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Childhood abuse *v.* neglect and risk for major psychiatric disorders

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Abstract

Background. Childhood maltreatment (CM) is a strong risk factor for psychiatric disorders but serves in its current definitions as an umbrella for various fundamentally different childhood experiences. As first step toward a more refined analysis of the impact of CM, our objective is to revisit the relation of abuse and neglect, major subtypes of CM, with symptoms across disorders.

Methods. Three longitudinal studies of major depressive disorder (MDD, $N = 1240$), bipolar disorder (BD, $N = 1339$), and schizophrenia (SCZ, $N = 577$), each including controls ($N = 881$), were analyzed. Multivariate regression models were used to examine the relation between exposure to abuse, neglect, or their combination to the odds for MDD, BD, SCZ, and symptoms across disorders. Bidirectional Mendelian randomization (MR) was used to probe causality, using genetic instruments of abuse and neglect derived from UK Biobank data ($N = 143\,473$).

Results. Abuse was the stronger risk factor for SCZ (OR 3.51, 95% CI 2.17–5.67) and neglect for BD (OR 2.69, 95% CI 2.09–3.46). Combined CM was related to increased risk exceeding additive effects of abuse and neglect for MDD (RERI = 1.4) and BD (RERI = 1.1). Across disorders, abuse was associated with hallucinations (OR 2.16, 95% CI 1.55–3.01) and suicide attempts (OR 2.16, 95% CI 1.55–3.01) whereas neglect was associated with agitation (OR 1.24, 95% CI 1.02–1.51) and reduced need for sleep (OR 1.64, 95% CI 1.08–2.48). MR analyses were consistent with a bidirectional causal effect of abuse with SCZ ($IVW_{forward} = 0.13$, 95% CI 0.01–0.24).

Conclusions. Childhood abuse and neglect are associated with different risks to psychiatric symptoms and disorders. Unraveling the origin of these differences may advance understanding of disease etiology and ultimately facilitate development of improved personalized treatment strategies.

Introduction

Childhood maltreatment (CM) and its detrimental consequences are a major public health concern (Chen, Turiano, Mroczek, & Miller, 2016; Gilbert et al., 2009; Heim, Shugart, Craighead, & Nemeroff, 2010; Vos et al., 2012). Across the world, approximately 35% of

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children have been exposed to emotional abuse, 23% to physical abuse, 18% to neglect (emotional and/or physical), and 13% to sexual abuse, based on self-report studies that suggest a much higher prevalence than informant-based prevalence rates of around 0.3% (Stoltenborgh, Bakermans-Kranenburg, Alink, & van Ijzendoorn, 2015). The impact of CM is not constrained to a single health outcome but increases the risk for a diversity of psychiatric disorders (Green et al., 2010), worse treatment outcomes (Cakir, Tasdelen Durak, Ozyildirim, Ince, & Sar, 2016; Misiak & Frydecka, 2016), decreased social function (Kilian et al., 2018), frequent hospitalizations (Slotema et al., 2017), and high risk for suicide (Bernegger et al., 2015; Hassan, Stuart, & De Luca, 2016). Such a broad range of adverse consequences points to large individual differences in responses to CM exposure (Edwards, Holden, Felitti, & Anda, 2003; Howes, McCutcheon, Owen, & Murray, 2017; Nemeroff, 2004; Vinkers et al., 2015; Whitfield, Dube, Felitti, & Anda, 2005) and may suggest diversity in pathways of the negative impact of CM.

A likely contributor to the diversity of outcomes of CM exposure is the nature of CM. CM is defined as one or multiple negative life events occurring before the age of 18 years, but the nature of these events diverge largely, and it is not self-evident they all have the same impact. Whereas there are many potential subdivisions of the overall experience of CM, a broad but relevant division is the distinction between abuse and neglect as they comprise fundamentally different psychological experiences. Abuse is defined as any non-accidental act which causes or creates a substantial risk, physical or emotional injury, and covers a highly threatening event. Abused children are more likely to perceive their harmful environment as dependent on their own behavior than neglected children (Humphreys & Zeanah, 2015). Neglect is defined as the shortcoming, deliberately or through negligence or inability, to take those actions necessary to provide a child with minimally adequate food, clothing, shelter, medical care, supervision, emotional stability, and growth and deprives the child from basic care and stimulating experiences. Differential effects of abuse and neglect have been reported with respect to brain development (Gauthier, Stollak, Messé, & Aronoff, 1996), recognition of emotional cues (Pollak, Cicchetti, Hornung, & Reed, 2000), social-emotional adjustment (Scientific Council on the Developing Child, 2012), the hypothalamic–pituitary–adrenocortical axis (Bruce, Fisher, Pears, & Levine, 2009), and amygdala and hippocampal volumes (Herzog et al., 2020; Teicher et al., 2018). For understanding the impact of CM on neural development, a conceptual framework distinguishing threat (i.e. abuse) and deprivation (i.e. neglect) has been suggested previously (Sheridan & McLaughlin, 2014). As to be expected when growing up in a harmful environment, childhood abuse and neglect often co-occur (Broekhof, Nordahl, Bjørnelv, & Selvik, 2022). Experiencing multiple types of CM is related to an accumulation of detrimental consequences later in life, suggesting a dose–response relationship (Hughes et al., 2017; Sala, Goldstein, Wang, & Blanco, 2014; Steine et al., 2017). The experience of both abuse and neglect could therefore be seen as a third and more severe type, that of combined CM. Despite these widely recognized psychological and neurodevelopmental differences between the experience of abuse *v.* neglect in childhood, no previous studies compared their relative differential impact across psychiatric disorders. Existing research on CM has often taken approaches that disregard comparing potential meaningful subdivisions of CM (Cohodes, Kitt, Baskin-Sommers, & Gee, 2021; Gee, 2021).

Previous studies investigated either one specific CM type, such as sexual abuse, specific disorders, or did not differentiate between CM types (Lewis, McElroy, Harlaar, & Runyan, 2016; Zhang et al., 2020). In these studies, childhood abuse has been related to higher risks of schizophrenia (SCZ) spectrum disorder (Croft et al., 2019; Heins et al., 2011). Childhood neglect, physical, and emotional abuse were associated with risk for major depressive disorder (MDD) (Betz, Rosen, Salokangas, & Kambeitz, 2022; Christ et al., 2019; Humphreys et al., 2020; Infurna, Reichl, Parzer, Schimmenti, & Bifulco, 2016; Martins, Von Werne Baes, De Carvalho Tofoli, & Juruena, 2014). In bipolar disorder (BD), the limited evidence pointed to a stronger association of childhood abuse with symptom severity than childhood neglect (Etain et al., 2013). Studies that compare risks of childhood abuse, childhood neglect, and their combination across MDD, BD, and SCZ are absent, despite their relevance from the perspective that if childhood abuse and neglect comprise different etiological pathways in the development of psychopathology (Heim et al., 2010), this may be reflected in distinct clinical profiles. Even within disorders, two individuals with the same diagnosis can experience different (core) symptoms (Brunoni, 2017; Cuthbert, 2015; Parker, 2006), and therefore examining symptom profiles across diagnosis could provide additional insight. Therefore, this study focuses on the relation between the CM types (i.e. abuse, neglect, and combined CM) and psychopathology later in life; both at disorder level (for MDD, BD, and SCZ) and trans-diagnostically, at the symptom levels. As a strategy to inform of causal directions, we additionally make use of Mendelian randomization (MR) (Davies, Holmes, & Davey Smith, 2018). MR is a method in epidemiological observational research that leverages genetic variants as instrumental variables (IVs) to explore the likelihood of causal relationships between an exposure (in this case, CM) and an outcome (psychopathology). The method can help mitigate confounding and reverse causation biases present in observational studies by making use of the fact that most genetic variation is at random in large populations, mimicking randomization of exposure in experimental studies. Recent research identified a genetic signal associated with CM exposure, capturing gene–environment correlations (Warrier et al., 2021). This allows exploring causal directions of the relationship between abuse and neglect on mental health outcomes, using bidirectional MR (Smith & Hemani, 2014).

In summary, the primary objective of this study is to investigate the relative impact of different types of CM, including abuse, neglect, and combined maltreatment, on psychiatric disorders, both at the disorder level (MDD, BD, SCZ) and trans-diagnostically at the symptom level. We aim to shed light on potential distinct clinical profiles associated with these maltreatment types and explore causal directions using MR, taking into account recent genetic findings related to CM exposure. This comprehensive approach offers valuable insights into the complex relationship between CM and later-life psychopathology.

Methods

Study participants

Data from three large longitudinal Dutch cohort studies were used for this study (total $N = 4037$): the genetic risk and outcome in psychosis study, focusing on SCZ spectrum disorders (GROUP, subsample total $N = 981$, SCZ cases: 577, MDD: 74, controls: 330) (Korver, Piotr, Boos, Simons, & De Haan, 2012), the

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Dutch Bipolar Cohort focusing on bipolar disorder (DBC, total $N = 1453$, BD: 1255, controls: 198) (Van Bergen et al., 2019), and the Netherlands Study of Depression and Anxiety (NESDA; total $N = 1603$, MDD: 1166, BD: 84, controls: 353) (Penninx et al., 2008, 2021), focusing on depressive disorders and anxiety. The distribution of diagnosis categories (MDD, BD, and SCZ) and controls in the total dataset, and for each cohort study, are displayed in online Supplementary Fig. S1. For the MR analyses, genetic data of 143 473 individuals with self-reported white European ancestry were retrieved from the UK Biobank, a large nation-wide cohort study from the United Kingdom (Bycroft et al., 2018; Sudlow et al., 2015). All procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Assessments

Baseline assessments in the three cohort studies included history of current psychiatric disorders, standardized interview for DSM diagnosis, or control status. In GROUP, the Comprehensive Assessment of Symptoms and History (CASH) (Andreasen, Flaum, & Arndt, 1992) and Schedules for Clinical Assessment in Neuropsychiatry (SCAN) (Wing et al., 1990) were administered. DBC used the Structural Clinical Interview for DSM-IV (SCID-I) (First, Spitzer, Gibbon, & Williams, 2002) and Mini-International Neuropsychiatric Interview-plus (MINI-plus) (Sheehan et al., 1998). NESDA used the Composite Interview Diagnostic Instrument (CIDI) (Robins et al., 1988). Inclusion criteria for the combined analysis were diagnoses of a major psychiatric disorder at baseline with available data on symptom level, and on CM. Participants diagnosed with solitary anxiety disorder at baseline were excluded due to lack of data on the symptom level in this group. In NESDA, data from multiple waves were collapsed, and MDD was defined as a lifetime diagnosis of MDD. Participants without a history of mental disorder assessed by either the SCID-I, CIDI, CASH, MINI-plus, or SCAN were included as controls. For assessment of CM under the age of 18 years, all three cohorts administered the Childhood Trauma Questionnaire-Short Form (CTQ) (Bernstein et al., 2003; Thombs, Bernstein, Lobbestael, & Arntz, 2009). Total CTQ-scores, subscale scores (physical abuse, emotional neglect, emotional abuse, physical neglect, and sexual abuse), and item-scores were reported in all cohorts. Incomplete CTQ scores (0.13% of items missing at random) were imputed at item-level using the multiple imputation algorithm for maximum likelihood estimation. Outcome ranges of pooled outcomes are presented in the result section. Based on the source publication of the CTQ (Bernstein, 1998; Bernstein et al., 2003; Thombs et al., 2009), abuse was defined as moderate or above scores on only CTQ dimensions emotional abuse (score $\geqslant 13$), physical abuse (score $\geqslant 10$), or sexual abuse (score $\geqslant 8$). Neglect was defined as moderate or above scores for only emotional neglect (score $\geqslant 15$) or physical neglect (score $\geqslant 10$). Subjects scoring moderate or above on both neglect and abuse subscales were classified as combined CM. Lastly, subjects with CTQ subscale scores below cutoff for both abuse and neglect were classified as 'no CM'. Comorbid psychiatric and somatic disorders were either unavailable or inconsistently reported across studies and were therefore not taken into account in the analysis.

Dataset harmonization on symptom level

The lifetime presence or absence of symptoms of SCZ, BD, and MDD was reported for all participants of GROUP and DBC. In NESDA, SCZ cases were not included since they fell outside the scope of the study. Therefore, only the presence or absence of bipolar and depressive disorder symptoms was reported for NESDA participants. Patients with completely lacking symptom data were excluded. For the control group and for GROUP participants assessed with the SCAN, symptom data were not available. To harmonize the available data from the SCID-I, CIDI, and CASH, all symptoms were scored dichotomously, with 0 = symptom not present, and 1 = symptom is present. In the DBC study, symptoms coded as 2 = 'possibly present' (in <1% of cases) were recoded into 0 = symptom not present. The SCZ symptoms that were scored on a 5-point Likert scale were recoded into dichotomous variables. Symptoms with an original score of 0–2 were reclassified as 0: not/not fully present, not/moderately severe, or not/moderately bizarre. Symptoms with a score of 3–5 were reclassified as 1: present, severe, or bizarre. All symptoms were kept as detailed as possible, for instance hypersomnia and insomnia were both used instead of being merged into a broader term such as sleep disturbances. Some symptoms, however, needed to be combined due to differences in structure of the SCID-I, CIDI, and CASH. Symptoms combined were, for MDD: weight loss + decreased appetite, weight gain + increased appetite, and for BD: expansive mood + irritable mood, increased activity + agitation. For SCZ, all types of delusions were merged into presence or absence of delusions. The same was applied for hallucinations, merging all types into one variable indicating presence or absence of hallucinations.

Statistical analyses

The data were analyzed using Statistical Package for the Social Sciences (SPSS, v26; SPSS Inc., Chicago, Illinois, USA). χ^2 tests were performed for analyzing differences in the distribution between groups. In a multivariate logistic regression model, the contribution of CM types abuse, neglect, and combined CM was modeled as three dichotomous indicators (with no CM as reference) with presence/absence of each diagnosis as the outcome. A significant Wald-test statistic for one of the CM types indicated that the experience of this CM type increased the likelihood of a certain diagnosis, as compared to the reference group of no CM. Subsequently, differences between abuse, neglect, and combined CM were analyzed in turn by adapting the reference categories. Similarly, the contribution of CTQ subtypes emotional abuse (EA), physical abuse (PA), sexual abuse (SA), emotional neglect (EN), and physical neglect (PN) for each diagnosis was estimated in a multivariate logistic regression model. At the symptom level, the contribution of abuse, neglect, and combined CM was estimated in a multivariate logistic regression model (with no CM as reference) for the presence or absence of each symptom as a dichotomous outcome. For all these analyses, the assumptions were verified and met. Logistic regression results are presented as odds ratios (OR) in the result section. Confounder analysis was performed by examining the relation of age, gender, and level of education (none, basic, low, intermediate, and high) as determinants, with CM types and diagnosis as the outcome. For education, educational level was coded by using four dummy variables signifying the difference compared to no education. Variables with a significant association with both diagnosis and

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CM were added as covariates to the multivariate models. Significance of the differences between the OR of a particular CM type between disorders was estimated with the same multivariate logistic regression models but alternating diagnosis categories as reference category in order to obtain head-to-head comparisons (for instance for the contribution of abuse to MDD as compared to SCZ).

The Relative Excess Risk due to Interaction (RERI) (Knol, van der Tweel, Grobbee, Numans, & Geerlings, 2007, 2011) was calcluated to measure the deviation from additivity of the exposure effect on an OR scale (Hosmer & Lemeshow, 1992). An RERI < 1 indicates a negative interaction and an RERI = 0 means no interaction or exact additivity. If RERI > 0, an interaction on an additive scale is indicated, meaning that the combined effect of two exposures is larger than the sum of the individual effects of the two exposures.

Mendelian randomization

In MR, IVs are genetic variants that are used as proxies of an exposure (e.g. CM), which can be used to estimate the causal effect on an outcome (e.g. psychopathology). In line with the previous genome-wide association studies (GWAS) study of CM in the UK Biobank (Warrier et al., 2021), an IV was derived from the UK Biobank. The UK Biobank participants completed the Childhood Trauma Screener (CTS), a retrospectively reported five-item questionnaire that consists of one question per CM subtype, with answers ranging from 0: never true, to 4: very often true (Grabe et al., 2012; Warrier et al., 2021). Abuse was defined when one or more CTS abuse items were scored >0, neglect when one or more neglect items were scored >0, and combined CM when abuse and neglect were both present. In order to ultimately perform bidirectional, two-sample MR, all available genetic data of UK Biobank participants with self-reported white European ancestry were included for GWAS) for traits abuse, neglect, and combined CM. All genotyped and imputed single nucleotide polymorphisms (SNPs) with a minor allele frequency >0.1%, that did not deviate from Hardy–Weinberg equilibrium ($p > 1 \times 10^{-6}$), had a genotyping rate of 95%, or, for imputed SNPs, had an imputation $R^2 > 0.4$, were used. Participants who had excessive genetic heterozygosity (i.e. who were >5 S.D. from the means of the first two genetic principal components), whose genetic sex did not match their reported sex or who had a genotyping rate <95%, were excluded. GWAS were conducted for over 15 million SNPs using FastGWA-GLMM (using GCTA version 1.93.2) (Jiang et al., 2019). Sex, year of birth, genotyping batch, and the first 10 genetic principal components were included as covariates.

Two-sample MR (Byrne, Yang, & Wray, 2017; Slob & Burgess, 2020) was performed to assess whether genetic predictors of abuse, neglect, and combined CM are associated with SCZ (Trubetskoy et al., 2022), BD (Mullins et al., 2021), and MDD (Howard et al., 2019). Putative causal links between CM type and diagnosis were investigated bidirectionally, i.e., whether a genetic predictor of CM type enhances the risk of SCZ, BD, and MDD (forward direction) or whether CM type liability is altered because of liability to SCZ, BD, or MDD (backward direction). To avoid bias in MR due to sample overlap (Burgess, Davies, & Thompson, 2016), UK Biobank was excluded from the GWAS data for the three mental health phenotypes of interest. In the first attempt to extract instruments using independent GWAS loci, the standard p value threshold of $p < 5 \times 10^{-8}$ was used. This p value threshold is applied in the MR backward analyses. In the MR forward analyses, no SNPs were selected at a p value threshold of $p < 5 \times 10^{-8}$, therefore the p value was stepwise increased in order to lower the SNP selection threshold, until at least two SNPs were selected. This led to a threshold of $p < 1 \times 10^{-6}$. As a follow-up analysis, designed to interrogate the influence of threshold variation and in order to gauge potential pleiotropy, the SNP selection threshold was further lowered by increasing the p value until the highest number of SNPs was included without significant evidence of horizontal pleiotropy as measured by the Egger's test (corresponding to the threshold $p < 3 \times 10^{-6}$). Then, to ensure independence between IVs, a strict clumping procedure was applied (LD $r^2 < 0.001$ within 10 Mb, using the 1000 G EUR as the reference panel). Following that, SNP alleles were harmonized between exposure GWAS and outcome GWAS before running the MR analyses. Each MR analysis was conducted using the following methods: inverse variance-weighted (IVW) MR, which assumes that all SNPs are valid instruments; median-weighted, which provides valid estimates even if up to 50% of the instruments are invalid (Bowden, Davey Smith, Haycock, & Burgess, 2016); Q statistic, as an assessment of heterogeneity and first indicator of whether there might be pleiotropy; MR-Egger, which accounts for pleiotropy by including an intercept term in the IVW model (Bowden, Smith, & Burgess, 2015); and MR-PRESSO, which accounts for pleiotropy by detecting and removing outliers (Verbanck, Chen, Neale, & Do, 2018). The mean F statistic was used to quantify instrument strength within the univariable IVW analyses, considering a mean $F < 20$ as indicative of weak instruments. The Steiger test was used to assess the validity of IVs and confirm the direction of causality (Burgess et al., 2019). All analyses were performed in R (R Studio Team, 2020), using the packages TwoSampleMR (Hemani et al., 2018), MendelianRandomization (Yavorska & Burgess, 2017), and MR-PRESSO (Verbanck et al., 2018).

Results

The analyses comprised 3156 cases and 881 controls. Of total cases, 14.3% was diagnosed with SCZ (N = 577), 30.7% with MDD ($N = 1240$), and 33.2% with BD ($N = 1339$). Demographics of the total sample are listed in Table 1.

χ^2 tests showed that the distribution of CM differed significantly across diagnoses including the controls ($\chi^2[9] = 225.17$–226.11, $p < 0.001$) as well as between patient groups only ($\chi^2[6] = 40.21$–40.34, $p < 0.001$). All types of CM were associated with the presence of MDD, BD, and SCZ in separate non-adjusted logistic regression models (online Supplementary Table S1).

Independent t tests for age showed significant differences between CM groups. Neglect and combined CM groups were significantly older ($t = 7.44$, $p < 0.01$ and $t = 4.31$, $p < 0.01$) and the abuse group was significantly younger ($t = 2.77$, $p = 0.01$) than individuals without CM. Compared to the control group, the MDD and BD diagnosis groups were significantly older ($t = 8.25$, $p < 0.01$ and $t = 5.22$, $p < 0.01$), whereas participants with SCZ were significantly younger ($t = 20.87$, $p < 0.01$). χ^2 tests showed that CM groups significantly differed by gender ($\chi^2[3] = 22.85$–23.58, $p < 0.01$), with more women in abuse and combined CM groups and relatively more men in the neglect and no CM groups. The CM groups also differed in level of education ($\chi^2[15] = 69.70$–70.77, $p < 0.01$): participants in the no CM group had higher education in contrast to the neglect and combined group, which included more non- and basic educated individuals.

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Table 1. Demographic characteristics of the total sample

	Abuse	Neglect	Combined CM	No CM	Total
Diagnosis	*N* (%)	*N* (%)	*N* (%)	*N* (%)	*N* (%)
MDD	85 (6.9%)	255 (20.6%)	276 (22.3%)	624 (50.3%)	1240 (100%)
BD	101 (7.5%)	293 (21.9%)	278 (20.8%)	667 (49.8%)	1339 (100%)
SCZ	77 (13.3%)	85 (14.7%)	97 (16.8%)	318 (55.1%)	577 (100%)
Control	51 (5.8%)	103 (11.7%)	60 (6.8%)	667 (75.7%)	881 (100%)
Gender	*N* (%)	*N* (%)	*N* (%)	*N* (%)	*N* (%)
Male	129 (7.3%)	342 (19.4%)	257 (14.5%)	1038 (58.7%)	1766 (100%)
Female	185 (8.1%)	393 (17.3%)	454 (20%)	1238 (54.5%)	2270 (100%)
Age	*M* (s.d.)	*M* (s.d.)	*M* (s.d.)	*M* (s.d.)	*M* (s.d.)
Total	43.3 (14.0)	49.9 (13.4)	48.1 (13.2)	45.6 (13.89)	46.64 (13.8)
Education	*N* (%)	*N* (%)	*N* (%)	*N* (%)	*N* (%)
No education	2 (5.6%)	12 (33.3%)	7 (19.4%)	15 (41.7%)	36 (100%)
Basic	10 (7.9%)	44 (34.6%)	30 (23.6%)	43 (33.9%)	127 (100%)
Low	64 (8.5%)	160 (21.3%)	153 (20.3%)	375 (49.9%)	752 (100%)
Intermediate	107 (8.3%)	221 (17.2%)	217 (16.9%)	741 (57.6%)	1286 (100%)
High	131 (7.2%)	297 (16.2%)	301 (16.4%)	1102 (60.2%)	1831 (100%)

MDD, major depressive disorder; BD, bipolar disorder; SCZ, schizophrenia; CM, childhood maltreatment; *N*, number; *M*, mean; s.d., standard deviation.

To adjust for these potential confounders, age, gender, and education were added as covariates in all the analyses.

ORs and confidence intervals (CIs) of the relation between CM type and major psychiatric disorder after adjusting the model for age, gender, and education are presented in Fig. 1. Variance inflation factors (VIFs) were <1.5 for each predicting variable, indicating absence of multicollinearity.

Childhood abuse, neglect, and combined CM were related to higher odds of MDD, BD, and SCZ compared to healthy controls. Comparing the relation between CM type and disorder shows that the association of both childhood abuse and neglect with MDD and BD was similar, with largely overlapping CIs, as shown in Fig. 1. The association of childhood abuse with SCZ, however, was significantly stronger than the association of childhood abuse with MDD ($p = 0.011$) and BD ($p = 0.048$) (see online Supplementary Table S2).

The RERI between CM types shows a significant additive interaction for combined CM in MDD (RERI = 1.4) and BD (RERI = 1.1) compared to the impact of abuse and neglect alone. This indicates that the combined effect of abuse and neglect is larger than the sum of their individual effects. Combined CM showed no additive interaction in SCZ (RERI = 0.6).

Comparing the impact of abuse, neglect, and their combination within diagnostic category (for instance, analysis whether the contribution of abuse was significantly larger that the contribution of neglect to SCZ risk) highlighted a significantly stronger effect of abuse than of neglect in risk for SCZ, and a disproportionately strong impact of combined CM as compared to abuse and neglect alone for MDD and BD, and compared to neglect for SCZ (online Supplementary Table S3), as also indicated by the RERIs.

The relation of abuse and neglect with symptoms of depression, mania, and psychosis across diagnosis

Logistic regression analyses showed that the presence of symptoms of depression, mania, and psychosis differed between CM types, as presented in Table 2. Childhood abuse was the strongest risk factor for feelings of worthlessness/guilt, suicide attempt, delusions, and hallucinations. Childhood neglect showed no association with symptoms of psychosis, and even an opposite relation to the development of delusions. Combined CM was, consequently, not significantly associated with delusions or hallucinations. Both childhood neglect and combined CM stood out as a significant risk factor for reduced need for sleep. Combined CM increased the risks for the same symptoms as abuse and neglect alone, except for delusions. Furthermore, combined CM increased the odds of depressive mood, retardation, and returning thoughts of death the most and showed many more statistically significant associations than abuse and neglect alone.

Online Supplementary Table S4 summarizes all statistically significant associations between types of CM and symptoms of depression, mania, and psychosis.

Impact of five CM subtypes across psychiatric disorders

χ^2 tests showed a significantly different distribution of the five CTQ subscales (emotional and physical abuse, sexual abuse, emotional, and physical neglect) across diagnosis ($\chi^2[15] = 132.84–134.27$, $p < 0.01$). The results of logistic regression of CTQ subscales on psychiatric diagnosis, while adjusting for age, gender, and education (no multicollinearity: VIFs < 1.5) are shown in Table 3. All abuse types were most strongly related to increased odds of SCZ compared to the other diagnoses. Physical abuse stood out as a risk factor specifically for SCZ. Neglect, and especially emotional neglect, was the strongest risk factor for MDD and BD.

Investigating evidence of causality between CM type and psychiatric disorders using MR

Forward MR analyses were consistent with a causal relationship of childhood abuse with SCZ (IVW = 0.125 [95% CI 0.01–0.24],

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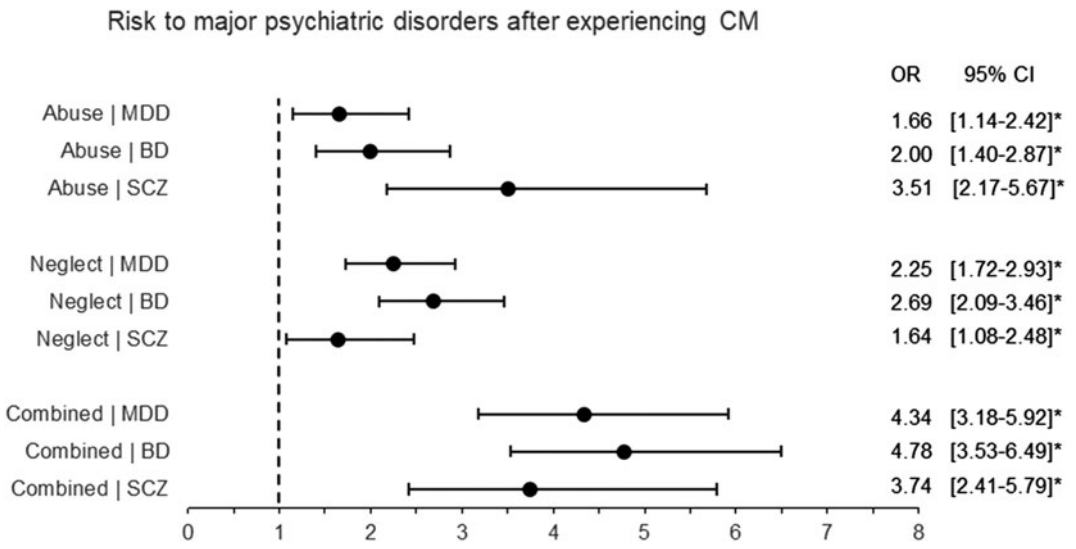

Figure 1. Forest plot of the adjusted multivariate logistic regression model of the relation between childhood maltreatment (CM) type (abuse, neglect, combined) and diagnosis (MDD, BD, SCZ) with age, gender, and education level added as covariates and healthy controls as the reference group. Dots represent odds ratios (OR), error bars represent 95% confidence intervals (CI). *Significant with $\alpha = 0.05$.

$p = 0.032$; online Supplementary Table S5), based on two SNPs. Steiger test indicated a correct direction of causality between the exposure and outcome. Cochran's Q statistic was statistically significant for the analysis of abuse against SCZ, indicating evidence of pleiotropy but may also be the consequence of the limited number of two SNPs. Such limited number of two selected SNPs was also insufficient to perform the weighted median, MR Egger regression, and MR pleiotropy residual sum and outlier (MR-PRESSO) methods. These methods were used as sensitivity analyses and showed no evidence for invalid instruments for the analyses when enough SNPs were selected (online Supplementary Table S5). The F statistic ranged from 24.3 to 45.6, indicating that the estimates were not likely subject to weak instrument bias. The follow-up MR analysis, in which the SNP selection threshold was lowered by increasing the p value to $p < 3 \times 10^{-6}$, confirmed statistical significance with no evidence of horizontal pleiotropy (IVW = 0.112 [95% CI 0.05–0.18], $p = 0.001$, Q p value 0.186, based on six SNPs; see online Supplementary Table S6). This suggests that the more lenient threshold of 1×10^{-6} is not the main explanation of the found relation, and that the suggestion of pleiotropy disappears with a higher number of SNPs selected. The relation between child abuse and SCZ is the only consistent statistically significant relation in the MR analyses. The MR results for the association between neglect and combined CM and psychiatric disorders showed no consistent patterns of statistically significant causal effect. Backward MR supported a causal relationship of genetic variants linked to SCZ on abuse, neglect, and combined CM (online Supplementary Table S5).

Discussion

This study presents data from three large cohort studies that show that childhood abuse, neglect, and their combination all significantly contribute to an increased risk of SCZ, BD, and MDD. However, childhood abuse and neglect differ in the strength of their relation to diagnosis and clinical symptom profile. Abuse was significantly stronger related to higher odds of developing SCZ compared to its impact on MDD and BD. Neglect was most strongly associated with risk for BD and MDD. Differences between childhood abuse and neglect were also present across diagnosis at the symptom-level. Childhood abuse was associated with a significantly higher risk of suicide attempts, feelings of worthlessness or guilt, delusions, and hallucinations, whereas neglect was significantly related to agitation and reduced need for sleep. Differential effects of child abuse and neglect at the symptom level were most prominent for symptoms of psychosis whereby abuse strongly increased the risk of delusions and hallucinations, in contrast to neglect.

In addition to the distinction between the effects of childhood abuse and neglect alone, this study also shows that experiencing both childhood abuse and neglect (combined CM) is related to disproportionally higher odds of MDD or BD, exceeding the mere additive effect of child abuse plus neglect. Accumulation of stressful life events has been noted before as a risk factor for MDD (Vinkers et al., 2014), and is consistent with the stress resilience model whereby symptoms of psychiatric disorders develop when the impact of adversity exceeds resilience thresholds (Carpenter et al., 2007; Heim et al., 2013; Houtepen et al., 2016; Tyrka, Price, Marsit, Walters, & Carpenter, 2012). On the symptom-level, combined maltreatment showed the same pattern, with higher risks for a multitude of symptoms, compared to abuse and neglect alone. Consequently, combined maltreatment exceeds a dose–response relationship and can be seen as a more detrimental type of CM for the risk for BD and MDD.

One of the most consistent findings of this study is the strong relation abuse with SCZ and positive psychotic symptoms. A strong relation between abuse and SCZ fits previous reports of a threefold increase in psychosis risk and hallucinations in patients with a history of child abuse (Croft et al., 2019; Marchi et al., 2022a; Read, Van Os, Morrison, & Ross, 2005; Van Os et al., 2020; Varese et al., 2012) and warrants the question about a possible causal relation between child abuse (and not neglect) and SCZ. The findings from the MR analyses lend further support for this hypothesis, even when based on a limited numbers of SNPs due to the modest discovery set of the UK Biobank ($N =$

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Table 2. Odds ratio with 95% confidence interval (OR [95%CI]) for presence of symptoms of depression (in MDD, BD and SCZ patients, $n = 3156$), mania and psychosis (in BD and SCZ patients; $n = 1916$) after experiencing abuse, neglect, or combined CM

	Abuse	Neglect	Combined
Symptoms of depression			
Depressive mood	1.55 [0.94–2.56]	1.39 [0.98–1.97]	**1.59 [1.1–2.3]***
Loss of interest	1 [0.64–1.58]	1.24 [0.88–1.75]	1.16 [0.82–1.63]
Weight loss/decreased appetite	1.06 [0.8–1.41]	1.04 [0.86–1.27]	1.15 [0.95–1.4]
Weight gain/increased appetite	1.31 [0.98–1.75]	1.2 [0.98–1.48]	**1.43 [1.17–1.75]***
Insomnia	1.08 [0.81–1.46]	1.06 [0.86–1.31]	1.23 [0.99–1.52]
Hypersomnia	1.26 [0.95–1.66]	1.12 [0.92–1.36]	**1.3 [1.07–1.57]***
Agitation	1.08 [0.82–1.44]	**1.24 [1.02–1.51]***	**1.44 [1.19–1.75]***
Retardation	1.06 [0.8–1.41]	1.01 [0.83–1.23]	**1.31 [1.07–1.59]***
Loss of energy	0.96 [0.6–1.54]	0.95 [0.67–1.35]	1.18 [0.82–1.71]
Worthlessness/guilt	**1.48 [1.02–2.14]***	1.04 [0.82–1.32]	**1.35 [1.05–1.73]***
Inefficient thinking	1.08 [0.64–1.81]	1.21 [0.82–1.79]	1.35 [0.89–2.04]
Returning thoughts of death	1.33 [0.98–1.82]	1.07 [0.87–1.32]	**1.52 [1.22–1.89]***
Suicide attempt	**2.16 [1.55–3.01]***	1.18 [0.89–1.55]	**1.48 [1.14–1.91]***
Symptoms of mania			
Expansive/irritable mood	1.3 [0.8–2.11]	1.2 [0.81–1.78]	1.2 [0.8–1.78]
Exaggerated confidence	0.87 [0.5–1.5]	1.45 [0.9–2.34]	**0.66 [0.45–0.97]***
Reduced need for sleep	1.27 [0.75–2.15]	**1.64 [1.08–2.48]***	**1.6 [1.05–2.44]***
Verbosity	0.88 [0.54–1.43]	0.94 [0.64–1.39]	1.29 [0.84–1.97]
Thought train	1.09 [0.66–1.82]	1.38 [0.94–2.04]	0.97 [0.67–1.39]
Reduced concentration	0.85 [0.55–1.32]	1.24 [0.88–1.75]	0.95 [0.68–1.32]
Increased activity	1.01 [0.56–1.82]	0.95 [0.61–1.49]	1.08 [0.68–1.71]
Reduced judgment	0.95 [0.65–1.4]	1.01 [0.76–1.34]	0.89 [0.67–1.18]
Symptoms of psychosis			
Delusions	**1.67 [1.08–2.58]***	**0.67 [0.47–0.96]***	0.94 [0.66–1.33]
Hallucinations	**1.56 [1.03–2.37]***	0.73 [0.52–1.04]	0.96 [0.68–1.36]

MDD, major depressive disorder; BD, bipolar disorder; SCZ, schizophrenia; CM, childhood maltreatment.
Analyses were adjusted for age, gender, and education.
*Significant with $\alpha = 0.05$.

Table 3. Odds ratio with 95% confidence interval (OR [CI]) for MDD, BD, or SCZ after experiencing a subtype of childhood maltreatment: emotional abuse or neglect, physical abuse or neglect, or sexual abuse

	Emotional abuse	Physical abuse	Sexual abuse	Emotional neglect	Physical neglect
MDD	1.69 [0.84–3.39]	0.69 [0.19–2.43]	**1.86 [1.17–2.96]***	**3.38 [2.31–4.95]***	**1.55 [1.10–2.19]***
BD	1.92 [0.99–3.73]	1.66 [0.64–4.33]	**2.13 [1.35–3.35]***	**3.75 [2.58–5.44]***	**2.05 [1.49–2.82]***
SCZ	**2.86 [1.19–6.83]***	**3.93 [1.25–12.32]***	**3.76 [2.02–6.99]***	**1.95 [1.06–3.58]***	1.45 [0.85–2.44]

MDD, major depressive disorder; BD, bipolar disorder; SCZ, schizophrenia.
Analyses were adjusted for age, gender, and education.
*Significant with $\alpha = 0.05$.

143 473). Such a relation would be of great importance to further promote public prevention programs and could provide a personalized treatment perspective for individuals suffering from SCZ with a history of abuse. Considering that a history of CM has a negative influence on prognosis and treatment outcomes (Trotta, Murray, & Fisher, 2015), the question is warranted to what extent individual trauma-focused therapy might decrease their burden (Van Den Berg et al., 2015; Van Den Berg et al., 2018), even in the absence of post-traumatic stress disorder (PTSD). Another prospect of an increased understanding of the CM–SCZ relationship could be the development of predictive models for antipsychotic treatment outcomes, as has previously

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been done for MDD (Williams, Debattista, Duchemin, Schatzberg, & Nemeroff, 2016). A clinical hypothesis could be that SCZ patients with a history of CM are less likely to respond to antipsychotics and more likely to trauma-focused therapy as compared to patients without such CM history. More fundamentally, these findings could be a starting point for etiology research into a distinct abuse–SCZ pathway. One possible direction for such studies could be the revisiting of molecular pathways linking CM to dopaminergic function specified by CM type (Howes et al., 2017). Previous research suggests several other psychological, social, and biological pathways from childhood adversity to SCZ (Alameda et al., 2020; Sideli et al., 2020) that could be refined by specifying CM type.

Another consideration on the differential relations between CM type and psychopathology is related to recent evidence of gene–environment correlations (Kendler & Eaves, 1986; Knafo & Jaffee, 2013). In the relation between CM and SCZ for instance, genetic liability to SCZ has been associated with CM (Sallis et al., 2021) and CM has been found to act as a mediator in the relation between genetic risk for SCZ and the occurrence of psychotic-like experiences (Marchi et al., 2022), pointing out a role of gene–environment correlation in the emergence of a mental health phenotype. For the current study, the joint effect of both environmental experiences and genetic vulnerability underlying the development of psychopathology (Dalvie et al., 2020; Kendler & Eaves, 1986) is very relevant and the results therefore should be viewed in light of a broader social context in which CM occurs (Marchi et al., 2022; Sideli et al., 2020; Vinkers et al., 2014). CM subtypes are likely associated with many potential confounders such as life stresses, parental psychopathology, and substance abuse (Doidge, Higgins, Delfabbro, & Segal, 2017), which occur more frequently in households with lower socio-economic status (Doidge et al., 2017; Sidebotham & Heron, 2006; Wu et al., 2004). Differential influences of abuse and neglect may well be related to specific environmental circumstances, similarly as childhood neglect has been associated with antisocial personality disorder of the care-taker (Mulder, Kuiper, van der Put, Stams, & Assink, 2018) and neuroticism of the child (Brents, James, Cisler, & Kilts, 2018; Hovens, Giltay, Van Hemert, & Penninx, 2016).

In addition to pinpointing the relevance of gene–environment effects, the current study underlines the importance of differentiating in the type of adverse childhood experiences with respect to their effects on mental health. Previous research already indicated the relevance of CM even within diagnostic category by reporting clinical and neurobiological differences between maltreated and non-maltreated individuals with the same primary DSM-5 diagnosis (Teicher & Samson, 2013; Teicher, Gordon, & Nemeroff, 2022). The current study underscores the potential for such refinements. A subdivision within diagnoses based on the effects of childhood adversities may contribute to developing alternative, transdiagnostic approaches in future research. Besides child abuse and neglect, subdividing CM experiences into emotional and physical trauma could also be further investigated (Spinhoven, Elzinga, Van Hemert, De Rooij, & Penninx, 2016). Ultimately, further differentiating the effects of various CM types might open doors to targeted therapy and prediction models.

Strengths of this study include the overall sample size with standardized diagnostic assessments, uniform measure of CM, the investigation of effects of CM on both disorder and symptom-level, and the addition of investigating causal inference using MR. However, the results should be interpreted in the context of limitations that are mostly related to the use of data from three separate cohort studies. Consequently, the analyses were restricted to MDD, BD, and SCZ and particularly disorders such as PTSD, anxiety disorders, or personality disorders (Afifi et al., 2011; Sistad, Simons, Mojallal, & Simons, 2021; Waxman, Fenton, Skodol, Grant, & Hasin, 2014) could not be taken into account. As another consequence of this approach, symptom-level information on psychosis was not present for the MDD cases. Whereas diagnostic classifications according to the DSM were made using completed validated diagnostic clinical assessments, the presence or absence of a particular symptom was defined based on harmonization of the CIDI, CASH, and SCID items (Andreasen et al., 1992; First et al., 2002; Robins et al., 1988). Also, the analysis of multiple symptoms and diagnosis constitute an element of multiple testing that was not adjusted for. Next to that, it is important to acknowledge the potential presence of reverse causality. The most important limitation is that although possible residual confounding or collider bias is minimized by the facts that all cohorts comprised of a mixture of primary and specialty psychiatric care patients, contributed controls recruited in a similar way, and included at least two diagnostic categories, they cannot be ruled out. Also, it should be noted that the MR analyses are preliminary as they are based on a different assessment of CM, and that the forward analysis could only be based on a small selection of SNPs with a sub-genome-wide significant threshold. The lack of association between the CM types and MDD and BD may therefore reflect the limited power of the MR analyses. In the analysis of abuse against SCZ, there is evidence of pleiotropy. This could be explained by increased variance due to the small selection of SNPs in the forward analysis, since the suggestion for pleiotropy disappears in the follow-up analysis including a larger selection of SNPs.

Overall, this study provides evidence that abuse and neglect differ in their impact on risk of major psychiatric disorders and its symptoms, and that their combination is most adverse. The strong relations of abuse with the risk of developing SCZ and hallucinations stand out and are consistent with the possibility of distinct etiological pathway for psychosis. Further understanding of relations between more narrowly defined CM types and psychopathology can increase our etiological understanding and may ultimately guide diagnostic refinements and treatment strategies.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291723003471

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References

Afifi, T. O., Mather, A., Boman, J., Fleisher, W., Enns, M. W., MacMillan, H., & Sareen, J. (2011). Childhood adversity and personality disorders: Results from a nationally representative population-based study. *Journal of Psychiatric Research*, *45*(6), 814–822. doi: 10.1016/J.JPSYCHIRES.2010.11.008

Alameda, L., Rodriguez, V., Carr, E., Aas, M., Trotta, G., Marino, P., … Murray, R. M. (2020). A systematic review on mediators between adversity and psychosis: Potential targets for treatment. *Psychological Medicine*, *50*(12), 1966–1976. doi: 10.1017/S0033291720002421

Andreasen, N. C., Flaum, M., & Arndt, S. (1992). The Comprehensive Assessment of Symptoms and History (CASH): An instrument for assessing diagnosis and psychopathology. *Archives of General Psychiatry*, *49*(8), 615–623. doi: 10.1001/ARCHPSYC.1992.01820080023004

Bernegger, A., Kienesberger, K., Carlberg, L., Swoboda, P., Ludwig, B., Koller, R., … Schosser, A. (2015). Influence of sex on suicidal phenotypes in affective disorder patients with traumatic childhood experiences. *PLoS ONE*, *10*(9), e0137763. doi: 10.1371/journal.pone.0137763

Bernstein, D. P., Stein, J. A., Newcomb, M. D., Walker, E., Pogge, D., Ahluvalia, T., … Zule, W. (2003). Development and validation of a brief screening version of the Childhood Trauma Questionnaire. *Child Abuse & Neglect*, *27*(2), 169–190. doi: 10.1016/S0145-2134(02)00541-0

Bernstein, L. F. (1998). Childhood Trauma Questionnaire: A retrospective self-report. *The Psychological Corporation. San Antonio, TX*.

Betz, L. T., Rosen, M., Salokangas, R. K. R., & Kambeitz, J. (2022). Disentangling the impact of childhood abuse and neglect on depressive affect in adulthood: A machine learning approach in a general population sample. *Journal of Affective Disorders*, *315*, 17–26. doi: 10.1016/j.jad.2022.07.042

Bowden, J., Davey Smith, G., Haycock, P. C., & Burgess, S. (2016). Consistent estimation in Mendelian randomization with some invalid instruments using a weighted median estimator. *Genetic Epidemiology*, *40*(4), 304–314. doi: 10.1002/gepi.21965

Bowden, J., Smith, G. D., & Burgess, S. (2015). Mendelian randomization with invalid instruments: Effect estimation and bias detection through Egger regression. *International Journal of Epidemiology*, *44*(2), 512–525. doi: 10.1093/ije/dyv080

Brents, L. K., James, G. A., Cisler, J. M., & Kilts, C. D. (2018). Personality variables modify the relationship between childhood maltreatment history and poor functional outcomes. *Psychiatry Research*, *268*, 229–237. doi: 10.1016/j.psychres.2018.07.010

Broekhof, R., Nordahl, H. M., Bjørnelv, S., & Selvik, S. G. (2022). Prevalence of adverse childhood experiences and their co-occurrence in a large population of adolescents: A Young HUNT 3 study. *Social Psychiatry and Psychiatric Epidemiology*, *57*, 2359–2366. doi: 10.1007/s00127-022-02277-z

Bruce, J., Fisher, P. A., Pears, K. C., & Levine, S. (2009). Morning cortisol levels in preschool-aged foster children: Differential effects of maltreatment type. *Developmental Psychobiology*, *51*(1), 14. doi: 10.1002/DEV.20333

Brunoni, A. R. (2017). Beyond the DSM: Trends in psychiatry diagnoses. *Archives of Clinical Psychiatry*, *44*(6), 154–158. doi: 10.1590/0101-60830000000142

Burgess, S., Davey Smith, G., Davies, N. M., Dudbridge, F., Gill, D., Glymour, … Theodoratou, E. (2019). Guidelines for performing Mendelian randomization investigations. *Wellcome Open Research*, *4*, 186. doi: 10.12688/wellcomeopenres.15555.1

Burgess, S., Davies, N. M., & Thompson, S. G. (2016). Bias due to participant overlap in two-sample Mendelian randomization. *Genetic Epidemiology*, *40*(7), 597–608. doi: 10.1002/gepi.21998

Bycroft, C., Freeman, C., Petkova, D., Band, G., Elliott, L. T., Sharp, K., … Marchini, J. (2018). The UK Biobank resource with deep phenotyping and genomic data. *Nature*, *562*(7726), 203–209. doi: 10.1038/s41586-018-0579-z

Byrne, E. M., Yang, J., & Wray, N. R. (2017). Inference in psychiatry via 2-sample Mendelian randomization – from association to causal pathway? *JAMA Psychiatry*, *74*(12), 1191–1192. doi: 10.1001/jamapsychiatry.2017.3162

Cakir, S., Tasdelen Durak, R., Ozyildirim, I., Ince, E., & Sar, V. (2016). Childhood trauma and treatment outcome in bipolar disorder. *Journal of Trauma and Dissociation*, *17*(4), 397–409. doi: 10.1080/15299732.2015.1132489

Carpenter, L. L., Carvalho, J. P., Tyrka, A. R., Wier, L. M., Mello, A. F., Mello, … Price, L. H. (2007). Decreased adrenocorticotropic hormone and cortisol responses to stress in healthy adults reporting significant childhood maltreatment. *Biological Psychiatry*, *62*(10), 1080–1087. doi: 10.1016/j.biopsych.2007.05.002

Chen, E., Turiano, N. A., Mroczek, D. K., & Miller, G. E. (2016). Association of reports of childhood abuse and all-cause mortality rates in women. *JAMA Psychiatry*, *73*(9), 920–927. doi: 10.1001/jamapsychiatry.2016.1786

Christ, C., De Waal, M. M., Dekker, J. J. M., van Kuijk, I., Van Schaik, D. J. F., Kikkert, M. J., … Messman-Moore, T. L. (2019). Linking childhood emotional abuse and depressive symptoms: The role of emotion dysregulation and interpersonal problems. *PLoS ONE*, *14*(2), 1–18. doi: 10.1371/journal.pone.0211882

Cohodes, E. M., Kitt, E. R., Baskin-Sommers, A., & Gee, D. G. (2021). Influences of early-life stress on frontolimbic circuitry: Harnessing a dimensional approach to elucidate the effects of heterogeneity in stress exposure. *Developmental Psychobiology*, *63*(2), 153–172. doi: 10.1002/DEV.21969

Croft, J., Heron, J., Teufel, C., Cannon, M., Wolke, D., Thompson, A., … Zammit, S. (2019a). Association of trauma type, age of exposure, and frequency in childhood and adolescence with psychotic experiences in early adulthood. *JAMA Psychiatry*, *76*(1), 79–86. doi: 10.1001/jamapsychiatry.2018.3155

Cuthbert, B. N. (2015). Research domain criteria: Toward future psychiatric nosologies. *Dialogues in Clinical Neuroscience*, *17*(1), 89–97. doi: 10.31887/dcns.2015.17.1/bcuthbert

Dalvie, S., Maihofer, A. X., Coleman, J. R. I., Bradley, B., Breen, G., Brick, L. A., … Nievergelt, C. M. (2020). Genomic influences on self-reported childhood maltreatment. *Translational Psychiatry*, *10*(1), 38. doi: 10.1038/s41398-020-0706-0

Davies, N. M., Holmes, M. V., & Davey Smith, G. (2018). Reading Mendelian randomisation studies: A guide, glossary, and checklist for clinicians. *BMJ (Online)*, *362*, k601. doi: 10.1136/bmj.k601

Doidge, J. C., Higgins, D. J., Delfabbro, P., & Segal, L. (2017). Risk factors for child maltreatment in an Australian population-based birth cohort. *Child Abuse and Neglect*, *64*, 47–60. doi: 10.1016/j.chiabu.2016.12.002

Edwards, V. J., Holden, G. W., Felitti, V. J., & Anda, R. F. (2003). Relationship between multiple forms of childhood maltreatment and adult mental health in community respondents: Results from the adverse childhood experiences study. *American Journal of Psychiatry*, *160*(8), 1453–1460. doi: 10.1176/appi.ajp.160.8.1453

Etain, B., Aas, M., Andreassen, O. A., Lorentzen, S., Dieset, I., Gard, S., … Henry, C. (2013). Childhood trauma is associated with severe clinical characteristics of bipolar disorders. *The Journal of Clinical Psychiatry*, *74*(10), 991–998. doi: 10.4088/JCP.13m08353

First, M. B., Spitzer, R. L., Gibbon, M., & Williams, J. B. W. (2002). *Structured clinical interview for DSM-IV-TR axis I disorders, research version, patient*

https://doi.org/10.1017/S0033291723003471 Published online by Cambridge University Press

edition with psychotic screen (*SCID-I/P W/PSY SCREEN*). New York: Biometrics Research, New York State Psychiatric Institute.

Gauthier, L., Stollak, G., Messé, L., & Aronoff, J. (1996). Recall of childhood neglect and physical abuse as differential predictors of current psychological functioning. *Child Abuse & Neglect*, *20*(7), 549–559. doi: 10.1016/0145-2134(96)00043-9

Gee, D. G. (2021). Early adversity and development: Parsing heterogeneity and identifying pathways of risk and resilience. *American Journal of Psychiatry*, *178*(11), 998–1013. doi: 10.1176/APPI.AJP.2021.21090944

Gilbert, R., Widom, C. S., Browne, K., Fergusson, D., Webb, E., & Janson, S. (2009). Burden and consequences of child maltreatment in high-income countries. *The Lancet*, *373*(9657), 68–81. doi: 10.1016/S0140-6736(08)61706-7

Grabe, H. J., Schulz, A., Schmidt, C. O., Appel, K., Driessen, M., Wingenfeld, K., … Freyberger, H. J. (2012). A brief instrument for the assessment of childhood abuse and neglect. *Psychiatrische Praxis*, *39*(3), 109–115. doi: 10.1055/s-0031-1298984

Green, J. G., McLaughlin, K. A., Berglund, P. A., Gruber, M. J., Sampson, N. A., Zaslavsky, A. M., & Kessler, R. C. (2010). Childhood adversities and adult psychiatric disorders in the national comorbidity survey replication I: Associations with first onset of DSM-IV disorders. *Archives of General Psychiatry*, *67*(2), 113–123. doi: 10.1001/ARCHGENPSYCHIATRY.2009.186

Hassan, A. N., Stuart, E. A., & De Luca, V. (2016). Childhood maltreatment increases the risk of suicide attempt in schizophrenia. *Schizophrenia Research*, *176*(2–3), 572–577. doi: 10.1016/j.schres.2016.05.012

Heim, C., Jeffrey Newport, D., Heit, S., Graham, Y. P., Wilcox, M., Bonsall, R., … Nemeroff, C. B. (2013). Pituitary-adrenal and autonomic responses to stress in women after sexual and physical abuse in childhood. *The Science of Mental Health: Stress and the Brain*, *9*(5), 84–89. doi: 10.1097/00005721-200111000-00023

Heim, C., Shugart, M., Craighead, W. E., & Nemeroff, C. B. (2010). Neurobiological and psychiatric consequences of child abuse and neglect. *Developmental Psychobiology*, *52*(7), 671–690. doi: 10.1002/dev.20494

Heins, M., Simons, C., Lataster, T., Pfeifer, S., Versmissen, D., Lardinois, M., … Myin-Germeys, I. (2011). Childhood trauma and psychosis: A case-control and case-sibling comparison across different levels of genetic liability, psychopathology, and type of trauma. *American Journal of Psychiatry*, *168*(12), 1286–1294. doi: 10.1176/appi.ajp.2011.10101531

Hemani, G., Zheng, J., Elsworth, B., Wade, K. H., Haberland, V., Baird, D., … Haycock, P. C. (2018). The MR-base platform supports systematic causal inference across the human phenome. *ELife*, *7*, 1–29. doi: 10.7554/eLife.34408

Herzog, J. I., Thome, J., Demirakca, T., Koppe, G., Ende, G., Lis, S., … Schmahl, C. (2020). Influence of severity of type and timing of retrospectively reported childhood maltreatment on female amygdala and hippocampal volume. *Scientific Reports 10*, 1903. doi: 10.1038/s41598-020-57490-0

Hosmer, D. W., & Lemeshow, S. (1992). Confidence interval estimation of interaction. *Epidemiology*, *3*(5), 452–456.

Houtepen, L. C., Vinkers, C. H., Carrillo-Roa, T., Hiemstra, M., Van Lier, P. A., Meeus, W., … Boks, M. P. M. (2016). Genome-wide DNA methylation levels and altered cortisol stress reactivity following childhood trauma in humans. *Nature Communications*, *7*, 10967. doi: 10.1038/ncomms10967

Hovens, J. G. F. M., Giltay, E. J., Van Hemert, A. M., & Penninx, B. W. J. H. (2016). Childhood maltreatment and the course of depressive and anxiety disorders: The contribution of personality characteristics. *Depression and Anxiety*, *33*(1), 27–34. doi: 10.1002/da.22429

Howard, D. M., Adams, M. J., Clarke, T. K., Hafferty, J. D., Gibson, J., Shirali, … McIntosh, A. M. (2019). Genome-wide meta-analysis of depression identifies 102 independent variants and highlights the importance of the prefrontal brain regions. *Nature Neuroscience*, *22*(3), 343–352. doi: 10.1038/s41593-018-0326-7

Howes, O. D., McCutcheon, R., Owen, M. J., & Murray, R. M. (2017a). The role of genes, stress, and dopamine in the development of schizophrenia. In *Biological psychiatry* (Vol. *81*, 1, pp. 9–20). Elsevier USA. doi: 10.1016/j.biopsych.2016.07.014

Hughes, K., Bellis, M. A., Hardcastle, K. A., Sethi, D., Butchart, A., Mikton, C., … Dunne, M. P. (2017). The effect of multiple adverse childhood experiences on health: A systematic review and meta-analysis. *The Lancet. Public health*, *2*(8), e356–e366. doi: 10.1016/S2468-2667(17)30118-4

Humphreys, K. L., LeMoult, J., Wear, J. G., Piersiak, H. A., Lee, A., & Gotlib, I. H. (2020). Child maltreatment and depression: A meta-analysis of studies using the Childhood Trauma Questionnaire. *Child Abuse and Neglect*, *102*(February), 104361. doi: 10.1016/j.chiabu.2020.104361

Humphreys, K. L., & Zeanah, C. H. (2015). Deviations from the expectable environment in early childhood and emerging psychopathology. *Neuropsychopharmacology*, *40*, 154–170. doi: 10.1038/npp.2014.165

Infurna, M. R., Reichl, C., Parzer, P., Schimmenti, A., & Bifulco, A. K. M. (2016). Associations between depression and specific childhood experiences of abuse and neglect: A meta-analysis. *Journal of Affective Disorders*, *190*, 47–55. doi: 10.1016/J.JAD.2015.09.006

Jiang, L., Zheng, Z., Qi, T., Kemper, K. E., Wray, N. R., Visscher, P. M., & Yang, J. (2019). A resource-efficient tool for mixed model association analysis of large-scale data. *Nature Genetics*, *51*, 1749–1755. doi: 10.1038/s41588-019-0530-8

Kendler, K. S., & Eaves, L. J. (1986). Models for the joint effect of genotype and environment on liability to psychiatric illness. *American Journal of Psychiatry*, *143*(3), 279–289. doi: 10.1176/ajp.143.3.279

Kilian, S., Asmal, L., Chiliza, B., Olivier, M., Phahladira, L., Scheffler, F., … Emsley, R. (2018). Childhood adversity and cognitive function in schizophrenia spectrum disorders and healthy controls: Evidence for an association between neglect and social cognition. *Psychological Medicine*, *48*(13), 2186–2193. doi: 10.1017/S0033291717003671

Knafo, A., & Jaffee, S. R. (2013). Gene-environment correlation in developmental psychopathology. *Development and Psychopathology*, *25*(1), 1–6. doi: 10.1017/S0954579412000855

Knol, M. J., van der Tweel, I., Grobbee, D. E., Numans, M. E., & Geerlings, M. I. (2007). Estimating interaction on an additive scale between continuous determinants in a logistic regression model. *International Journal of Epidemiology*, *36*(5), 1111–1118. doi: 10.1093/ije/dym157

Knol, M. J., VanderWeele, T. J., Groenwold, R. H. H., Klungel, O. H., Rovers, M. M., & Grobbee, D. E. (2011). Estimating measures of interaction on an additive scale for preventive exposures. *European Journal of Epidemiology*, *26*(6), 433–438. doi: 10.1007/s10654-011-9554-9

Korver, N., Piotr Q.J., Boos H.B.M., Simons C.J.P., & De Haan, L. G. I. (2012). Genetic Risk and Outcome of Psychosis (GROUP), a multi-site longitudinal cohort study focused on gene–environment interaction: Objectives, sample characteristics, recruitment and assessment. *International Journal of Methods in Psychiatric Research*, *21*, 205–221. doi: 10.1002/mpr.1352

Lewis, T., McElroy, E., Harlaar, N., & Runyan, D. (2016). Does the impact of child sexual abuse differ from maltreated but non-sexually abused children? A prospective examination of the impact of child sexual abuse on internalizing and externalizing behavior problems. *Child Abuse & Neglect*, *51*, 31–40. doi: 10.1016/J.CHIABU.2015.11.016

Marchi, M., Elkrief, L., Alkema, A., van Gastel, W., Schubart, C. D., van Eijk, K. R., … Boks, M. P. (2022a). Childhood maltreatment mediates the effect of the genetic background on psychosis risk in young adults. *Translational Psychiatry*, *12*(1), 219. doi: 10.1038/s41398-022-01975-1

Martins, C. M. S., Von Werne Baes, C., De Carvalho Tofoli, S. M., & Juruena, M. F. (2014). Emotional abuse in childhood is a differential factor for the development of depression in adults. *Journal of Nervous and Mental Disease*, *202*(11), 774–782. doi: 10.1097/NMD.0000000000000202

Misiak, B., & Frydecka, D. (2016). A history of childhood trauma and response to treatment with antipsychotics in first-episode schizophrenia patients. *The Journal of Nervous and Mental Disease*, *204*(10), 787–792. doi: 10.1097/NMD.0000000000000567

Mulder, T. M., Kuiper, K. C., van der Put, C. E., Stams, G. J. J. M., & Assink, M. (2018). Risk factors for child neglect: A meta-analytic review. *Child Abuse and Neglect*, *77*, 198–210. doi: 10.1016/j.chiabu.2018.01.006

Mullins, N., Forstner, A. J., O'Connell, K. S., Coombes, B., Coleman, J. R. I., Qiao, Z., … Andreassen, O. A. (2021). Genome-wide association study of more than 40,000 bipolar disorder cases provides new insights into the underlying biology. *Nature Genetics*, *53*(6), 817–829. doi: 10.1038/s41588-021-00857-4

Nemeroff, C. B. (2004). Neurobiological consequences of childhood trauma. *Journal of Clinical Psychiatry*, *65*, 18–28.

Parker, G. (2006). Through a glass darkly: The disutility of the DSM nosology of depressive disorders. *Canadian Journal of Psychiatry*, *51*(14), 879–886. doi: 10.1177/070674370605101403

Penninx, B. W. J. H., Beekman, A. T. F., Smit, J. H., Zitman, F. G., Nolen, W. A., Spinhoven, P., … Van Dyck, R. (2008). The Netherlands Study of Depression and Anxiety (NESDA): rationale, objectives and methods. *International Journal of Methods in Psychiatric Research*, *17*(3), 121–140. doi: 10.1002/mpr.256

Penninx, B. W. J. H., Eikelenboom, M., Giltay, E. J., van Hemert, A. M., Riese, H., Schoevers, R. A., & Beekman, A. T. F. (2021). Cohort profile of the longitudinal Netherlands Study of Depression and Anxiety (NESDA) on etiology, course and consequences of depressive and anxiety disorders. *Journal of Affective Disorders*, *287*, 69–77. doi: 10.1016/J.JAD.2021.03.026

Pollak, S. D., Cicchetti, D., Hornung, K., & Reed, A. (2000). Recognizing emotion in faces: Developmental effects of child abuse and neglect. *Developmental Psychology*, *36*(5), 679–688. doi: 10.1037/0012-1649.36.5.679

R Studio Team. (2020). *RStudio: Integrated development for R*. Boston, MA: RStudio, PBC. http://www.rstudio.com/

Read, J., Van Os, J., Morrison, A. P., & Ross, C. A. (2005). Childhood trauma, psychosis and schizophrenia: A literature review with theoretical and clinical implications. *Acta Psychiatrica Scandinavica*, *112*(5), 330–350. doi: 10.1111/j.1600-0447.2005.00634.x

Robins, L. N., Wing, J., Wittchen, H. U., Helzer, J. E., Babor, T. F., Burke, J., … Towle, L. H. (1988). The composite international diagnostic interview: An epidemiologic instrument suitable for use in conjunction with different diagnostic systems and in different cultures. *Archives of General Psychiatry*, *45*(12), 1069–1077. doi: 10.1001/ARCHPSYC.1988.01800360017003

Sala, R., Goldstein, B. I., Wang, S., & Blanco, C. (2014). Childhood maltreatment and the course of bipolar disorders among adults: Epidemiologic evidence of dose-response effects. *Journal of Affective Disorders*, *165*, 74–80. doi: 10.1016/j.jad.2014.04.035

Sallis, H. M., Croft, J., Havdahl, A., Jones, H. J., Dunn, E. C., Davey Smith, G., … Munafò, M. R. (2021). Genetic liability to schizophrenia is associated with exposure to traumatic events in childhood. *Psychological Medicine*, *51*(11), 1814–1821. doi: 10.1017/S0033291720000537

Scientific Council on the Developing Child, N. (2012). *The science of neglect: The persistent absence of responsive care disrupts the developing brain*. www.developingchild.net

Sheehan, D. V., Lecrubier, Y., Sheehan, K. H., Amorim, P., Janavs, J., Weiller, E., … Dunbar, G. C. (1998). The Mini-International Neuropsychiatric Interview (M.I.N.I.): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *Journal of Clinical Psychiatry*, *59*(20), 22–33.

Sheridan, M. A., & McLaughlin, K. A. (2014). Dimensions of early experience and neural development: Deprivation and threat. *Trends in Cognitive Sciences*, *18*(11), 580–585. doi: 10.1016/j.tics.2014.09.001

Sidebotham, P., & Heron, J. (2006). Child maltreatment in the 'children of the nineties': A cohort study of risk factors. *Child Abuse and Neglect*, *30*(5), 497–522. doi: 10.1016/j.chiabu.2005.11.005

Sideli, L., Murray, R. M., Schimmenti, A., Corso, M., La Barbera, D., Trotta, A., & Fisher, H. L. (2020). Childhood adversity and psychosis: A systematic review of bio-psycho-social mediators and moderators. *Psychological Medicine*, *50*(11), 1761–1782. doi: 10.1017/S0033291720002172

Sistad, R. E., Simons, R. M., Mojallal, M., & Simons, J. S. (2021). The indirect effect from childhood maltreatment to PTSD symptoms via thought suppression and cognitive reappraisal. *Child Abuse & Neglect*, *114*, 104939. doi: 10.1016/J.CHIABU.2021.104939

Slob, E. A. W., & Burgess, S. (2020). A comparison of robust Mendelian randomization methods using summary data. *Genetic Epidemiology*, *44*(4), 313–329. doi: 10.1002/gepi.22295

Slotema, C. W., Niemantsverdriet, M. B. A., Blom, J. D., van der Gaag, M., Hoek, H. W., & Sommer, I. E. C. (2017). Suicidality and hospitalisation in patients with borderline personality disorder who experience auditory verbal hallucinations. *European Psychiatry*, *41*(1), 47–52. doi: 10.1016/j.eurpsy.2016.10.003

Smith, G. D., & Hemani, G. (2014). Mendelian randomization: Genetic anchors for causal inference in epidemiological studies. *Human Molecular Genetics*, *23*(R1), 89–98. doi: 10.1093/hmg/ddu328

Spinhoven, P., Elzinga, B. M., Van Hemert, A. M., De Rooij, M., & Penninx, B. W. (2016). Childhood maltreatment, maladaptive personality types and level and course of psychological distress: A six-year longitudinal study. *Journal of Affective Disorders*, *191*, 100–108. doi: 10.1016/j.jad.2015.11.036

Steine, I. M., Winje, D., Krystal, J. H., Bjorvatn, B., Milde, A. M., Grønli, J., … Pallesen, S. (2017). Cumulative childhood maltreatment and its dose-response relation with adult symptomatology: Findings in a sample of adult survivors of sexual abuse. *Child Abuse and Neglect*, *65*, 99–111. doi: 10.1016/j.chiabu.2017.01.008

Stoltenborgh, M., Bakermans-Kranenburg, M. J., Alink, L. R. A., & van Ijzendoorn, M. H. (2015). The prevalence of child maltreatment across the globe: Review of a series of meta-analyses. *Child Abuse Review*, *24*(1), 37–50. doi: 10.1002/CAR.2353

Sudlow, C., Gallacher, J., Allen, N., Beral, V., Burton, P., Danesh, J., … Collins, R. (2015). UK Biobank: An open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *PLoS Medicine*, *12*(3), 1–10. doi: 10.1371/journal.pmed.1001779

Teicher, M. H., Anderson, C. M., Ohashi, K., Khan, A., Mcgreenery, C. E., Bolger, E. A., … Vitaliano, G. D. (2018). Differential effects of childhood neglect and abuse during sensitive exposure periods on male and female hippocampus HHS Public Access. *Neuroimage*, *169*, 443–452. doi: 10.1016/j.neuroimage.2017.12.055

Teicher, M. H., Gordon, J. B., & Nemeroff, C. B. (2022). Recognizing the importance of childhood maltreatment as a critical factor in psychiatric diagnoses, treatment, research, prevention, and education. *Molecular Psychiatry*, *27*(3), 1331–1338. doi: 10.1038/S41380-021-01367-9

Teicher, M. H., & Samson, J. A. (2013). Childhood maltreatment and psychopathology: A case for ecophenotypic variants as clinically and neurobiologically distinct subtypes. *The American Journal of Psychiatry*, *170*(10), 1114–1133. doi: 10.1176/APPI.AJP.2013.12070957

Thombs, B. D., Bernstein, D. P., Lobbestael, J., & Arntz, A. (2009). A validation study of the Dutch Childhood Trauma Questionnaire-Short Form: Factor structure, reliability, and known-groups validity. *Child Abuse and Neglect*, *33*(8), 518–523. doi: 10.1016/j.chiabu.2009.03.001

Trotta, A., Murray, R. M., & Fisher, H. L. (2015). The impact of childhood adversity on the persistence of psychotic symptoms: A systematic review and meta-analysis. *Psychological Medicine*, *45*(12), 2481–2498. doi: 10.1017/S0033291715000574

Trubetskoy, V., Pardiñas, A. F., Qi, T., Panagiotaropoulou, G., Awasthi, S., Bigdeli, T. B., Bryois, J., … van Os, J. (2022). Mapping genomic loci implicates genes and synaptic biology in schizophrenia. *Nature*, *604*(7906), 502–508. doi: 10.1038/s41586-022-04434-5

Tyrka, A. R., Price, L. H., Marsit, C., Walters, O. C., & Carpenter, L. L. (2012). Childhood adversity and epigenetic modulation of the leukocyte glucocorticoid receptor: Preliminary findings in healthy adults. *PLoS ONE*, *7*(1), e30148. doi: 10.1371/journal.pone.0030148

Van Bergen, A. H., Verkooijen, S., Vreeker, A., Abramovic, L., Hillegers, M. H., Spijker, A. T., … Boks, M. P. M. (2019). The characteristics of psychotic features in bipolar disorder. *Psychological Medicine*, *49*(12), 2036–2048. doi: 10.1017/S0033291718002854

Van Den Berg, D., De Bont, P. A. J. M., Van Der Vleugel, B. M., De Roos, C., De Jongh, A., Van Minnen, A., & Van Der Gaag, M. (2018). Long-term outcomes of trauma-focused treatment in psychosis. *The British Journal of Psychiatry*, *212*(3), 180–182. doi: 10.1192/BJP.2017.30

Van Den Berg, D. P. G., De Bont, P. A. J. M., Van Der Vleugel, B. M., De Roos, C., De Jongh, A., Van Minnen, A., & Van Der Gaag, M. (2015). Prolonged exposure vs eye movement desensitization and reprocessing vs waiting list for posttraumatic stress disorder in patients with a psychotic disorder: A randomized clinical trial. *JAMA Psychiatry*, *72*(3), 259–267. doi: 10.1001/JAMAPSYCHIATRY.2014.2637

Van Os, J., Pries, L. K., Delespaul, P., Kenis, G., Luykx, J. J., Lin, B. D., … Guloksuz, S. (2020). Replicated evidence that endophenotypic expression of schizophrenia polygenic risk is greater in healthy siblings of patients compared to controls, suggesting gene-environment interaction. The EUGEI study. *Psychological Medicine*, *50*(11), 1884–1897. doi: 10.1017/S003329171900196X

Varese, F., Smeets, F., Drukker, M., Lieverse, R., Lataster, T., Viechtbauer, W., … Bentall, R. P. (2012). Childhood adversities increase the risk of psychosis:

https://doi.org/10.1017/S0033291723003471 Published online by Cambridge University Press

A meta-analysis of patient-control, prospective- and cross-sectional cohort studies. *Schizophrenia Bulletin*, *38*(4), 661–671. doi: 10.1093/SCHBUL/SBS050

Verbanck, M., Chen, C. Y., Neale, B., & Do, R. (2018). Detection of widespread horizontal pleiotropy in causal relationships inferred from Mendelian randomization between complex traits and diseases. *Nature Genetics*, *50*(5), 693–698. doi: 10.1038/s41588-018-0099-7

Vinkers, C. H., Joëls, M., Milaneschi, Y., Kahn, R. S., Penninx, B. W. J. H., & Boks, M. P. M. (2014). Stress exposure across the life span cumulatively increases depression risk and is moderated by neuroticism. *Depression and Anxiety*, *31*(9), 737–745. doi: 10.1002/DA.22262

Vinkers, C. H., Kalafateli, A. L., Rutten, B. P., Kas, M. J., Kaminsky, Z., Turner, J. D., & Boks, M. P. (2015). Traumatic stress and human DNA methylation: A critical review. *Epigenomics*, *7*(4), 593–608. doi: 10.2217/epi.15.11

Vos, T., Flaxman, A. D., Naghavi, M., Lozano, R., Michaud, C., Ezzati, M., … Murray, C. J. L. (2012). Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: A systematic analysis for the Global Burden of Disease Study 2010. *The Lancet*, *380*(9859), 2163–2196. doi: 10.1016/S0140-6736(12)61729-2

Warrier, V., Kwong, A. S. F., Luo, M., Dalvie, S., Croft, J., Sallis, H. M., … Cecil, C. A. M. (2021). Gene–environment correlations and causal effects of childhood maltreatment on physical and mental health: A genetically informed approach. *The Lancet Psychiatry*, *8*(5), 373–386. doi: 10.1016/S2215-0366(20)30569-1

Waxman, R., Fenton, M. C., Skodol, A. E., Grant, B. F., & Hasin, D. (2014). Childhood maltreatment and personality disorders in the USA: Specificity of effects and the impact of gender. *Personality and Mental Health*, *8*(1), 30–41. doi: 10.1002/PMH.1239

Whitfield, C. L., Dube, S. R., Felitti, V. J., & Anda, R. F. (2005). Adverse childhood experiences and hallucinations. *Child Abuse and Neglect*, *29*(7), 797–810. doi: 10.1016/j.chiabu.2005.01.004

Williams, L. M., Debattista, C., Duchemin, A. M., Schatzberg, A. F., & Nemeroff, C. B. (2016). Childhood trauma predicts antidepressant response in adults with major depression: Data from the randomized international study to predict optimized treatment for depression. *Translational Psychiatry*, *6*(5), e799. doi: 10.1038/TP.2016.61

Wing, J. K., Babor, T., Brugha, T., Burke, J., Cooper, J. E., Giel, R., … Sartorius, N. (1990). SCAN: Schedules for clinical assessment in neuropsychiatry. *Archives of General Psychiatry*, *47*(6), 589–593. doi: 10.1001/ARCHPSYC.1990.01810180089012

Wu, S. S., Ma, C. X., Carter, R. L., Ariet, M., Feaver, E. A., Resnick, M. B., & Roth, J. (2004). Risk factors for infant maltreatment: A population-based study. *Child Abuse and Neglect*, *28*(12), 1253–1264. doi: 10.1016/j.chiabu.2004.07.005

Yavorska, O. O., & Burgess, S. (2017). MendelianRandomization: An R package for performing Mendelian randomization analyses using summarized data. *International Journal of Epidemiology*, *46*(6), 1734–1739. doi: 10.1093/ije/dyx034

Zhang, S., Lin, X., Yang, T., Zhang, S., Pan, Y., Lu, J., & Liu, J. (2020). Prevalence of childhood trauma among adults with affective disorder using the Childhood Trauma Questionnaire: A meta-analysis. *Journal of Affective Disorders*, *276*, 546–554. doi: 10.1016/J.JAD.2020.07.001

https://doi.org/10.1017/S0033291723003471 Published online by Cambridge University Press