

Supplementary Material

Methods

Delta method

The standard errors for the indirect effect of childhood maltreatment on schizophrenia were estimated using the Delta method (Thompson et al., 2016) in the following way:

$$SE(\text{indirect effect}) = \sqrt{a^2 * SE(b)^2 + b^2 * SE(a)^2}$$

where a^2 was the total effect of childhood maltreatment on loneliness/isolation obtained in univariable MR, b^2 the direct effect of loneliness/isolation on schizophrenia obtained in multivariable MR, and $SE(a)^2$ and $SE(b)^2$ the standard errors for a and b path estimates, respectively. All terms were squared.

Instrument selection for schizophrenia

We selected all genome-wide significant SNPs associated with schizophrenia ($p < 5 \times 10^{-8}$) and clumped them using $r^2 < 0.001$ and a 1000 kb window size. After clumping, 155 independent variants were identified. Out of the 155 variants, 129 and 147 were extracted from childhood maltreatment and loneliness/isolation GWASs, respectively. The remaining SNPs were dropped, either due to being absent from the outcome GWAS or for being palindromic with intermediate allele frequencies. In MVMR analysis, schizophrenia-associated SNPs were combined with loneliness/isolation-associated SNPs, which were then clumped and extracted from childhood maltreatment GWAS. The pruned set included 133 SNPs.

Results

Forward univariable MR: sensitivity analyses

Sensitivity analyses estimates for the effect of childhood maltreatment on loneliness/isolation were generally concordant in terms of direction and magnitude (apart from MR-Egger). However, the significance was variable (Supplementary Table 1; Supplementary Figure 4). MR-Egger intercept and Cochran's Q statistic indicated no evidence of horizontal pleiotropy (intercept = 0.02, $SE = 0.01$, $p = 0.131$) and little heterogeneity among the genetic variants ($Q_{IVW} = 17.65$, $p = 0.024$).

Reverse univariable MR: sensitivity analyses

MR-Egger intercept for the effect of schizophrenia on childhood maltreatment and loneliness/isolation suggested no evidence of horizontal pleiotropy (maltreatment intercept = 0.00, $SE = 0.00$, $p = 0.748$; loneliness/isolation intercept = 0.00, $SE = 0.00$, $p = 0.617$), albeit there was large heterogeneity among the genetic variants (maltreatment: $Q_{IVW} = 280.37$, $p < 0.001$; loneliness/isolation: $Q_{IVW} = 368.21$, $p < 0.001$). Leave-one-out analysis indicated that no single SNP was driving the IVW estimates for neither of the reverse MR analyses (Supplementary Figures 10 and 11). No evidence of weak instrument bias was detected (maltreatment $F = 41.70$; loneliness $F = 36.59$; Supplementary Tables 5 and 6).

Reverse MVMR: sensitivity analyses

The MR-Egger estimate for the effect of schizophrenia on childhood maltreatment was similar in magnitude to the direct effect ($b = 0.03$, $CI = 0.02$ to 0.05 , $p = 0.196$), although not significant (Figure 4; Supplementary Table 4). The MR-Egger estimate for the effect of loneliness/isolation on childhood maltreatment was significant and comparable to the direct effect ($b = 0.44$, $CI = 0.26$ to 0.61 , $p < 0.001$; Supplementary Table 4). The MR-Egger

intercept test revealed no evidence of horizontal pleiotropy (intercept = 0.00, se = 0.00, $p = 0.770$). Conditional F -statistic detected no bias due to weak instruments for schizophrenia ($F = 24.46$) but some bias for loneliness/isolation ($F = 4.91$). The modified Cochran's Q statistic revealed presence of heterogeneity among the genetic variants ($Q_{A-IVW} = 235.09$, $p < 0.001$), indicating that some of the schizophrenia or loneliness/isolation-associated variants may be pleiotropic.

References

Thompson, J. R., Minelli, C., & Del Greco M, F. (2016). Mendelian Randomization using Public Data from Genetic Consortia. *The International Journal of Biostatistics*, 12(2), 20150074. <https://doi.org/10.1515/ijb-2015-0074>