 1.000 |
| Body Mass Index | 83 | IVW | 1.11 (0.98-1.24) | 0.060 | 0.540 |
|  |  | Weighted Median | 1.10 (0.99-1.23) | 0.071 | 0.568 |
|  |  | MR Egger | 1.22 (0.95-1.56) | 0.128 | 1.000 |
| HbA1C | 44 | IVW | 1.01 (0.76-1.33) | 0.800 | 1.000 |
|  |  | Weighted Median | 1.12 (0.84-1.50) | 0.459 | 1.000 |
|  |  | MR Egger | 1.32 (0.76-1.32) | 0.294 | 1.000 |
| Glucose Tolerance | 7 | IVW | 0.98 (0.85-1.14) | 0.800 | 1.000 |
|  |  | Weighted Median | 1.10 (0.87-1.15) | 0.993 | 1.000 |
|  |  | MR Egger | 1.85 (0.95-3.32) | 0.094 | 0.846 |
| LDL | 74 | IVW | 0.99 (0.93-1.05) | 0.679 | 1.000 |
|  |  | Weighted Median | 0.97 (0.90-1.03) | 0.322 | 1.000 |
|  |  | MR Egger | 0.98 (0.90-1.07) | 0.692 | 1.000 |
| Leptin | 4 | IVW | 2.54 (1.02-6.31) | 0.044 | 0.440 |
|  |  | Weighted Median | 1.98 (0.93-4.21) | 0.076 | 0.568 |
|  |  | MR Egger | 3.13 (0.71-7.23) | 0.215 | 1.000 |

HDL=high-density lipoprotein; HbA1C=glycated haemoglobin; LDL=low-density lipoprotein; IVW=inverse variance weighted regression; SNPs=single nucleotide polymorphisms  
aNumber of SNPs remaining after clumping for independence  
**b** Each analysis method (IVW, Weighted Median and MR Egger) corrected using the Holm-Bonferroni method for 10 cardiometabolic markers  
Estimates represent ORs for schizophrenia per SD increase in exposure (per unit-increase in log-odds of exposure for T2DM)

**MR Analyses using Inflammation-Related Genetic Variants for IR and Other Cardiometabolic Traits**After testing only inflammatory-related variants for cardiometabolic traits, we found consistent evidence across several MR methods for associations of inflammation-related genetically-predicted fasting insulin (IVW OR=2.76; 95% C.I., 1.08-7.11; corrected *p=*0.040), triglycerides (IVW OR=2.86; 95% C.I., 1.23-6.66; corrected *p=*0.035), and HDL (IVW OR=0.52; 95% CI, 0.33-0.82; corrected *p=*0.030) with schizophrenia (Table 2; Fig 1 & Fig 2).

**Table 2: MR Analyses of Inflammatory-Related Cardiometabolic SNPs and Schizophrenia**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Risk Factor** | **SNPs, No.** | **Method** | **Odds Ratio (95% C.I.)** | ***p*-value** | **Corrected *p*-valuea** |
| Fasting Insulin | 5 | IVW | 2.76 (1.08-7.11) | 0.010 | 0.040 |
|  |  | Weighted Median | 2.76 (1.31-5.82) | 0.008 | 0.040 |
|  |  | MR Egger | 3.63 (0.41-31.98) | 0.329 | 1.000 |
| Triglycerides | 5 | IVW | 2.86 (1.23-6.66) | 0.007 | 0.035 |
|  |  | Weighted Median | 2.90 (1.36-6.17) | 0.015 | 0.060 |
|  |  | MR Egger | 1.31 (0.85-2.02) | 0.251 | 1.000 |
| HDL | 4 | IVW | 0.52 (0.33-0.82) | 0.005 | 0.030 |
|  |  | Weighted Median | 0.56 (0.37-0.83) | 0.006 | 0.036 |
|  |  | MR Egger | 0.42 (0.18-1.03) | 0.153 | 0.918 |
| Fasting Plasma Glucose | 2 | IVW | 1.53 (0.39-5.97) | 0.537 | 0.537 |
| Type 2 Diabetes Mellitus | 7 | IVW | 0.94 (0.59-1.48) | 0.776 | 1.000 |
|  |  | Weighted Median | 1.05 (0.26-4.32) | 0.941 | 1.000 |
|  |  | MR Egger | 1.40 (0.32-6.08) | 0.668 | 1.000 |
| HbA1C | 7 | IVW | 1.20 (0.67-2.13) | 0.546 | 1.000 |
|  |  | Weighted Median | 0.93 (0.46-1.85) | 0.832 | 1.000 |
|  |  | MR Egger | 1.68 (0.39-7.21) | 0.508 | 1.000 |
| Body Mass Index | 6 | IVW | 1.35 (0.88-2.08) | 0.169 | 0.338 |
|  |  | Weighted Median | 1.16 (0.80-1.69) | 0.425 | 0.425 |
|  |  | MR Egger | 0.68 (0.35-1.34) | 0.383 | 1.000 |
| LDL | 13 | IVW | 0.96 (0.79-1.17) | 0.687 | 0.687 |
|  |  | Weighted Median | 0.91 (0.80-1.04) | 0.181 | 0.362 |
|  |  | MR Egger | 0.81 (0.58-1.14) | 0.254 | 1.000 |

HDL=high-density lipoprotein; HbA1C=glycated haemoglobin; LDL=low-density lipoprotein; IVW=inverse variance weighted regression; SNPs=single nucleotide polymorphisms  
a Each analysis method (IVW, Weighted Median and MR Egger) corrected using the Holm-Bonferroni method for 7 cardiometabolic markers  
Estimates represent ORs for schizophrenia per SD increase in exposure (per unit-increase in log-odds of exposure for T2DM

**Fig 1: MR Analyses Testing Associations between Insulin Resistance Phenotypes (Fasting Insulin (A), Triglycerides (B) and HDL (C)) and Schizophrenia, Highlighting Inflammation-Related SNPs.**Points in plots represent the association of the 53 insulin-resistance single nucleotide polymorphisms (SNPs) and their association with schizophrenia (Y axis) and the exposure (X axis). SNPs in purple represent inflammatory-related SNPs. SNPs in green represent non-inflammatory SNPs. Whiskers represent SNP standard errors. Lines on plot represent inverse-variance weighted regression of non-inflammatory SNPs (green) and inflammatory-related SNPs (purple).

**Fig 2: MR Analyses Testing Associations between Cardiometabolic Traits and Schizophrenia**

Forest plot presents ORs and 95% CIs for associations between cardiometabolic traits and schizophrenia using IVW MR analyses based on all single nucleotide polymorphisms (SNPs) associated with each risk factor (green) and immune-related SNPs (purple). See Table 1 and 2 for the number of SNPs used in each analysis. HDL=High Density Lipoprotein; T2DM=Type 2 Diabetes Mellitus; BMI=Body Mass Index; FPG=Fasting Plasma Glucose; LDL=Low-Density Lipoprotein; HbA1C=Glycated Haemoglobin; Glucose Tol= Glucose Tolerance.

**Sensitivity Analysis: Adjustment for Inflammation**

MVMR analysis for inflammation-related SNPs of fasting insulin, triglycerides and HDL with schizophrenia showed that the univariable associations fully attenuated after controlling for the genetic associations of these variants with CRP. Controlling for CRP had negligible effect on MR estimates based on all genetic variants (Fig 3; S1-2 Results).

**Fig 3: Multivariable MR Analysis Testing Associations between Insulin Resistance Phenotypes and Schizophrenia After Controlling for Genetic Associations for CRP**

Forest plot presents ORs and 95% CIs for inverse-variance weighted regression (IVW) MR associations between insulin resistance phenotypes and schizophrenia using all single nucleotide polymorphisms (SNPs) (dark green), and after controlling for association of these SNPs with C-reactive protein (CRP) using multivariable MR (MVMR) (light green). The forest plot also presents ORs and 95% CIs for IVW MR associations between insulin resistance phenotypes and schizophrenia using inflammation-related SNPs (dark purple), and after controlling for association of these SNPs with CRP using MVMR (light purple). HDL=high-density lipoprotein.

**Test for Bidirectionality using Schizophrenia as Exposure**

We did not find statistically significant MR associations between schizophrenia and any cardiometabolic trait after correction for multiple testing (S3 Results; S1 Fig). Similarly, we did not find statistically significant MR associations of inflammation-related schizophrenia variants with cardiometabolic traits after correction for multiple testing (S4 Results; S1 Fig).

**Test for Horizontal Pleiotropy**

We did not find statistically significant evidence for horizontal pleiotropy in any cardiometabolic exposure-schizophrenia analyses with the MR-Egger regression intercept test. However, MR-PRESSO analysis determined that horizontal pleiotropy was likely to have affected estimates for all ten exposures in the all-SNP analysis (all *p≤*0.020). Following outlier correction, evidence weakened for the association with leptin (MR-PRESSO IVW β=0.44, S.E. 0.37, *p*=0.445). In the inflammation-related sensitivity analyses, there was evidence for horizontal pleiotropy using MR-PRESSO for T2DM and LDL only.

In the bidirectional schizophrenia-cardiometabolic factor analyses, both MR-PRESSO and the MR-Egger regression intercept suggested horizontal pleiotropy affecting the outcomes of HDL, BMI and LDL (all *p*<0.05). Following outlier correction, there was evidence for a weak protective effect of schizophrenia on BMI (β=-0.04, S.E. 0.02, *p*=0.014). MR-PRESSO additionally revealed possible horizontal pleiotropy affecting the outcomes of triglycerides, T2DM, and fasting insulin (all *p*<0.05) in the bidirectional analysis (S5-12 Results).

**Test for Heterogeneity of Instruments**

In the analyses based on all-SNPs, the majority of cardiometabolic traits demonstrated evidence of heterogeneity (S5-8 Results). There was limited evidence of heterogeneity in the sensitivity analyses based on inflammation-related SNPs for T2DM, BMI and HbA1C only.

**Test for Measurement Error**

Results for the *I2GX* tests for SNP-exposure associations revealed some evidence for potential measurement error which may have biased MR Egger analyses in the analyses with leptin, IGT, T2DM and schizophrenia as exposures (S13 Results).

**Discussion**

**Main Findings**

We conducted bidirectional uni- and multi-variable two-sample MR analyses using large publicly available genomic datasets to first examine whether there are associations that support a causal relationship between IR and related cardiometabolic traits and schizophrenia, and second, to examine whether there is evidence to support that inflammation may be a shared causal mechanism for IR and schizophrenia.We report that evidence in support of a causal association between genetically-predicted levels of triglycerides, HDL and leptin and schizophrenia was weak, in that the evidence of these associations did not survive correction for multiple testing, estimates were inconsistent across MR methods, and may have been affected by horizontal pleiotropy. However, we found stronger and more consistent evidence for an association of the IR phenotype of fasting insulin, triglycerides and HDL [11] with schizophrenia when we examined only genetic variants also associated with inflammation. In MVMR analyses adjusting for CRP, those estimates attenuated fully to the null. We found no evidence in bidirectional analyses in support of a causal relationship of schizophrenia with IR (Panels C&D in S1 Methods). Together, our results are therefore most consistent with inflammation as a common cause for IR and schizophrenia (Panel A in S1 Methods).

**Inflammation as a Common Cause for Schizophrenia and Insulin Resistance**

Three aspects of our results point toward inflammation as a common cause for IR and schizophrenia (Panel A in S1 Methods). First, we did not find convincing overall evidence for a causal relationship between IR and schizophrenia (likely ruling out Panel B in S1 Methods). Second, in our analyses of inflammatory-related variants for the cardiometabolic traits, we found strong and consistent evidence supporting that inflammation-related IR may have a causal relationship with schizophrenia. Third, we used MVMR to evidence that after controlling for CRP, an archetypal general inflammatory marker, the associations between inflammation-related genetic variants for IR and schizophrenia completely attenuated. This result suggests that the observed associations for the inflammatory-related variants are at least in part explained by inflammation. Together, the results are consistent with the idea that inflammation may be a common causal mechanism for IR and schizophrenia.

Evidence for a common-causal mechanism between IR and schizophrenia may help to explain why schizophrenia is associated with higher rates of IR even in early stages of illness, when the cumulative effects of medication and lifestyle factors are relatively small [12, 38]. Anti-inflammatory agents, of which several have shown promise in treating the symptoms of schizophrenia [39], should therefore be considered as a putative therapeutic target for prevention and treatment of cardiometabolic disorders in schizophrenia.

We used CRP, an archetypal downstream inflammatory marker, as a means of gauging the effect of systemic inflammation in MVMR analysis, rather than hypothesizing a specific role for CRP in the relationship between IR and schizophrenia. Nevertheless, CRP has observationally shown in both cross-sectional [40] and longitudinal [41] research to be associated with schizophrenia, although such findings are limited by the potential of residual confounding and reverse causality. Interestingly however, MR findings have reported that genetically-predicted CRP may have a protective-effect on schizophrenia [21], with authors positing that a genetically-attenuated ability to produce CRP may predispose to more insidious and chronic infections. In our MVMR analysis, attenuation of IR-schizophrenia associations after controlling for CRP is consistent with inflammation being associated with both exposure and outcome, albeit ‘negatively’ with the latter. Further research is needed to explore potential mechanisms of association between CRP and schizophrenia.

Furthermore, many of the SNPs included in the inflammation-related analysis were associated with neutrophils and/or lymphocytes. A raised neutrophil to lymphocyte ratio (NLR) is a marker of systemic inflammation and is known to be associated with schizophrenia [42] and IR [43]. We were unable to find large GWAS studies conducted in European populations for NLR, or for other inflammatory markers which we might have used in MVMR analyses in place of CRP.

Based on our findings, we are unable to completely rule out the possibility that IR may mediate an inflammation-schizophrenia association (Panel B in S1 Methods), since there was some evidence of an association between IR and schizophrenia, albeit weak and inconsistent. These findings are broadly similar to one previous MR study [17], which reported only weak evidence of an association between the homeostasis model assessment (HOMA), a measure of IR, on schizophrenia. Another MR study [16] reported a genetic association between fasting insulin and schizophrenia, although the evidence attenuated after adjustment for BMI. To account for BMI, we obtained summary statistics for genetic variants related to IR after controlling for BMI [44]. The previous MR study included an ethnically heterogeneous sample, increasing the potential for population stratification bias. We used genetic data from a more ethnically homogenous GWAS of schizophrenia [24]. Nevertheless, while our results in the all-SNP analysis suggested weak evidence for triglycerides and HDL, which may reflect an IR phenotype, the evidence did not survive correction for multiple testing and requires replication in future when larger GWAS samples are available.

The implications of our findings with regard to shared causal mechanisms should not distract clinicians from focusing on the assessment and management of malleable lifestyle factors related to cardiometabolic disorders in people with schizophrenia. Factors such as poorer diet, reduced exercise and smoking, which are associated with schizophrenia [7, 45, 46], may predispose to an inflammatory state [47]. Therefore, it is possible that lifestyle factors exacerbate a feedback loop between inflammation, IR and schizophrenia by increasing both inflammation and IR, eventually leading to T2DM and other cardiometabolic disorders such as obesity and CVD. In addition to the potential therapeutic potential of anti-inflammatory medications, malleable lifestyle factors must continue to remain crucial targets [48, 49] for the prevention of cardiometabolic morbidity in people with schizophrenia.

**Additional Findings**

We found evidence for an association between leptin and schizophrenia, though the evidence did not survive correction for multiple testing and may have been affected by horizontal pleiotropy. Leptin, primarily an adipokine known to function as a satiety factor, also functions as a pro-inflammatory cytokine [50] and has high structural and functional overlap with IL-6 [51]. Leptin levels have been reported in observational studies to be associated with schizophrenia [52] and correlate with IL-6 levels in people with schizophrenia [53]. Previous MR studies have reported evidence for associations between IL-6 and schizophrenia [21] thus IL-6 may represent a putative pleiotropic mechanism for our result. However, our results require replication when larger GWAS for leptin are available.

We also report that after outlier correction, schizophrenia had a weak protective effect on BMI. This finding complements estimates from previous research [54] using linkage disequilibrium (LD) score regression, though we are able to advance previous findings since genetic correlation analyses are unable to test direction of association. This finding suggests that weight-gain associated with schizophrenia is unlikely to be a feature of the illness itself but could be attributed to iatrogenic or lifestyle effects. Moreover, the ‘lean insulin-resistance’ phenotype may be associated with higher levels of inflammation [55], and warrants further research in the context of schizophrenia, particularly since in younger patients, the ‘lean’ nature of the phenotype may mean that important cardiometabolic investigations may be overlooked in the clinic.

**Strengths and Limitations**

Strengths of this study include the use of a large set of cardiometabolic traits and large GWAS datasets, through which we were able to test specific biological mechanisms. We chose SNPs reaching genome-wide significance from large GWAS and meta-GWAS for IR and related cardiometabolic traits. We performed a comprehensive set of sensitivity analyses to check MR assumptions. Furthermore, whilst weak-instrument bias may be a factor in MR analysis, in two-sample MR this bias tends toward the null [56], thus would not explain the positive associations we describe. We corrected for multiple testing to minimise potential type I error.

Our study has some limitations. We did not select SNPs in known coding regions for the exposures, for example the *IRS-1* gene for IR [57]. We took this step on the assumption that many mechanisms at play may not yet be fully understood. For example, whilst the heritability of cardiometabolic traits such as obesity is as high as 70%, the variance currently explained by known genetic variants is but a small fraction of this [58]. In addition, selecting SNPs from many different GWAS studies featuring large sample sizes may increase the risk of sample-overlap between exposure and outcome variables and can bias the results in either direction, depending on the proportion of overlap [27]. Also, we chose a stringent *p-*value threshold to define inflammatory-related SNPs. In doing so, we may be at risk of overlooking some SNPs with true inflammatory associations. However, we chose this stringent *p­-*value threshold since we aimed to highlight a specific biological pathway, and relaxation of *p-*value thresholds may have increased the risk of pleiotropy through other mechanisms. In the future, larger and better-powered GWAS may identify more SNPs for analysis and at greater resolution, potentially unearthing a larger number of inflammatory-related SNPs, which would be helpful to confirm our findings. Additionally, the full range of gene-products from the genetic variants we used as proxies for the cardiometabolic traits is unknown, and so we are unable to comment on potential biological mechanisms of association other than inflammation, which may also be relevant. Finally, our analyses were based on data from mostly European participants, so it is unclear whether our results apply to other populations. Large-scale GWAS and replication of our analyses in other populations are required to answer this question.

**Conclusion**It is well established that certain antipsychotic drugs and lifestyle factors such as smoking, lack of exercise and poor diet are important contributors to cardiometabolic comorbidity in people with schizophrenia. In addition to this, our findings suggest that inflammation may be a common cause for schizophrenia and cardiometabolic disorders, which may at least partly explain why they so commonly co-occur in clinical practice. Lifestyle modification and careful prescription of certain antipsychotic medications remain crucial malleable targets to reduce the significant impact that comorbid cardiometabolic disorders place on the quality and length of life in people with schizophrenia. In addition, our findings suggest that targeting inflammation could be an important therapeutic target for the treatment and prevention of cardiometabolic disorders in people with schizophrenia. Future research should seek to examine the biological mechanisms which underpin how inflammation can simultaneously increase the risk of both IR and schizophrenia.

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**Supporting Information Captions**

S1 Methods: Directed Acyclic Graphs Outlining Potential Mechanisms of Association between Inflammation, Insulin Resistance and Schizophrenia

S2 Methods: GWAS used for SNP Selection

S3 Methods: SNPs used as instruments for fasting insulin, triglycerides and high-density lipoprotein

S4 Methods: SNPs used as instruments for fasting plasma glucose

S5 Methods: SNPs used as instruments for type 2 diabetes mellitus

S6 Methods: SNPs used as instruments for body mass index

S7 Methods: SNPs used as instruments for glucose tolerance

S8 Methods: SNPs used as instruments for low density lipoprotein

S9 Methods: SNPs used as instruments for glycated haemoglobin

S10 Methods: SNPs used as instruments for leptin

S11 Methods: MR Analysis Methods

S12 Methods: Inflammation-related SNPs for fasting insulin, triglycerides and high-density lipoprotein

S13 Methods: Inflammation-related SNPs for low density lipoprotein

S14 Methods: Inflammation-related SNPs for fasting plasma glucose

S15 Methods: Inflammation-related SNPs for glycated haemoglobin

S16 Methods: Inflammation-related SNPs for type 2 diabetes mellitus

S17 Methods: Inflammation-related SNPs for body mass index

S18 Methods: Inflammation-related SNPs for schizophrenia

S19 Methods: SNPs used for CRP in MVMR Analysis

S1 Results: Multivariable MR (MVMR) Results for IR-Phenotype Exposures (All-SNP analysis) with Addition of CRP as Exposure

S2 Results: Multivariable MR (MVMR) Results for IR-Phenotype Exposures (Inflammation-related-SNP analysis) with Addition of CRP as Exposure

S3 Results: MR Analyses using all SNPs for Schizophrenia and Cardiometabolic Outcomes

S4 Results: The Association between Inflammation-Related Schizophrenia SNPs and Cardiometabolic Outcomes

S5 Results: Cochran’s Q Tests for Heterogeneity and MR Egger Intercept Tests for Horizontal Pleiotropy for the Association between all Cardiometabolic SNPs and Schizophrenia

S6 Results: Cochran’s Q Tests for Heterogeneity and MR Egger Intercept Tests for Horizontal Pleiotropy for the Association between Inflammation-Related Cardiometabolic SNPs and Schizophrenia

S7 Results: Cochran’s Q Tests for Heterogeneity and MR Egger Intercept Tests for Horizontal Pleiotropy for the Association between Schizophrenia SNPs and Cardiometabolic Outcomes

S8 Results: Cochran’s Q Tests for Heterogeneity and MR Egger Intercept Tests for Horizontal Pleiotropy for the Association between Inflammation-Related Schizophrenia SNPs and Cardiometabolic Outcomes

S9 Results: MR-PRESSO Tests of Cardiometabolic All-SNP Analysis to Examine For and Correct Horizontal Pleiotropy

S10 Results: MR-PRESSO Tests of Inflammation-Related Cardiometabolic SNPs to Examine-For and Correct Horizontal Pleiotropy

S11 Results: MR-PRESSO Tests of Schizophrenia All-SNP Analysis to Examine For and Correct Horizontal Pleiotropy

S12 Results: MR-PRESSO Tests of Inflammation-Related Schizophrenia SNP Analysis to Examine For and Correct Horizontal Pleiotropy

S13 Results: I2GX Statistics to Examine for Potential Violation of the ‘No Measurement Error’ (NOME) Assumption for MR Egger Analyses

S1 Checklist: STROBE-MR: Guidelines for strengthening the reporting of Mendelian randomization studies

S2 Checklist: STROBE: Guidelines for Reporting Observational Studies

S1 Fig: Forest Plot Illustrating MR Analyses of Schizophrenia as Outcome using All SNPs (green) and Inflammation-Related SNPs (purple)