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Genetically Determined Schizophrenia is not associated with Impaired Glucose Homeostasis

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Abstract

Here, we used data from large genome-wide association studies to test the presence of causal relationships, conducting a Mendelian randomization analysis, and shared molecular mechanisms, calculating the genetic correlation, among schizophrenia, type 2 diabetes (T2D), and impaired glucose homeostasis. Although our Mendelian randomization analysis was well-powered, no causal relationship was observed among schizophrenia, T2D, and traits related to glucose impaired homeostasis. Similarly, we did not observe any global genetic overlap among these traits. These findings indicate that there is no causal relationships or shared mechanisms between schizophrenia and impaired glucose homeostasis.

Keywords

Psychiatry; Metabolic Disorders; Genetics; Mendelian Randomization; Genetic Correlation

1. Introduction

Although there is a well-established association between schizophrenia and type 2 diabetes (T2D), the mechanisms underlying this association remain unclear. Observational studies on relatively small cohorts including antipsychotic-naïve individuals with first-episode

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Contributors

R.P., J.G., D.J.S. were involved in the design of the study. R.P. carried out all analysis. R.P. wrote the manuscript which was subsequently revised by all authors. All authors contributed to and have approved the final manuscript.

Conflict of Interest

Dr. Stein is a consultant to Biocodex, Lundbeck, Novartis, and Servier and is a speaker for Eli Lilly and Company, GlaxoSmithKline, Lundbeck, and Servier. The other authors declare no conflict of interest.

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schizophrenia have reported impaired glucose homeostasis, suggesting that the association does not merely reflect the effects of antipsychotic drugs on metabolic regulation (Perry et al., 2016; Pillinger et al., 2017; Steiner et al., 2017). It has been suggested that overlapping inflammatory processes in schizophrenia and T2D may contribute to the association between these (Perry et al., 2016). Such causal hypotheses can be tested by assessing relevant genetic data with methods such as genetic correlation and Mendelian randomization (MR) analyses (Emdin et al., 2017). The Psychiatric Genomics Consortium (PGC), the DIABetes Genetics Replication And Meta-analysis (DIAGRAM) Consortium, and the Meta-Analyses of Glucose and Insulin-related traits Consortium (MAGIC) have conducted genome-wide association studies (GWAS) of cohorts including thousand individuals and identified numerous risk loci associated to schizophrenia, T2D, and impaired glucose homeostasis. Here, we used this publicly-available GWAS data to investigate the extent to which these traits share causal mechanisms. We conducted a two-sample MR (i.e., instrumental variable analysis based on a genetic variable) (Burgess et al., 2013) to test whether schizophrenia causes impaired glucose homeostasis. Linkage Disequilibrium (LD) score regression analysis (Bulik-Sullivan et al., 2015) was used to test the genetic overlap (i.e., shared risk alleles) between schizophrenia and impaired glucose homeostasis.

2. Materials and Methods

We used GWAS summary statistics for schizophrenia from the PGC (<https://www.med.unc.edu/pgc/results-and-downloads>) (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014), T2D from the DIAGRAM consortium (<http://diagram-consortium.org/downloads.html>) (Morris et al., 2012), and traits related to impaired glucose homeostasis (i.e., fasting glucose, fasting glucose adjusted for BMI, fasting insulin, fasting insulin adjusted for BMI, fasting proinsulin, hemoglobin A_{1C}, homeostatic model assessment–insulin resistance, oral glucose challenge test) from MAGIC (<https://www.magicinvestigators.org/downloads/>) (Dupuis et al., 2010; Manning et al., 2012; Saxena et al., 2010; Soranzo et al., 2010; Strawbridge et al., 2011). MR analysis were conducted using the R package *MendelianRandomization* (<https://cran.r-project.org/web/packages/MendelianRandomization/index.html>). We used LD-independent SNPs associated with schizophrenia at a genome-wide significance level ($p < 5 \times 10^{-8}$) as the instrumental variable (Supplemental Table 1). The coefficients related to SNP-exposure (schizophrenia associations) and SNP-outcome (associations of T2D and traits related to impaired glucose homeostasis; one for each MR analysis) were combined using an inverse-variance-weighted (IVW) approach to give an overall estimate of the causal effect (Burgess et al., 2013). MR-Egger regression intercept was considered to verify the presence of pleiotropic effects of the SNPs on the outcome (Bowden et al., 2015). To investigate shared molecular mechanisms, we used information about genetic overlap (i.e., shared risk alleles) from LD Hub v1.4.0 (<http://ldsc.broadinstitute.org/ldhub/>) (Zheng et al., 2017), calculated using the LD regression score method (available at <https://github.com/bulik/ldsc>) (Bulik-Sullivan et al., 2015). The power calculation for the Mendelian randomization analysis was based on a previously published analytical approach (Brion et al., 2013), considering sample size, the observed association between phenotypes and the proportion of variance explained for the association between the SNP or allele score and the exposure variable.

3. Results

In the MR and LD score regression analyses, no significant result was observed with respect to genetically determined schizophrenia (Table 1). We observed trend results ($p < 0.1$) for homeostatic model assessment–insulin resistance (HOMA-IR, $p = 0.07$) and for the presence of pleiotropy for fasting proinsulin ($p = 0.055$). However, after Bonferroni correction for multiple testing, these findings were non-significant ($p = 0.63$ and $p = 0.495$, respectively). We evaluated the presence of global genetic overlap (i.e., shared risk alleles) of schizophrenia with T2D and traits related to glucose impaired homeostasis considering data from LD score regression analysis: no genetic correlation reached nominal or trend significance ($p > 0.1$). We also conducted a reverse MR, testing whether genetically determined T2D affects schizophrenia risk (i.e., the instrumental variable was extracted from T2D GWAS; Supplemental Table 2): a non-significant outcome was observed (IVW: Estimate=0.065, SE=0.091, $p = 0.49$; MR-Egger intercept: Estimate=-0.042, SE=0.044, $p = 0.341$). The present study was adequately powered to detect a causal association between schizophrenia and T2D. According to a recent meta-analysis (Perry et al., 2016), individuals with first-episode psychosis have a 5-fold increased risk to meet the criteria for impaired glucose tolerance than controls (odds ratio = 5.44, 95% CI = 2.63–11.27). Genome-wide significant risk loci for schizophrenia (i.e., variants considered for the instrumental variable) explain 3.4% of disease variation (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). According to these parameters, our Mendelian randomization analysis theoretically had more than 95% statistical power to detect an association between schizophrenia and impaired glucose tolerance at a Bonferroni-corrected significance ($p = 5.6 \times 10^{-3}$), considering the sample size of the T2D dataset (12,171 cases and 56,862 controls) (Morris et al., 2012).

4. Discussion

In contrast with results from observational studies, our findings from analyses of genetic information indicate that schizophrenia is not causally related to impaired glucose homeostasis and that there is no major genetic overlap between these traits. The genetic contribution of schizophrenia to impaired glucose homeostasis was investigated previously, with conflicting results (Liu et al., 2013; Padmanabhan et al., 2016). There are more data and methods available now to test these hypotheses, and accordingly, we applied MR and LD score regression to large GWAS data, providing a deeper investigation of this topic. Our power analysis indicated that our Mendelian randomization study is well-powered (i.e., >95% of statistical power). This is in accordance with previous studies that used these GWAS data to successfully investigate other causal associations using similar analytic approaches (Hartwig et al., 2016; Polimanti et al., 2017; van 't Hof et al., 2017; Wang et al., 2017). Thus, it is unlikely that our negative result is due to a lack of statistical power. MR and genetic correlation approaches were developed to investigate causal relationships and shared molecular mechanisms, respectively (Pasaniuc and Price, 2017). Genetic investigations are less biased by confounders than observational studies (Emdin et al., 2017). Accordingly, we hypothesize that the results observed in epidemiological studies are affected by some unidentified variables. Nevertheless, our approach has a number of important limitations. Our MR findings may be limited by the dose–response linear relation

assumed and by differences in the age of onset between SCZ, T2D and traits related to glucose impaired homeostasis. That said, the information obtained from genetic data may be useful in developing novel studies of the mechanisms involved in the glucose impaired homeostasis observed in patients with schizophrenia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Results of the MR analysis (IVW and MR-Egger) and LD Score regression analysis considering genetic information regarding schizophrenia, T2D, and traits related to glucose impaired homeostasis.

Trait	IVW			MR-Egger intercept			LD score regression		
	Estimate	SE	P value	Estimate	SE	P value	r_g	SE	P value
T2D	-0.010	0.053	0.855	-0.030	0.030	0.312	-0.028	0.055	0.618
FG	0.002	0.009	0.859	-0.001	0.004	0.744	-0.038	0.042	0.366
FG _{adj}	<0.001	0.009	0.961	-0.003	0.005	0.575	-0.034	0.037	0.353
FI	0.003	0.008	0.687	<0.001	0.004	0.914	-0.039	0.058	0.500
FI _{adj}	0.006	0.007	0.444	-0.002	0.004	0.607	0.012	0.053	0.823
proI	-0.011	0.018	0.527	0.016	0.008	0.055	-0.011	0.083	0.893
HbA _{1C}	<0.001	0.008	0.958	-0.001	0.004	0.812	0.007	0.066	0.915
HOMA-IR	0.019	0.010	0.070	-0.004	0.005	0.396	-0.106	0.065	0.104
2hrGlu	-0.060	0.047	0.202	-0.004	0.023	0.860	-0.003	0.0664	0.968

Abbreviations: T2D, type 2 diabetes; FG, fasting glucose; FG_{adj}, FG adjusted for BMI; FI, fasting insulin; FI_{adj}, FI adjusted for BMI; proI, fasting proinsulin; HbA_{1C}, hemoglobin A_{1C}; HOMA-IR, homeostatic model assessment–insulin resistance; 2hrGlu, oral glucose challenge test.