The Role of Loneliness and Social Isolation in Mediating the Relationship Between Childhood Maltreatment and Schizophrenia: A Genetically Informed Approach

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Author Note

VB, GZ and EW conceived the study, GZ compiled the data and GZ and VB conducted the analyses. LHW provided critical feedback on the draft. All authors drafted and approved the final manuscript. LHW is supported by a doctoral studentship from the Economic and Social Research Council. VB and EW are supported by the European Union's Horizon 2020 research and innovation programme (EarlyCause, grant n° 848158). EW also received funding from UK Research and Innovation (UKRI) under the UK government's Horizon Europe / ERC Frontier Research Guarantee [BrainHealth, grant number EP/Y015037/1]. We have no conflict of interest to disclose. The code behind this analysis has been made publicly available on GitHub at https://github.com/VilteBaltra/loneliness-mediation. Some of the results in the manuscript have previously been presented in preliminary form at the European Neuropsychopharmacology conference (2022).

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Abstract

Observational studies have found loneliness and social isolation to mediate the relationship between childhood maltreatment and schizophrenia. Limitations with observational studies (e.g., confounding and reverse causation), however, have meant the robustness of these relationships has thus far not been explored. To address this gap, the current study utilised genomic structural equation modelling (Genomic SEM) and Mendelian randomisation (MR) to perform a genetic mediation analysis between childhood maltreatment, loneliness/isolation, and schizophrenia, using summary statistics from three genome-wide association studies (sample sizes 105,318-487,647). Whilst we observed a putative effect of both childhood maltreatment (inverse variance weighted [IVW] OR = 3.44 per standard deviation [SD] increase, 95% confidence interval [CI] 1.66 to 7.13, $p < 0.001$) and loneliness/isolation (OR = 2.98, 95% CI 1.37 to 6.46, $p = 0.006$) on schizophrenia, our hypothesis that loneliness/isolation would mediate the relationship between childhood maltreatment and schizophrenia was not supported (Genomic SEM indirect effect = -0.05, *SE* = 0.05, $p = 0.255$; MR indirect effect = 0.10, *SE* = 0.11, $p = 0.369$). Furthermore, reverse mediation analysis indicated that the effect may be in the opposite direction (Genomic SEM indirect effect = 0.11, *SE* = 0.02, $p < 0.001$; MR indirect effect = 0.01, *SE* = 0.00, $p < 0.001$), accounting for 20.3%-28.9% of the total effect. The current results suggest that intervening upon loneliness/isolation in individuals with a history of childhood maltreatment is unlikely to reduce schizophrenia risk. In contrary, targeting loneliness/isolation in individuals with a genetic predisposition towards schizophrenia may diminish childhood maltreatment risk.

Keywords: Childhood Maltreatment, Social Isolation, Loneliness, Schizophrenia, Mediation

General Scientific Summary

This study suggests that loneliness/social isolation does not mediate the relationship between childhood maltreatment and schizophrenia. Contrary to previous research, our results indicate that targeting loneliness and social isolation in individuals with a history of childhood maltreatment is unlikely to diminish schizophrenia risk. In fact, we find evidence of mediation in the reverse direction, whereby a genetic predisposition to schizophrenia increases the risk of loneliness/social isolation, which in turn increases childhood maltreatment risk.

The Role of Loneliness and Social Isolation in Mediating the Relationship Between Childhood Maltreatment and Schizophrenia: A Genetically Informed Approach

Childhood maltreatment, defined as the physical, sexual, or emotional abuse or neglect of a child by a care figure (Stoltenborgh, Bakermans-Kranenburg, & van IJzendoorn, 2013; Stoltenborgh et al., 2011), is a major global concern affecting up to 36% of the population worldwide (Gilbert et al., 2009; Stoltenborgh et al., 2015). It is thought to be a risk factor for psychopathology in adulthood, including the development and maintenance of schizophrenia (Agnew-Blais & Danese, 2016; Bonoldi et al., 2013; Mayo et al., 2017; Velikonja et al., 2015; Warrier et al., 2021), a chronic mental health condition pathologized by persistent psychotic symptoms, including hallucinations, delusions, impaired social and interpersonal functioning (Galderisi et al., 2014; Roehr, 2013). Importantly, schizophrenia is also associated with high rates of unemployment, homelessness, and low quality of life (Eack & Newhill, 2007; Jin & Mosweu, 2017), calling for more research to better understand the risk factors for schizophrenia.

Observational studies have identified loneliness as a potential mediator of the relationship between childhood maltreatment and schizophrenia (Shevlin et al., 2015; Steenkamp et al., 2022). Loneliness, defined as the subjective dissatisfaction felt from one's perceived level of social connection being less than what is desired, and social isolation, the objective lack of social connections (Perlman, 1982), have prevalence rates of 10.5% (Beutel et al., 2017; operationalised as being frequently alone or having few contacts) and 20.8% (d'Hombres et al., 2021; operationalised as engaging in social activities once a month or less) respectively. Surveys indicate that individuals with schizophrenia have approximately 2.3 times higher rates of loneliness than the general population (Badcock et al., 2015; Eglit et al., 2018; Stain et al., 2012). Whilst limited research has explored the role of loneliness in the association between childhood maltreatment and psychosis, it has consistently been identified

as a mediator of this relationship. For example, Shevlin et al. (2015) observed that loneliness mediated the relationship between childhood abuse and psychosis, even when controlling for background risk factors such as sex, age, ethnicity, cannabis use, and education. Similarly, Steenkamp et al. (2022) found that loneliness mediated the association between childhood abuse and the severity of psychosis. Comparable findings were also observed when examining social functioning and loneliness in individuals with sub-clinical psychosis levels (Boyda & McFeeters, 2015). A plausible explanation for this relationship has been proposed, whereby victims of childhood maltreatment may become sensitised to feelings of loneliness, which, as a result, could increase positive symptoms of psychosis (Steenkamp et al., 2022).

If loneliness does mediate the association between maltreatment and schizophrenia, targeted interventions aimed at reducing feelings of loneliness/isolation could be offered to victims of childhood maltreatment, as a preventative measure for later life psychosis. However, limitations with observational studies (e.g., unmeasured confounding and reverse causation) have meant that the robustness of this mediatory relationship has thus far not been explored. Employing genetically informed methods, such as Mendelian randomisation – that are less susceptible to confounding, reverse causation, and measurement error – may help to address these challenges and provide insights into putative causal effects (Davey Smith & Ebrahim, 2005; Pingault et al., 2018). This is because (1) genetic variants are fixed at conception and therefore cannot be modified by disease onset, and (2) genetic variants are randomly allocated during meiosis, which minimizes confounding and measurement biases when these are being used as instrumental variables for modifiable risk factors (Davey Smith et al., 2007; Pingault et al., 2018).

As such, to address limitations of observational research, the current study investigated the extent to which the relationship between childhood maltreatment and schizophrenia is mediated by a combined phenotype of loneliness and social isolation

(hereafter loneliness/isolation) using two complementary, genetically informed methods: genomic structural equation modelling and multivariable Mendelian randomisation. We hypothesised that the relationship between childhood maltreatment and schizophrenia would be mediated by loneliness/isolation.

Methods

Sources of Data

Ethical approval was granted by the local ethics committee (Project: 21-108). Openly accessible genome-wide summary statistics were selected for each trait from the most recent and largest GWASs at the time of data analysis (see Table 1). To reduce the likelihood of false positive results due to differing allele frequencies across admixed populations (Caliebe et al., 2022; Patterson et al., 2006), only studies of European ancestry were selected.

Childhood Maltreatment summary statistics were obtained from Warrier et al.'s (Warrier et al., 2021) meta-analysis, which included GWAS summary statistics from the Psychiatric Genomics Consortium (PGC; *n* = 26,290) as well as individual-level data from four cohort studies: the UK Biobank (UKBB; *n* =143,473), Avon Longitudinal Study of Parents and Children (ALSPAC; *n* = 8346), Adolescent Brain Cognitive Development Study (ABCD; *n* = 5400), and Generation R (GenR: *n* = 1905). Childhood maltreatment was defined as emotional and physical neglect, and emotional, physical, and sexual abuse. Prospective reports of childhood maltreatment were largely reported by a parent or caregiver, whereas retrospective reports were self-reported. Mean age ranged from 10-64 years. Association testing was conducted using linear mixed-effects models in the UKBB, ALSPAC, and ABCD, which accounted for both relatedness and population stratification. Additionally, in the UKBB and ABCD, 20 genetic principal components (PCs) were included to further control for population stratification. In GenR, a linear regression was employed for association analyses, with five PCs included as covariates.

Loneliness/Isolation summary statistics were obtained from Day, Ong, and Perry's (2018) multi-trait GWAS (MTAG), which looked at a combined loneliness and social isolation phenotype using UK Biobank data (effective N = 487,647). Loneliness/isolation was defined based on self-reported responses to the following questions: (1) 'Do you often feel lonely?'; (2) 'Including yourself, how many people are living together in your household?' and 'How often do you visit friends or family or have them visit you?'; and (3) 'How often are you able to confide in someone close to you?'. Cases were defined as those who (a) perceived themselves as lonely, (b) lived alone and never visited family or friends outside their household, or (c) could never or almost never confide in someone. The multi-trait GWAS combined summary statistics from three GWASs based on each of these three questions. Relatedness and cryptic population structure were accounted for by using a linear mixed model in association analyses.

Schizophrenia summary statistics for autosomal SNPs were obtained from Trubetskoy et al. (2022) PGC Wave 3 GWAS meta-analysis of European ancestry cohorts (53,386 cases and 77,258 controls). Cases were defined as individuals with schizophrenia, schizoaffective disorder, or schizophrenia spectrum disorder. Controls consisted of screened and unscreened individuals for schizophrenia and other psychoses. Cases were recruited from community-based samples, hospital settings with ascertainment for clozapine treatment, or mixed (i.e., community/hospital) setting. Diagnostic strategy included research diagnostic interview, review of medical records, consensus diagnosis, and mixed strategy. Detailed diagnostic strategy and case-control sample description for approximately 75 European cohorts included in this meta-analysis are available in the original study (Trubetskoy et al., 2022). Within each cohort, a subset of the first 20 genetic PCs were included as covariates in GWAS analyses. By default, all cohorts included the first four PCs and any additional PC associated with case-control status.

Genetic Mediation using Genomic SEM

To perform a genetic mediation analysis, we used genomic structural equation modelling (Genomic SEM; Grotzinger et al., 2019), which uses summary statistics to model the genetic covariance structure of complex traits. The data were analysed in R (v4.0.3; R Core Team, 2020) as per developer instructions (https://gist.github.com/MichelNivard/04bf4ddcf3c32f905175de3058ca967a).

First, summary statistics underwent quality control, whereby only high-quality, common single nucleotide polymorphisms (SNPs) (INFO > 0.9 with minor allele frequency > 0.01) that were also available in HapMap3 reference panel were retained. The formatted files were used as input to Linkage Disequilibrium (LD) score regression (Bulik-Sullivan et al., 2015a,b), which estimated the genetic correlation between each pair of traits and returned the genetic covariance and its associated sampling covariance matrices. Subsequently, the genetic mediation model was specified using diagonally weighted least squares estimation (Grotzinger et al., 2019), whereby childhood maltreatment was included as the predictor, schizophrenia as the outcome and loneliness/isolation as the mediator.

Mediation analysis enabled us to decompose the total effect of childhood maltreatment on schizophrenia into direct and indirect effects. The direct effect represented the effect of childhood maltreatment on schizophrenia controlling for loneliness/isolation, whereas the indirect effect captured the portion of the total effect that is mediated by loneliness/isolation. To account for the presence of potential bidirectional effects, we ran a subsequent genetic mediation, in which schizophrenia was included as the predictor, loneliness/isolation as the mediator, and childhood maltreatment as the outcome.

Genetic Mediation using Mendelian Randomisation

To gain insights into putatively causal effects, we performed Mendelian randomisation (MR) mediation analysis using the TwoSample MR package (version 0.5.6;

Hemani, Tilling, & Davey Smith, 2017). MR is a causal inference technique that uses genetic variants as instrumental variables for an exposure of interest. To ensure genetic variants are valid instrumental variables, three key MR assumptions need to be satisfied: (1) genetic variants should be associated with the exposure, (2) genetic variants should not be associated with any confounders of the exposure-outcome relationship, (3) genetic variants should not affect the outcome via any other path than the modelled exposure (i.e., there should be no horizontal pleiotropy) (Lawlor et al., 2008). The latter assumption is what sets MR analysis apart from Genomic SEM. Specifically, unlike Genomic SEM which uses genetic covariance structure to analyse pleiotropy involving multiple genes and traits, MR assumes the absence of horizontal pleiotropy and includes sensitivity analyses, such as MR-Egger intercept test, to test for it. The advantage of using MR over conventional observational epidemiology techniques is that it offers some protection from reverse causality and unmeasured confounding (Davey Smith, 2004). In the present study, we used two-sample univariable MR to estimate the *total effect* of childhood maltreatment on (i) schizophrenia and (ii) loneliness/isolation (i.e., path *a*; Figure 1a). Two-sample multivariable MR was used to estimate the *direct effect* of childhood maltreatment on schizophrenia controlling for loneliness/isolation, and the *direct effect* of loneliness/isolation on schizophrenia controlling for childhood maltreatment (i.e., path *b*; Figure 1b). The total effect of loneliness/isolation on schizophrenia was also estimated, although it was not of primary interest. All analyses were performed in R (version 4.2.1; R Core Team, 2020). Post hoc power calculation for the MR analyses was conducted separately for each exposure-outcome combination using a web-based tool (https://sb452.shinyapps.io/power/; Burgess, 2014). Power to detect an indirect effect was obtained by multiplying the power for path *a* (maltreatment->loneliness/isolation) and path *b* (loneliness/isolation->schizophrenia) (Kenny & Judd, 2014).

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Commented [VB2]: unchanged analysis, added for clarification

Instrument Selection. In univariable MR, we selected 14 independent ($r^2 < 0.1$ within a 1000 kb window size, as defined by the authors), genome-wide significant SNPs ($p < 5 \times 10^{-8}$) associated with childhood maltreatment from the GWAS by Warrier et al. (2021) and extracted these same SNPs from the schizophrenia outcome GWAS (Trubetskoy et al., 2022). As four of the 14 SNPs were not available in the outcome GWAS and one of the 14 SNPs was palindromic with intermediate allele frequencies, our final set of instruments included nine SNPs. For loneliness/isolation, all 15 independent SNPs ($p < 5 \times 10^{-8}$) that were associated with loneliness/isolation (Day et al., 2018) were extracted from the outcome schizophrenia GWAS. In multivariable MR, we combined genome-wide significant SNPs associated with childhood maltreatment or loneliness/isolation into a single set of instruments, resulting in 24 SNPs. As only independent variants were retained (using default multivariable MR settings of $r^2 < 0.001$ within a 10,000 kb window size), one of the 24 SNPs was removed due to being in LD with another variant. This final set of 23 SNPs was then extracted from the schizophrenia outcome GWAS (Trubetskoy et al., 2022). SNP effects for the exposure and outcome data were harmonised to correspond to the same effect allele. When dealing with palindromic SNPs, we attempted to infer positive strand alleles. When this was not possible, SNPs with intermediate allele frequencies (MAF > 0.42) were excluded.

Univariable MR. To estimate the genetically predicted effect of childhood maltreatment on (1) schizophrenia and (2) loneliness/isolation, and (3) the genetically predicted effect of loneliness/isolation on schizophrenia, we carried out a two-sample univariable MR analysis using the inverse variance weighing (IVW) method (Burgess, Butterworth, & Thompson, 2013) separately for each exposure-outcome combination. These were followed by a range of sensitivity analyses, including MR Egger (Bowden, Davey Smith, & Burgess, 2015), the weighted median (Bowden, Davey Smith, Haycock, & Burgess,

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2016), the simple mode (Hartwig et al., 2017), the weighted mode (Burgess, Foley, Allara, Staley, & Howson, 2020) and the leave-one-out (Burgess, Bowden, Fall, Ingelsson, & Thompson, 2017) methods. The resulting logistic betas for schizophrenia risk were exponentiated to obtain odds ratios (OR). Sensitivity analyses assessed the robustness of our findings to the potential bias of horizontal pleiotropy, where the genetic variants affect the risk of schizophrenia through other pathways than the modelled exposure. A discrepancy in effect estimates from the primary IVW analysis and the range of sensitivity analyses were indicative of potential violations of the MR assumptions. Instrument strength was assessed using the *F*-statistic, where $F < 10$ was indicative of weak instruments (Burgess et al., 2011). Heterogeneity of genetic variants was evaluated using Cochran's *Q* statistic (Bowden et al., 2019).

Multivariable MR. Next, we used multivariable MR to estimate (1) the direct effect of childhood maltreatment on the risk of schizophrenia while controlling for loneliness/isolation and (2) the direct effect of loneliness/isolation on schizophrenia, controlling for childhood maltreatment. In multivariable MR, genetic variants can be associated with more than one exposure, which enables the estimation of direct effects of each exposure, conditional on the other modelled exposures (Burgess & Thompson, 2015; Carter et al., 2021). As before, MR-Egger regression was used as a sensitivity analysis (Bowden et al., 2015) using the Mendelian randomisation package (version 0.6.0; Yavorska & Burgess, 2017). Instrument strength was evaluated using a conditional *F*-statistic and heterogeneity was assessed via a modified form of the Cochran's *Q* statistic (Sanderson et al., 2021), estimated using the MVMR package (version 0.3) with default settings (Sanderson, Davey Smith, Windmeijer, & Bowden, 2019). Logistic betas for schizophrenia risk were exponentiated.

Commented [VB4]: unchanged analysis, added for clarification

Mediation Analysis. To estimate the degree to which the effect of childhood maltreatment on schizophrenia risk is mediated by loneliness/isolation (i.e., the indirect effect), we applied the product of coefficients method (Burgess et al., 2015) by multiplying the total effect of childhood maltreatment on loneliness/isolation obtained in univariable MR (i.e., path *a*) with the direct effect of loneliness/isolation on schizophrenia obtained in multivariable MR (i.e., path *b*). The standard errors (*SE*) for the indirect effect were estimated using the Delta method (Thompson et al., 2016); see Methods section of the Supplementary Material). Note that the product of coefficients method was applied on the non-exponentiated coefficients.

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Reverse MR. We tested for the presence of bidirectional effects by repeating the above analyses in the reverse direction. This permitted us to estimate the genetically predicted effect of schizophrenia on childhood maltreatment and loneliness/isolation, as well as to examine the reverse mediation pathway. Instrument selection for reverse MR is detailed in the Methods section of the Supplementary Material.

Transparency and Openness

All data and code on which study conclusions are based are publicly available and may be accessed via links included in the Data and Code Availability section. The data were analysed in R (version 4.0.3; R Core Team, 2020) using Genomic SEM (version 0.0.5; Grotzinger et al., 2019), TwoSampleMR (version 0.5.6; Hemani, Tilling, & Davey Smith, 2017) and MVMR (version 0.3; Sanderson, Davey Smith, Windmeijer, & Bowden, 2019) packages. This study was not preregistered. Where applicable, JARS guidelines (Kazak, 2018) were followed.

Results

All three phenotypes were genetically correlated. Childhood maltreatment was strongly correlated with loneliness/isolation ($r_g = 0.64$, $SE = 0.04$, $p < 0.001$) and moderately

correlated with schizophrenia (r_g = 0.38, *SE* = 0.03, $p < 0.001$). In contrast, only a weak genetic correlation was observed between loneliness/isolation and schizophrenia (r_g = 0.19, *SE* = .03, $p < 0.001$).

Genetic Mediation using Genomic SEM

Genetic mediation analysis revealed a significant total effect of childhood maltreatment on schizophrenia (total effect = 0.38, *SE* = 0.04, $p < 0.001$; Figure 2). Childhood maltreatment was also positively associated with loneliness/isolation (*a* path = 0.43, *SE* = 0.05, $p < 0.001$), while loneliness/isolation showed no association with schizophrenia when controlling for childhood maltreatment (*b* path= -0.08, *SE* = 0.05, p = 0.108). The mediating effect of loneliness/isolation was not significant (indirect effect = -0.05, *SE* = 0.05, p = 0.255). In line with this non-significant indirect effect, we continued to observe a positive association between childhood maltreatment and schizophrenia after controlling for loneliness/isolation (direct effect = 0.43, *SE* = 0.07, $p < 0.001$). Taken together, these results suggest that loneliness/isolation does not mediate the relationship between childhood maltreatment and schizophrenia (Figure 2).

In contrast to the findings above, mediation analysis in the reverse direction identified a significant effect of genetic liability to schizophrenia on childhood maltreatment (total effect = 0.38, *SE* = 0.03, $p < 0.001$) that attenuated after adjusting for loneliness/isolation (direct effect = 0.27, *SE* = 0.04, $p < 0.001$). Additionally, the mediating effect of schizophrenia liability on childhood maltreatment via loneliness/isolation was significant (indirect effect = 0.11, *SE* = 0.02, $p < 0.001$), with 28.9% of the total effect being mediated by loneliness/isolation (Supplementary Figure 1).

Genetic Mediation using Mendelian Randomisation

Results from univariable MR revealed an effect of childhood maltreatment on schizophrenia (OR_{IVW} = 3.44 per standard deviation [SD] increase, 95% confidence interval

[CI] 1.66 to 7.13, $p < 0.001$), with consistent direction of effect estimates across all sensitivity analyses (Figure 3; Supplementary Table 1; Supplementary Figure 2). While MR-Egger showed no evidence of horizontal pleiotropy (intercept = -0.09, *SE* = 0.08, $p = 0.331$), some heterogeneity was detected ($Q_{IVW} = 56.51$, $p < 0.001$). A significant effect of loneliness/isolation on schizophrenia was also observed ($OR_{IVW} = 2.98$ per SD increase, 95% CI 1.37 to 6.46, $p = 0.006$), with consistent effect estimates across all sensitivity analyses apart from MR-Egger, which was not significant and in the opposite direction (Figure 3; Supplementary Table 1, Supplementary Figure 3). As before, MR-Egger showed no evidence of horizontal pleiotropy (intercept = 0.05, *SE* = 0.03, $p = 0.103$). However, there was heterogeneity among the genetic variants ($Q_{IVW} = 69.04$, $p < 0.001$), suggesting that one or more of the loneliness/isolation-associated variants may be pleiotropic. The effect of childhood maltreatment on loneliness/isolation (i.e., path *a*) was also significant ($b_{IVW} = 0.23$ per SD increase, 95% CI 0.13 to 0.32, $p < 0.001$), albeit only partly supported by the sensitivity analyses (see Results section of the Supplementary Material; Supplementary Table 1; Supplementary Figure 4). Leave-one-out analysis suggested that no single SNP was driving the IVW estimates for the above analyses (Supplementary Figures 5-7). No evidence of weak instrument bias was detected (maltreatment $F = 40.39$; loneliness = 38.75; Supplementary Tables 2 and 3).

Commented [VB6]: unchanged results (Table S7), just reporting path *a* here for clarification (hence subsequent figure numbers changed)

Results from multivariable MR revealed a direct effect of childhood maltreatment on schizophrenia ($OR_{IVW} = 3.49$ per SD increase, 95% CI 1.75 to 6.95, $p < 0.001$), which was comparable in magnitude to its total effect ($OR_{IVW} = 3.44$). The MR-Egger estimate for the direct effect was consistent with the estimate from the IVW analysis (OR = 3.98 per SD increase, 95% CI 0.73 to 21.58, $p = 0.109$), albeit not significant. No evidence of horizontal pleiotropy was detected as the MR-Egger intercept was close to zero (intercept = -0.00, *SE* = 0.03, $p = 0.867$). Conditional *F*-statistics for childhood maltreatment and loneliness/isolation

were 10.16 and 12.27 respectively, suggesting no bias due to weak instruments. However, the modified Cochran's Q statistic indicated presence of heterogeneity among the genetic variants ($Q_{A\text{-}IVW}$ = 86.21, $p < 0.001$).

Compared to the total effect of loneliness/isolation on schizophrenia, the direct effect of loneliness/isolation (i.e., *b* path) attenuated from an OR of 2.98 to 1.55 (95% CI 0.61 to 3.94, $p = 0.360$), suggesting that the effect of loneliness/isolation was not independent from childhood maltreatment. Correspondingly, the multivariable MR-Egger estimate was also not significant (OR = 1.95 per SD increase, 95% CI 0.11 to 35.34, $p = 0.650$) (Figure 3; Supplementary Table 1).

Mediation analysis using the product of coefficients method revealed that, in line with findings using Genomic SEM, the indirect effect of childhood maltreatment was not significant (indirect effect = 0.10, $SE = 0.11$, $p = 0.369$), indicating a lack of mediation.

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Reverse MR. Results from univariable MR in the reverse direction revealed a modest effect of schizophrenia liability on childhood maltreatment (b_{IVW} = 0.05 per SD increase, 95% CI 0.03 to 0.06, $p < 0.001$), with relatively consistent evidence across sensitivity analyses (Figure 4; Supplementary Table 4; Supplementary Figure 8). The IVW estimate for the effect of schizophrenia on loneliness/isolation (path *a*) was also significant (b_{IVW} = 0.02 per SD increase, 95% CI 0.01 to 0.03, $p < 0.001$); however, it was not robustly supported by the sensitivity analyses (Figure 4; Supplementary Table 4; Supplementary Figure 9). Results for the remaining sensitivity analyses are detailed in the Results section of the Supplementary Material.

In MVMR analysis, we observed a direct effect of schizophrenia liability on childhood maltreatment after controlling for loneliness/isolation (b_{IVW} = 0.04 per SD increase, 95% CI 0.02 to 0.05, $p < 0.001$; Figure 4), which was slightly smaller than the total effect (OR_{IVW} = 0.05); and a direct effect of loneliness/isolation on childhood maltreatment

after controlling for schizophrenia liability (b_{IVW} = 0.44 per SD increase, 95% CI 0.26 to 0.62, $p < 0.001$; Supplementary Table 4). Sensitivity analyses for MVMR are reported in the Results section of the Supplementary Material. In line with findings from Genomic SEM, mediation analysis revealed a significant mediating effect of schizophrenia on childhood maltreatment via loneliness/isolation (indirect effect = 0.01, *SE* = 0.00, $p < 0.001$), which accounted for 20.3% of the total effect. Note that alternative mediation analysis (schizophrenia -> childhood maltreatment -> loneliness/isolation) was not performed given the lack of robust support for a total effect of schizophrenia on loneliness/isolation.

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Post hoc power calculation. At an alpha level of 0.05, we had over 80% power to detect small-to-medium sized effects in our univariable MR analyses. Our power to detect an indirect effect from childhood maltreatment to schizophrenia via loneliness/isolation was 93.4% (calculated given 100% power for path *a* and 93.4% power for path *b*). Power for each exposure-outcome combination and detailed information regarding input parameters is provided in Supplementary Table 7.

Discussion

The current study explored the degree to which loneliness/isolation mediates the relationship between childhood maltreatment and schizophrenia using two genetically-informed methods: Genomic SEM and Mendelian randomisation. Positive genetic correlations were observed between all three traits, suggesting a shared genetic underpinning. However, contrary to our hypothesis, we found no support for the mediating role of loneliness/isolation, indicating that loneliness/isolation is not a robust mediatory factor. These findings suggest that the development of schizophrenia, which might be exacerbated by early life abuse or neglect, is unlikely to be explained through loneliness/isolation. In contrast, we find evidence of mediation in the reverse direction, whereby a genetic predisposition to

schizophrenia might increase loneliness/isolation, which in turn could increase childhood maltreatment risk.

In line with a growing body of literature (Brown et al., 2014; Croft et al., 2019; Schaefer et al., 2018; South et al., 2015), the present study found a bidirectional direct effect between childhood maltreatment and schizophrenia, indicating that experiencing early life abuse or neglect may increase risk of developing schizophrenia in later life. This also corroborated findings from a recent Mendelian randomisation study that reported a bidirectional effect between childhood maltreatment and schizophrenia (Warrier et al., 2021). Additionally, a strong genetic association between childhood maltreatment and loneliness/isolation was observed, which aligned with existing observational research, in which victims of childhood maltreatment were found to present with lower levels of interpersonal functioning due to mistrust and suspicion of others (Blanchard-Dallaire & Hébert, 2014; Boyda & McFeeters, 2015). It is plausible that early life trauma predisposes individuals to develop negative schemas about others, which can increase feelings of mistrust (Cukor & McGinn, 2006; Karatzias et al., 2016; Tezel et al., 2015), and may in turn compromise the development of long-lasting relationships (Blanchard-Dallaire & Hébert, 2014). Clinical interventions should therefore aim to reduce feelings of loneliness and social isolation for individuals who have experienced childhood maltreatment (e.g., through community groups).

Unexpectedly, when controlling for childhood maltreatment, we observed no relationship between loneliness/isolation and schizophrenia. This finding contradicts previous research, which reports a positive – and potentially causal – association between the two traits (Andreu-Bernabeu et al., 2022; Boyda & McFeeters, 2015; Steenkamp et al., 2022). The discrepancy in findings may be driven by differences in the type of data analysed (i.e., genetic instead of phenotypic), the type of mediator used (e.g., loneliness/isolation as

opposed to difficulties in social engagement), and/or the choice of covariates (i.e., controlling for childhood maltreatment or not). Our multivariable MR results indeed indicate that covarying factors might play an important role. Specifically, in line with existing research (Andreu-Bernabeu et al., 2022), univariable MR revealed a unidirectional effect of loneliness/isolation on schizophrenia. However, this effect largely disappeared when controlling for childhood maltreatment, suggesting that the relationship between loneliness/isolation and schizophrenia is not independent from childhood maltreatment.

Most importantly, the hypothesis that loneliness/isolation would mediate the relationship between childhood maltreatment and schizophrenia was not supported when using Genomic SEM or MR. This finding contradicted previous phenotypic research which argues that loneliness/isolation can mediate the relationship between childhood maltreatment and schizophrenia (Boyda & McFeeters, 2015; Shevlin et al., 2015; Steenkamp et al., 2022), and suggests instead that the emergence of schizophrenia, which may be aggravated by early life maltreatment, is unlikely to be explained through loneliness/isolation. While previous observational studies found evidence of mediation, they focused on different aspects of psychosis and used a variety of different measures and definitions of childhood maltreatment. For instance, two studies only considered positive symptoms of psychosis rather than including the whole spectrum of symptoms commonly observed in schizophrenia (Boyda & McFeeters, 2015; Steenkamp et al., 2022), while another only assessed the effects of physical and sexual abuse (Shevlin et al., 2015), instead of including a more comprehensive measure of childhood maltreatment that also accounts for emotional abuse and/or physical and emotional neglect. Therefore, it is difficult to conclude to what extent differences in findings were driven by the heterogeneity in study design (e.g., genetically informed vs phenotypic designs) and/or differences in the type of measures used.

Interestingly, mediation analysis in the reverse direction identified loneliness/isolation as lying on the pathway from schizophrenia liability to childhood maltreatment, with up to 29% of this relationship explained by loneliness/isolation. One way to interpret this finding is that individuals with a genetic predisposition toward schizophrenia may experience difficulties in forming and maintaining social connections. This may in turn lead to social isolation, fewer protective factors (e.g., making individuals less likely or less able to seek help in at-risk or abusive environments – and less likely to be identified by others as someone in need of help) and consequently a greater risk for childhood maltreatment. Gene–environment correlations provide alternative explanations: parents with a genetic predisposition toward schizophrenia may create an environment for their children that increases the risk of loneliness/isolation and childhood maltreatment (i.e., passive gene–environment correlation); children's genetic make-up influences their behaviours and choice of environments, which may foster loneliness/isolation and/or childhood maltreatment (i.e., active gene–environment correlation); and, children's genetic make-up impacts their behaviour and characteristics, evoking reactions from others to that behaviour or characteristic (i.e., reactive gene-environment correlation) (Griffiths, 2005; Jaffee & Price, 2007; Knafo & Jaffee, 2013; Plomin et al., 1977; Warrier et al., 2021).

Our study has to be seen in light of the following limitations. First, due to methodological constraints, the current findings cannot be extrapolated to non-European ancestry individuals. Secondly, the present study only modelled the shared genetic architecture between childhood maltreatment, loneliness/isolation, and schizophrenia. Additional genetic and phenotypic confounds (e.g., education, cannabis use, adult victimisation) were not considered, which could inform our understanding of the gene-environment correlations that may increase schizophrenia risk (Hernán et al., 2004; Lutz et al., 2017; Warrier et al., 2021). Third, as alleles are assigned randomly only within but not

across families, the important MR assumption of no genetic confounding may be violated. However, as all GWASs included here controlled for population stratification, we consider this assumption to likely be upheld.

Lastly, our ability to draw strong causal inferences from our results is limited. This largely stems from the difficulty in disentangling causality from pleiotropic effects, as observed associations may arise due to multiple scenarios, namely: (i) independent genetic effects on trait 1 and 2 (i.e., horizontal pleiotropy), (ii) genetic effects on trait 1, which then causes trait 2 (the basis of MR), (iii) and/or genetic effects on trait 2, which then causes trait 1 (i.e., reverse MR). Considering that pleiotropy was not detected by our sensitivity analyses, it is possible that our findings are driven by either one of the latter two scenarios. Nonetheless, drawing strong causal environmental inferences from MR would be inappropriate, as the crucial assumption on the absence of horizontal pleiotropy cannot be completely ruled out.

Despite these limitations, the fact that our results were consistent across two divergent methods (Genomic SEM and MR) provides greater confidence in the robustness of our findings. Future studies should investigate alternative mediatory personality (e.g., neuroticism) and lifestyle factors (e.g., smoking) in the relationship between childhood maltreatment and schizophrenia to inform intervention-based treatment programmes. While observational studies have already identified factors such as perceived discrimination, emotion dysregulation, mood symptoms, and the lack of social support as potential mediators in the association between childhood abuse and psychosis (Sideli et al., 2020), little has been done to assess the robustness of these relationships using genetically informed techniques.

To the best of our knowledge, the current study is the first to explore the mediating role of loneliness/isolation in the relationship between childhood maltreatment and schizophrenia using genetic data. Using high powered GWAS summary statistics (N = 105,318 - 487,647), our results suggest that loneliness/isolation does not mediate the

association between childhood maltreatment and schizophrenia. In fact, we find evidence of mediation in the opposite direction. As such, whilst there may be merit in clinical interventions targeting loneliness/isolation in individuals who have experienced childhood maltreatment (e.g., social conditioning interventions; Shevlin et al., 2015), the current results suggest that targeting loneliness/isolation in this group is unlikely to reduce the risk of developing schizophrenia. Greater benefits may be observed by intervening upon loneliness/isolation in individuals with a genetic predisposition towards schizophrenia, as this may diminish childhood maltreatment risk. Taken together, these findings provide key novel insights into the link between childhood maltreatment and schizophrenia, with significant implications for targeted clinical interventions.

Data and Code Availability

All datasets analysed in the present study are publicly available. Summary statistics for childhood maltreatment and loneliness/social isolation can be obtained from the University of Cambridge Apollo repository (childhood maltreatment: https://www.repository.cam.ac.uk/handle/1810/318326; loneliness/social isolation: https://www.repository.cam.ac.uk/handle/1810/277812). Summary statistics for schizophrenia can be obtained from the Walters group data repository (https://walters.psycm.cf.ac.uk). Analysis code for this study has been made publicly available on GitHub and can be accessed at https://github.com/VilteBaltra/loneliness-mediation.

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Table 1

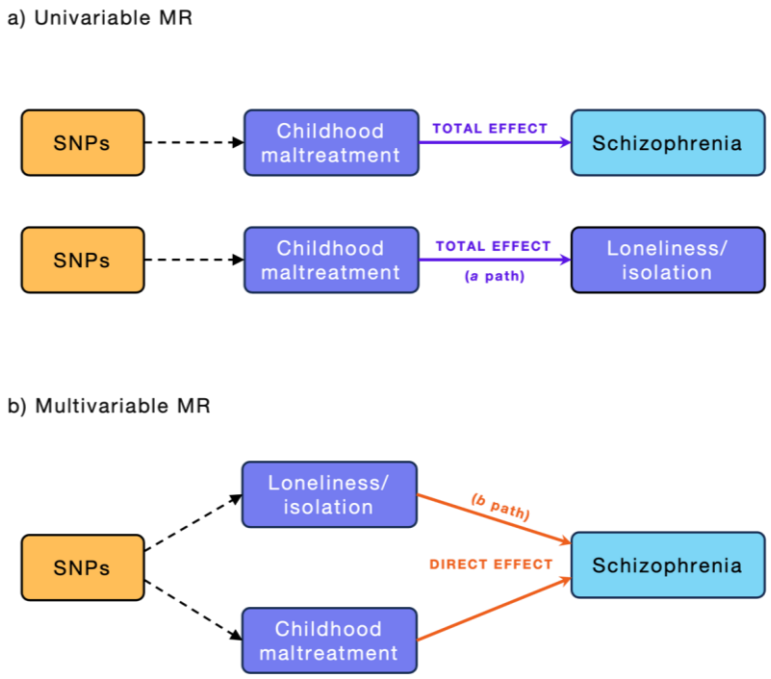
Characteristics of the Contributing Genome-wide Association Studies

Phenotype	**Assessment**	***N***	**Age**	**GWAS**	h^2_{SNP}
Childhood Maltreatment	Self-report / Parent-report	185,414	10-64	Warrier et al. (2021)	8%
Loneliness/Isolation	Self-report	487,647	40-69	Day et al. (2018)	4.2%
Schizophrenia	*Multiple sources	130,644	NA	Trubetskoy et al. (2022)	24%

Note. h^2_{SNP} = SNP heritability reported in the respective GWASs; *N* = sample size; Age = mean age in years across contributing cohorts; GWAS = genome-wide association study. *Cases were ascertained based on multiple sources of information such as medical records, semi-structured interviews, and clinical evaluation by psychiatrists. More detailed information on assessment methods is included in the original study by Trubetskoy et al. (2022).

Figure 1

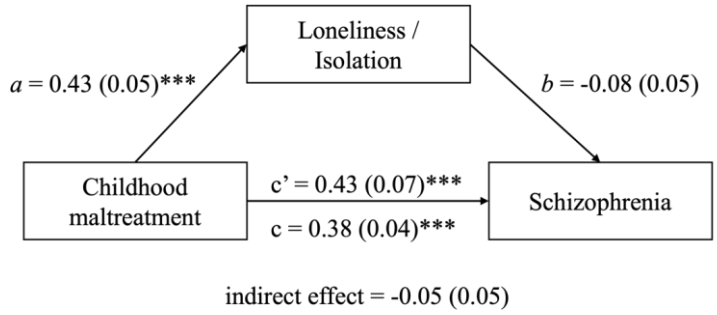
Estimation of the Total and Direct Effects from Mendelian Randomisation Analysis



Note. The purple arrow represents the total effect of childhood maltreatment (exposure) on schizophrenia (outcome) and the total effect on loneliness/isolation (mediator; path *a*). Orange arrows represent (i) the direct effect of childhood maltreatment on schizophrenia and (ii) the direct effect of loneliness/isolation on schizophrenia (path *b*). MR = Mendelian randomisation; SNPs = single nucleotide polymorphisms.

Figure 2

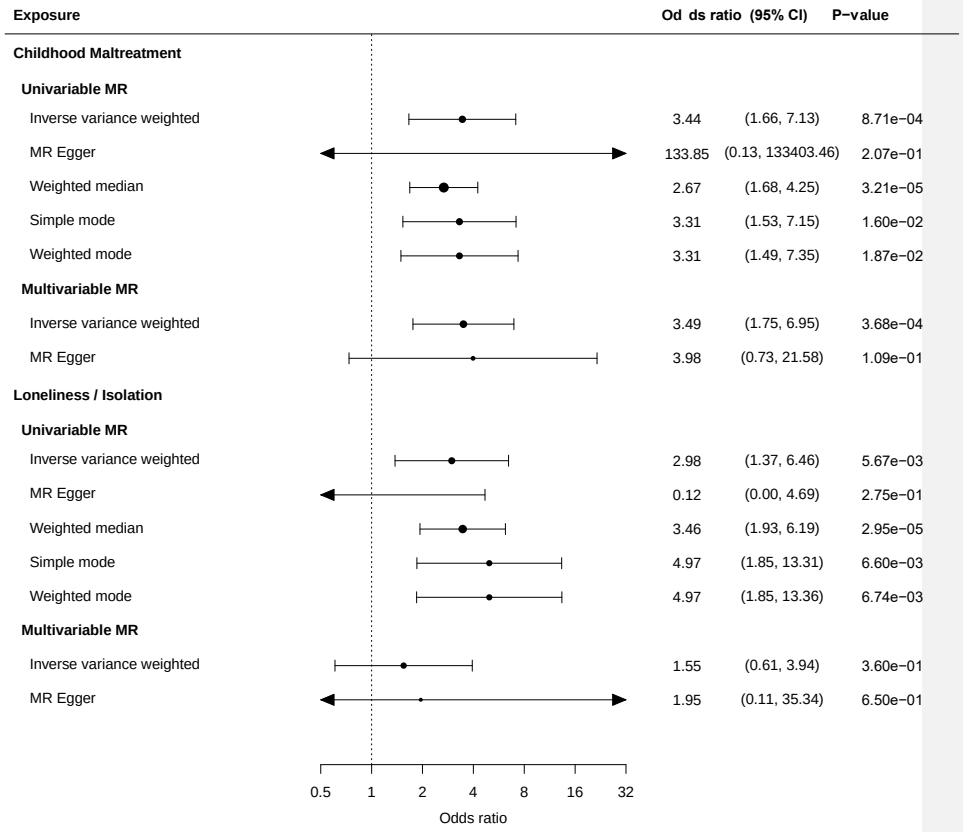
Genetic Mediation Analysis Estimating the Mediating Effect of Loneliness/Isolation in the Relationship between Childhood Maltreatment and Schizophrenia



Note. Standardised regression weights and the corresponding standard errors (in parentheses) are reported. *a* path = effect of the predictor (childhood maltreatment) on the mediator (loneliness/isolation); *b* path = effect of the mediator (loneliness/isolation) on the outcome (schizophrenia); c' path = direct effect of childhood maltreatment on schizophrenia; *c* path = total effect of childhood maltreatment on schizophrenia. *** $p < 0.001$.

Figure 3

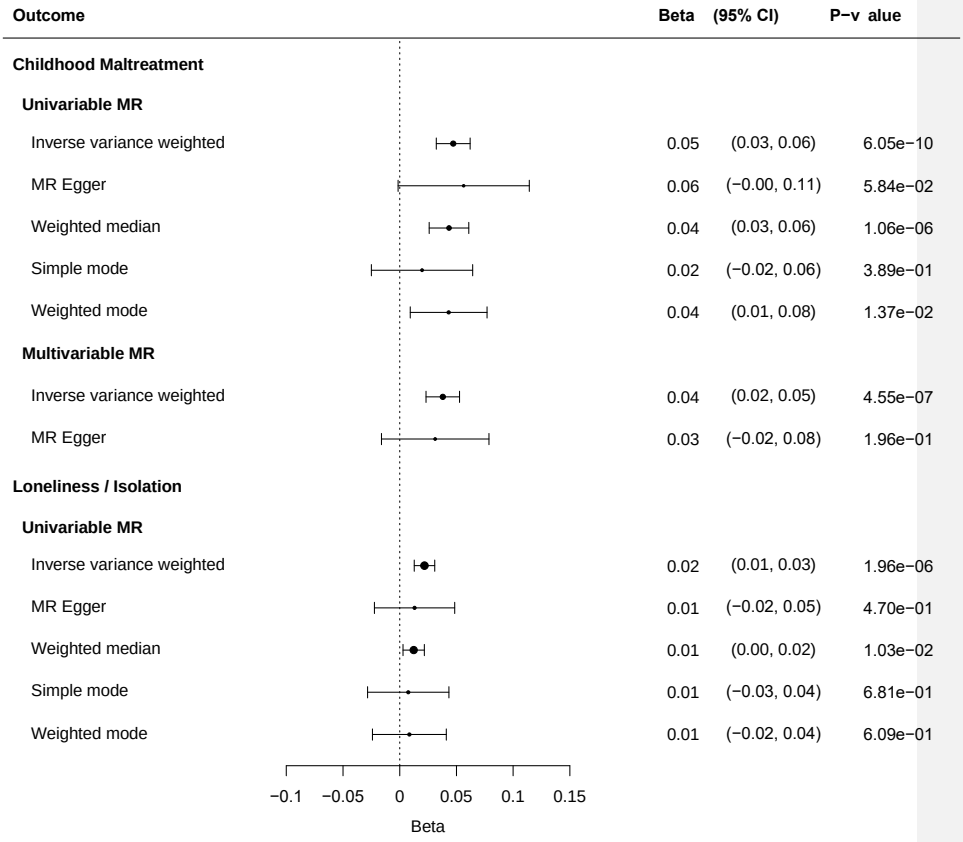
Univariable and Multivariable Mendelian Randomisation Estimates for the Effect of Genetically Predicted Childhood Maltreatment and Loneliness/Isolation on Schizophrenia Risk



Note. Error bars represent 95% confidence intervals. MR = Mendelian randomisation; CI = confidence interval. Confidence intervals of the MR-Egger estimate for childhood maltreatment are wider, consistent with the lower statistical power of this method (Slob & Burgess, 2020).

Figure 4

Univariable and Multivariable Mendelian Randomisation Estimates for the Effect of Genetically Predicted Schizophrenia on Childhood Maltreatment and Loneliness/Isolation Risk



Note. Error bars represent 95% confidence intervals. MR = Mendelian randomisation; CI = confidence interval.