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Childhood adversity and psychosis: a systematic review of bio-psycho-social mediators and moderators

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Review Article

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Abstract

The association between childhood adversity (CA) and psychosis has been extensively investigated in recent years. An increasing body of research has also focused on the mediating or moderating role of biological and psychological mechanisms, as well as other risk factors that might account for the link between CA and psychosis. We conducted a systematic search of the PsychINFO, Embase, Ovid, and Web of Science databases for original articles investigating the role of genetic vulnerabilities, environmental factors, psychological and psychopathological mechanisms in the association between CA and psychosis up to August 2019. We included studies with individuals at different stages of the psychosis continuum, from subclinical psychotic experiences to diagnosed disorders. From the 28 944 records identified, a total of 121 studies were included in this review. Only 26% of the studies identified met the criteria for methodological robustness. Overall, the current evidence suggests that CA may be associated with psychosis largely independently of genetic vulnerabilities. More consistent and robust evidence supports interaction between early and recent adversities, as well as the mediating role of attachment and mood symptoms, which is suggestive of an affective pathway between CA and psychosis across the continuum from subclinical experiences to diagnosable disorder. This review highlighted numerous methodological issues with the existing literature, including selection bias, heterogeneity of measurement instruments utilised, and lack of control for potential confounders. Future research should address these limitations to more accurately estimate mediation and moderation effects on the CA-psychosis association to inform the development of preventive interventions.

Introduction

The term childhood adversity (CA) is a broad concept which includes child maltreatment (all forms of physical and/or emotional ill-treatment, sexual abuse, neglect or negligent treatment or commercial or other exploitation by an adult), peer victimization (e.g. bullying), experiences of parental loss and separation, war-related trauma, natural disasters, and witnessing domestic or non-domestic violence (Butchart, Putney, Furniss, & Kahane, 2006). CA is a major public health problem as it has been linked with increased mortality and morbidity rates (Gilbert et al., 2008) and with long-lasting adverse consequences for mental health, including the development of depression, post-traumatic stress disorder (PTSD), suicide, and substance misuse (Afifi et al., 2008; Chen et al., 2010; Evans, Hawton, & Rodham, 2004; Infurna et al., 2016; Li, D'Arcy, & Meng, 2016; Norman et al., 2012; Simpson & Miller, 2002; Weich, Patterson, Shaw, & Stewart-Brown, 2009).

Psychotic disorders encompass various categories of severe mental disorders, including non-affective psychosis (e.g. schizophrenia), affective psychosis (e.g. bipolar disorder, mania or major depressive disorder with psychotic features), and other psychotic disorders (due to alcohol or substance use or to general medical conditions). Evidence suggests that psychotic symptoms refer to five broad domains: positive psychotic symptoms (e.g. delusions and hallucinations), negative symptoms (e.g. reduced drive and volition), cognitive alterations (e.g. memory or executive function impairment), depressive symptoms, and mania (van Os & Kapur, 2009). The role of CA in psychosis has recently been established: meta-analyses indicate that childhood maltreatment accounts for up to one-third of the individuals affected with psychosis (Varese et al., 2012) and it is associated with an increased risk for subclinical psychosis and clinically-relevant psychotic disorders, in terms of both onset (Kraan, Velthorst, Smit, de Haan, & van der Gaag, 2015; Mayo et al., 2017; Velikonja, Fisher, Mason, & Johnson, 2015)

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and persistence (Agnew-Blais & Danese, 2016; Trotta et al., 2015b). However, the prevalence of CA among patients with schizophrenia is not significantly greater than in patients with affective psychoses, personality disorders, and depression (Matheson, Shepherd, Pinchbeck, Laurens, & Carr, 2013), suggesting that CA represents a common, rather than specific, risk factor.

A growing body of literature has investigated possible biological and psychological mechanisms, as well as the mediating or moderating role of other risk factors that might account for the link between CA and psychosis. Existing narrative reviews have focused on the effect of CA in individuals with a positive family history of psychosis or with particular genotypes, such as specific variants of *BDNF* or *COMT* (Ayhan, McFarland, & Pletnikov, 2016; Uher, 2014), and described the interaction of CA with cannabis use and adult life events or psychosocial stressors (Beards & Fisher, 2014; Parakh & Basu, 2013; Pelayo-Teran, Suarez-Pinilla, Chadi, & Crespo-Facorro, 2012; van Winkel, Van Nierop, Myin-Germeys, & van Os, 2013; van Zelst, 2008). A role for insecure attachment styles, dysfunctional cognitive schema, reasoning biases, and non-psychotic symptoms has also been evidenced in the literature (Bebbington, 2015; Freeman & Garety, 2014; Rafiq, Campodonico, & Varese, 2018). Moreover, several mediating pathways linking CA with positive psychotic symptoms have been hypothesised, such as internal source monitoring processes and dissociation mediating the association between childhood sexual abuse and auditory verbal hallucinations, and reasoning biases and attachment insecurity mediating the relationship between neglect, parental separation, and persecutory delusions (Bentall et al., 2014). These findings seem suggestive of an affective pathway to psychosis, linking CA to positive psychotic symptoms via psychological mechanisms and affective symptoms (Isvoranu et al., 2017; Myin-Germeys & van Os, 2007).

In light of the growing body of literature in this area, this paper aims to systematically review the potential mediating and moderating factors involved in the relationship between CA and psychosis. For the purpose of this review, the definition of CA was limited to physical, sexual, and emotional abuse, as well as physical and emotional neglect, plus separation and parental death occurring prior to 18 years of age. In order to keep the review focused and maximize the effect of CA on psychosis, we did not include those studies where CA was only represented by indirect forms of abuse and maltreatment (e.g. parental discord, communication deviance, witnessing interpersonal violence) or by peer victimization (e.g. bullying). Informed by previous reviews, which suggested possible moderators and mediators of the CA – psychosis relationship (Ayhan et al., 2016; Beards & Fisher, 2014; Bebbington, 2015; Freeman & Garety, 2014; Parakh & Basu, 2013; Pelayo-Teran et al., 2012; Rafiq et al., 2018; Uher, 2014; van Winkel et al., 2013; van Zelst, 2008), we will investigate the effect of genetic vulnerabilities, and biopsychosocial risk factors (e.g. substance use, adult life events and prolonged social stress), as well as psychological mechanisms (e.g. attachment styles), and non-psychotic symptoms (e. g. depression) as moderators or mediators of the effect of CA on psychosis. We refer to mediation as the mechanisms through which the effect of CA on psychosis may be explained (e.g. depression). We refer to interaction as the way in which the effect of CA on psychosis may be modified by the presence of another factor (e.g. a genetic polymorphism) (Baron & Kenny, 1986; Kraemer, Stice, Kazdin, Offord, & Kupfer, 2001). Therefore, mediation studies help to clarify the biological or psychological mechanisms underpinning the CA-psychosis relationship that may be the targets for preventive intervention, while moderation studies identify the conditions under which an exposure influences a particular outcome and thus indicate vulnerable groups that might benefit most from these interventions (Wu & Zumbo, 2008). Following the continuum model of psychosis (van Os, Linscott, Myin-Germeys, Delespaul, & Krabbendam, 2009) we will include studies of subclinical psychotic phenomena in members of the general population, as well as individuals at different stages of psychosis, i.e. individuals with prodromal symptoms of psychosis or at ultra-high risk (UHR), as well as those experiencing a first episode of psychosis (FEP) and those with non-FEP psychotic disorders. We acknowledge that since the role of CA in psychosis has been increasingly recognised, the literature on potential pathways linking CA with psychosis and moderators of this association has become quite vast, involving numerous possible mediators/moderators, study populations, study designs, and statistical models. This suggests that a summary of the existing literature might be challenging, but at the same time very much needed in order to identify potentially vulnerable populations and pathological mechanisms through which CA links to psychosis and, ultimately, to inform possible preventative and therapeutic interventions.

Methods

Search strategy and selection criteria

A systematic review of the literature on biological, psychological, and social risk factors mediating or moderating the effect of CA on psychotic symptoms and disorders was carried out, following the PRISMA guidelines (Moher, Liberati, Tetzlaff, & Altman, 2009), using the PsychINFO, Embase classic and Embase, Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) databases. Keywords related to (*a*) childhood adversities were connected with each other by the Boolean operator OR, and the same process was repeated for terms related to (*b*) psychosis, (*c*) mediation or moderation, and (*d*) specific mediating/moderating factors; second, the above four strings were connected with each other using the Boolean operator AND. The full list of the search terms used is provided in online Supplementary Tables S1 and S2 and was developed by LS who is an experienced librarian. A systematic database search from 1806 up to the 31st August 2019 was conducted. Database filters were applied to exclude articles published before January 1956, non-human studies and those without abstracts. Conference proceedings were also searched along with the reference lists of the selected papers to identify any additional relevant papers.

Studies were included if (*a*) they were original articles, (*b*) they were published in English, (*c*) they had a case-control, cross-sectional or cohort design, (*d*) they had psychotic disorders, psychotic symptoms, or psychotic/psychosis-like experiences (PLEs) as an outcome, (*e*) one of the exposures was CA (occurring prior to 18 years of age), and (*f*) the mediating or moderating effect of at least one other factor was investigated. A diagnosis of psychotic disorder, schizophrenia, or schizoaffective disorder, based on DSM Criteria, Research Diagnostic Criteria, International Classification of Diseases, Ninth Revision (ICD-9), ICD-10, or psychiatrist or psychologist evaluation was considered eligible. Dimensional measures were defined in terms of individuals in the general population reporting psychotic symptoms, including subclinical psychotic experiences. Studies were excluded if (*a*) they had a

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case report or review design, (*b*) the timing of social adversities was not specified (e.g. the distinction between childhood and adult sexual abuse was not clear), or (*c*) involved a clinical sample that included organic aetiology of psychosis or substance-induced psychosis, with no separate data provided. Studies conducted on the same sample were included only if they analysed the relationship between CA and different mediators/moderators or their joint effect on different outcomes (e.g. psychotic disorder and PLEs).

Studies were critically appraised using a modified version of the quality assessment tool employed in the Trotta *et al.* (2015b) review (see online Supplementary Tables S3–S5). A study was defined as methodologically robust if it achieved a score above 15 for studies assessing the moderating/mediatory effect of genes (maximum score = 21) or above 13 for studies involving only environmental or psychological mediators/moderators (maximum score = 19) corresponding to a 70% cut-off on the quality assessment scale. For papers reporting the findings of different analyses or different studies, separate scores were calculated. Two researchers (LS and AT) independently conducted the quality assessment of each study included (Cohen's $k = 0.898$, $p < 0.001$). Any disagreements (e.g. in score attribution for selection bias, results, and confounders) were resolved via a discussion between LS, AT, and HLF.

Results

From the 28 944 initial records identified by the search, 24 004 articles were selected for the title and abstract screening, and subsequently 943 articles for full-text screening. A total of 114 papers were included in the review (Fig. 1). These 114 papers utilised data from 85 community and clinical samples and are summarised in online Supplementary Tables S6 and S7 by type of sample and the mediating or moderating factor investigated. Since four papers reported the findings of two different studies, and another three analysed both moderation and mediation effects, the total number of appraised studies was 121. Of these studies, 55 analysed moderation, 60 mediation, and three both moderation and mediation. Several studies investigated the effect of more than one moderator or mediating variable.

Methodological appraisal

Only 26.4% (32/121) of the studies satisfied our criteria for robustness (scored over 70% on the quality assessment scale; online Supplementary Tables S4 and S5). The most common limitations were related to selection bias, with 57.9% ($n = 70$) of the studies using unspecified or inadequate selection strategies, and 71.1% ($n = 86$) reporting low or undefined participation rate, thus limiting generalizability. Although the majority of the studies (78.5%, $n = 95$) included at least 100 participants and some large epidemiological studies involved more than 1000 (see online Supplementary Tables S6 and S7), the insufficient sample size could have affected the power of the studies and is particularly an issue for interaction studies (Ma, Thabane, Beyene, & Raina, 2016; van Os, Rutten, & Poulton, 2008). Another main caveat is the quality and heterogeneity of the measurement instruments utilized. Only 11.6% ($n = 14$) of the studies assessed CA using documented evidence (Debost et al., 2017; Paksarian, Eaton, Mortensen, Merikangas, & Pedersen, 2015; Räikkönen et al., 2011; Walker, Cudeck, Mednick, & Schulsinger, 1981; Wicks, Hjern, & Dalman, 2010) or semi-structured interviews (such as the Childhood Experience of Care and Abuse (CECA) interview; Bifulco, Brown, and Harris, 1994), while the majority relied on self-report instruments (most frequently the Childhood Trauma Questionnaire (CTQ): Bernstein et al., 1994, 2003). The latter instruments may be more susceptible to recall bias in clinical populations, although some studies have suggested they are not (Schäfer et al., 2011). Moreover, the quality of information about genetic, environmental, or psychological mediators varied widely across studies, as well as the validity of the outcome measures. In only one-third of the studies (29.8%, $n = 36$), did the assessment of psychosis involve clinical diagnosis or standardized measures.

Most of the studies, including robust prospective (Lataster, Myin-Germeys, Lieb, Wittchen, & van Os, 2012; Mansueto et al., 2019; Ouellet-Morin et al., 2015) and semi-prospective studies (Janssen et al., 2005; Konings et al., 2012; van Nierop et al., 2014), retrospectively assessed CA with self-report measures, and only a few robust studies used register-based information (Debost et al., 2017; Paksarian et al., 2015; Räikkönen et al., 2011; Walker et al., 1981; Wicks et al., 2010), thus preventing inferences about causality from being drawn. A recent meta-analysis found that prospective and retrospective measures of CA may identify different risk pathways to mental illness (Baldwin, Reuben, Newbury, & Danese, 2019). According to a recent study, retrospective self-report measures may be more strongly associated with mental health problems, compared to prospective reports, particularly in relation to affective symptoms (Newbury et al., 2018b). Taking into account the possible effect of affective symptoms on memory bias and the limitation in establishing causality, this study suggested that retrospective measures may be still useful to assess CA in clinical populations.

Of the total, 74% of the studies ($n = 90$) provided information on the distribution of the main exposures and 93.4% ($n = 113$) statistically tested the interaction or mediation model. However, robust statistical tests for interaction (e.g. including interaction terms in linear regressions for multiplicative models, Risk Difference and Interaction Contrast Ratios for additive models) and mediation (e.g. Sobel's test or estimate of the direct and indirect effects) were used by only some of the studies. In total, 74% ($n = 89$) controlled the analysis for potential confounders (though 34.7%, $n = 42$, only adjusted for basic socio-demographic variables), and only half of the interaction studies (55.2%, 32/58) investigated potential gene-environment or environment–environment correlations, suggesting that alternative explanations might have been overlooked.

Given the heterogeneity of the designs employed by the studies included in this review, along with the variety of exposures, mediators, moderators and outcomes analysed, it was not possible to conduct a quantitative synthesis of the findings. Therefore, a narrative review of the studies that met our quality assessment threshold is provided below and a summary of the data extracted is presented in Tables 1 and 2. In addition a visual summary of both robust and less robust studies is provided in Figs 2 and 3.

Interaction studies

Genetic risk factors

The role of genetic factors in the association between CA and psychotic disorders has been investigated in terms of gene–environment correlation (rGE), that is genes influencing exposure to CA, and gene–environment interaction (G × E), that is genes influencing sensitivity to the effects of CA once exposed, using quantitative (e.g. affected relatives) or molecular (e.g. specific

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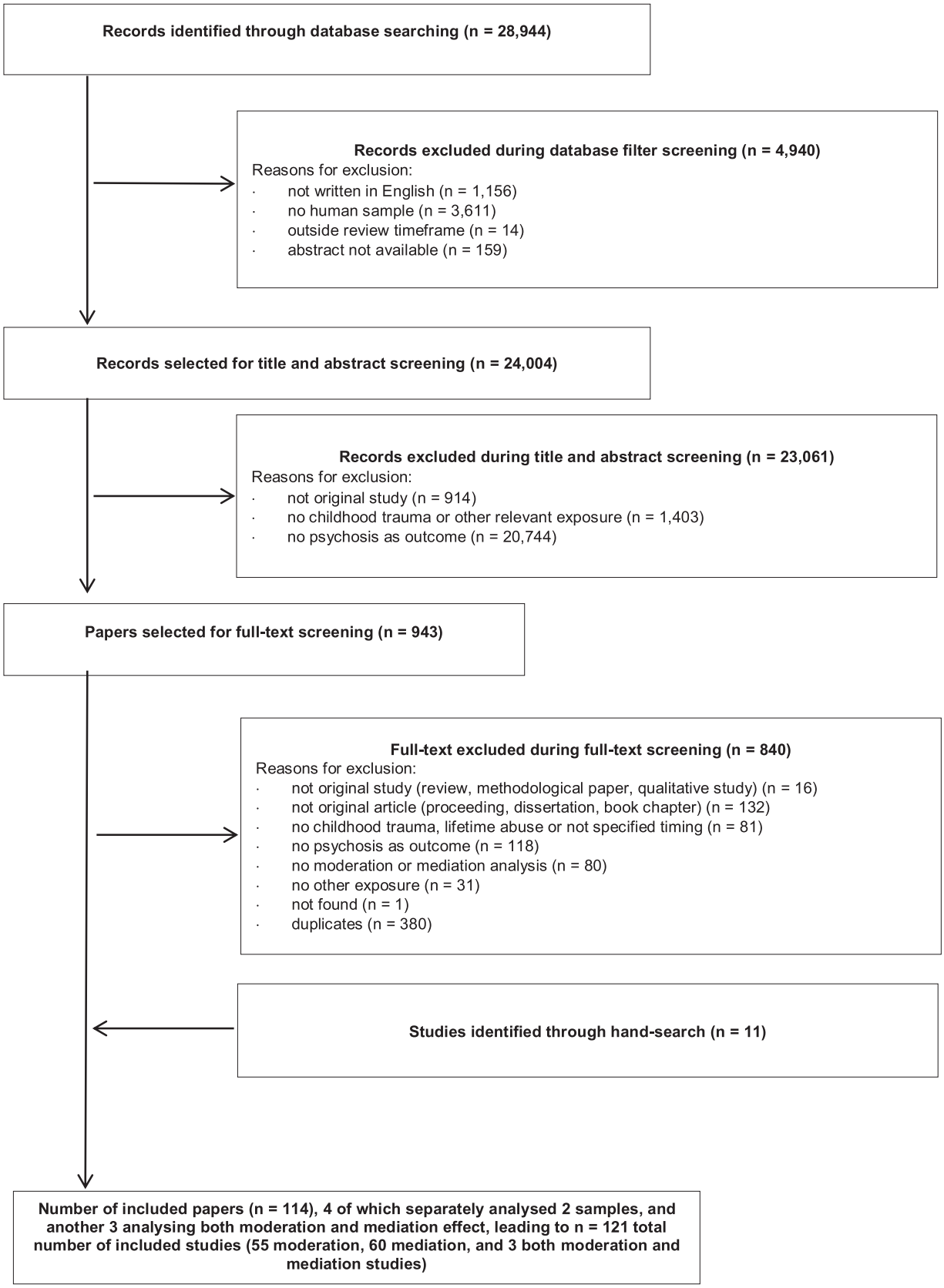

Fig. 1. Flow chart of literature screening.

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Table 1. Summary of the findings of methodologically robust interaction and moderation studies by type of exposure and population

Authors, year, study name, country	Sample	Type of childhood adversity	Measure of childhood adversity	Other exposures	Measure of other exposures	Outcome definition and measure	Confounders	Main findings	Quality score
Genetic risk factors									
General population samples									
(Vinkers et al., 2013) Genetic Risk and Outcome of Psychosis (GROUP) study NETHERLANDS and BELGIUM	*N* = 339	Emotional, physical, and sexual abuse, and physical and emotional neglect (*mean* = 1.33, *range:* 1.0–2.95)	CTQ-SF (Bernstein et al., 2003)	COMT Val/Val *n* = 24, 7%), Met/Val (*n* = 49, 14%), Met/Met (*n* = 27, 8%)		Positive, negative and depressive PLEs (*mean* = 0.38, *range* 0.0–1.29) CAPE (Konings, Bak, Hanssen, van Os, & Krabbendam, 2006)	Gender, age, ethnicity, and family relatedness	After adjusting for the main effect of the three exposures, childhood adversity interacted with COMT genotype ($\beta = -0.15$, $p = 0.010$)	16
(Paksarian et al., 2015) DENMARK	*N* = 985058	Maternal separation, paternal separation, and separation from both parents before age of 15 (proportion of any separation ranging from 2.82 to 25.31%)	Danish CRS (Pedersen, Gøtzsche, Møller, & Mortensen, 2006)	Parental history of psychiatric disorders (approximated maternal history *n* = 60709, 6.16%; approximated paternal history *n* = 54095, 5.49%)	Danish CRS (Pedersen et al., 2006)	Narrow schizophrenia defined as ICD-8 code 295 (excluding 295.79) or ICD-10 (World Health Organization, 1992a; 1992b) code F20 (*n* = 6469) and broad schizophrenia defined as ICD-8 codes 295, 297 and 298.39, or ICD-10 (World Health Organization, 1992a; 1992b) codes F20–F29 (*n* = 11 464) Danish Psychiatric Central Register	Gender, age, birth period, calendar year of follow-up, history of mental disorders in siblings, urbanicity at birth and parental age	Interaction between psychiatric parental history and parental separation on broad schizophrenia was found across all 15 age bands (*LR* test ranging from 14.99, $p = 0.002$ (age 1) to 30.06, $p < 0.001$ (age 15))	15
(Ramsay et al., 2013) Adolescent Brain Development (ABD) study Challenging Times (CT) study IRELAND	*N* = 237	Sexual and physical abuse and witnessing parental violence before the age of 11–13 (ABD study) or 12-15 (CT study) (*n* = 21)	K-SADS (Kaufman et al., 1997)	*COMT rs4680* and *BDNF rs6265* SNPs *COMT Val/Val* (*n* = 65) *v. Val/Met* and *Met/Met* (*n* = 161) *BDNF Val/Val* (*n* = 152) *v. Val/Met* and *Met/Met* (*n* = 70)		Diagnosis of psychotic experience according to DSM-IV (*n* = 37) K-SADS (Kaufman et al., 1997)	Gender, education, and cannabis use	The *BDNF-Val66Met* × childhood adversity interaction was not related to psychotic experiences (*adj.* OR 1.07, 95% CI 0.08–14.92, $p = 0.958$). The *COMT Val158Met* × adversity interaction showed only a trend for significance (*adj.* OR 17.16, 95% CI 0.86–344.25, $p = 0.063$)	16
(Wicks et al., 2010) SWEDEN	*N* = 13163 adoptees *N* = 2.9 million Swedish-born persons (non-adoptees)	Adoptive parental unemployment (adoptee: 2%; Swedish born: 5.6%), single-parent household (adoptee: 3.2%; Swedish born: 9.9%), living in rented house when the participants were 1–5 years old	Swedish population and housing census	Parental history of psychosis (adoptee: *n* = 898, Swedish born: *n* = 2.9 million)	National patient register	Non-affective psychosis (adoptees: *n* = 230; Swedish born; *n* = 24 768) National Patient Register	Gender, age, and the other two socioeconomic indicators	Additive interaction between genetic liability and parental unemployment was marginally significant both in the adoptee (*synergy index* = 3.19, 95% CI 1.01–10.07) and the Swedish born sample (*synergy index* = 1.18, 95% CI 1.03–1.36), while the interactions between genetic liability and single-parenthood was significant only in the Swedish born sample (*synergy index* (adoptee) = 2.63, *95%* CI 0.97–7.11; *synergy index* (Swedish born) = 1.22, 95% CI 1.08–1.3). In both samples, interaction between parental history for psychosis and rented housing was not significant (*synergy index* (adoptee) = 1.16, *95%* CI 0.61–2.23; *synergy index* (Swedish born) = 0.09, *95%* CI 0.98–1.20)	18

(*Continued*)

Table 1. (*Continued.*)

Authors, year, study name, country	Sample	Type of childhood adversity	Measure of childhood adversity	Other exposures	Measure of other exposures	Outcome definition and measure	Confounders	Main findings	Quality score
Non- First-Episode Psychosis (FEP), mixed, or unspecified clinical samples									
(Debost et al., 2017) DENMARK	*N* = 1,699 patients with schizophrenia *N* = 1,681 matched controls	Parental chronic somatic disease (cases: *n* = 373, 22.1%; controls: *n* = 288, 17.1%), parental loss (cases: *n* = 77, 4.5%; controls: *n* = 50, 3.0%, maltreatment or abuse before age of 15 (cases: *n* = 7, 0.4%; controls: *n* = .2, 0.1%)	Danish CRS (Pedersen et al., 2006) Charlson Comorbidity Index (Charlson, Pompei, Ales, & MacKenzie, 1987)	*COMT Val158Met*: *Met/Met* (cases: *n* = 521, 30.7%; controls: *n* = 493, 29.3%) *v. Val/Met* (cases: *n* = 831, 48.9%; controls: *n* = 819, 48.7%) *v. Val/Val* (cases: *n* = 347, 20.4%; controls: *n* = . 369, 22.0%) *MTHFR C677T*: *C/C* (cases: *n* = 839, 49.4%; controls: *n* = 829, 49.3%) *v. C/T* (cases: *n* = 704, 41.4%; controls: *n* = 724, 43.1%) *v. T/T* (cases: *n* = 156, 9.2%; controls: *n* = . 128, 7.6%)		Diagnosis of ICD-8 or ICD-10 schizophrenia Danish Psychiatric Central Register	Gender, age, month of birth, parental history of mental disorders, and PRS	No interaction between childhood adversities and *COMT Val/Val* (*adj. IRR* $p = 0.12$) and *MHTHFR T/T* was found (*adj. IRR* $p = 0.06$). Furthermore, the three-way *COMT* × *MTHFR* × childhood adversities interaction was not significant (*adj. IRR* $p = 0.06$)	18
First-Episode Psychosis (FEP) or Ultra-high risk or genetic high-risk clinical samples									
(Ajnakina et al., 2014) Genetic And Psychosis (GAP) study ENGLAND	*N* = 291 patients with ICD-10 FEP *N* = 218 healthy controls	Parental separation (cases: *n* = 153, 55.4%; controls: *n* = 79, 36.4%), physical (cases: *n* = 63, 22.7%; controls: *n* = 34, 15.7%) and sexual abuse (cases: *n* = 42, 15.0%; controls: *n* = 25, 11.5%) before age of 17	CECA-Q (Bifulco, Bernazzani, Moran, and Jacobs, 2005)	Lifetime cannabis use, frequency of cannabis use, and type of cannabis used *FKBP5 rs1360780* polymorphisms: *CC* (cases: *n* = 118, 40.5%; controls: *n* = 96, 44.0%); *CT* (cases: *n* = 130, 44.7%; controls: *n* = 98, 45.0%); *TT* (cases: *n* = 43, 14.8%; controls: *n* = 24, 11.0%)	CEQ (Barkus, Stirling, Hopkins, & Lewis, 2006) and CEQmv (Di Forti et al., 2009)	Diagnosis of ICD-10 non-organic psychotic disorders SCAN (World Health Organization, 1992a; 1992b)	Gender, age, and genetic ancestry. Interaction between genes and child adversities were adjusted also for lifetime cannabis use, frequency of cannabis use, and type of cannabis used	Parental separation was associated with psychosis and, marginally, with genotype ($\chi^2 = 6.13$, $p = 0.05$), with exclusive effect in the case group, suggesting G E (cases: $\chi^2 = 6.9$, $p = 0.03$; controls: $\chi^2 = 1.06$, $p = 0.59$). The multiplicative interaction between parental separation, cannabis, and *FKBP5* showed an effect only at trend level (*adj.* OR = 0.31, 95% CI 0.09–1.04, $p = 0.06$)	18
(Trotta et al., 2015a) Genetic And Psychosis (GAP) study ENGLAND	*N* = 224 patients with ICD-10 FEP *N* = 256 healthy controls	Parental separation (cases: *n* = 158, 56.0%; controls: *n* = 90, 35.3%) and loss (cases: *n* = 33, 11.7%; controls: *n* = 16, 6.3%), physical (cases: *n* = 65, 22.8%; controls: *n* = 39, 15.3%) and sexual abuse (cases: *n* = 41, 14.4%; controls: *n* = 28, 11.0%) before age of 17	CECA-Q (Bifulco et al., 2005)	Family (cases: *n* = 94, 42.0%; controls: *n* = 70, 28.0%) and parental history (cases: *n* = 65, 29.5%; controls: *n* = 49, 20.8%) of mental disorders and family (cases: *n* = 38, 17.3%; controls: *n* = 12, 5.1%) and parental history (cases: *n* = 28, 12.8%; controls: *n* = 8, 3.4%) of psychosis	FIGS (NIMH Genetics Initiative, 1992)	Diagnosis of ICD-10 psychotic disorders SCAN (World Health Organization, 1992a; 1992b)	Gender, age, ethnicity, and education	Parental separation was the only adversity associated with psychosis. However, no G × E was found between separation and family mental illnesses (*ICR* = – 3.18, 95% CI −6.33 to 0.04, $p = 0.047$) or parental mental illnesses (*ICR* = −3.50, 95% CI −6.60to 0.40, $p = 0.027$). And the same was true for the other adversities. Furthermore, no evidence of rGE was found	15
(Trotta et al., 2016) Genetic And Psychosis (GAP) study ENGLAND	*N* = 285 patients with ICD-10 FEP *N* = 256 healthy controls	Parental separation and loss, physical and sexual abuse, being taken in institutional care and multiple family arrangement before age of 17 (cases: *n* = 82, 28.8%; controls: *n* = 130, 50.8%)	CECA-Q (Bifulco et al., 2005)	Polygenic risk score		Diagnosis of ICD-10 psychotic disorders SCAN (World Health Organization, 1992a; 1992b)	Population stratification, gender, age, and education	No rGE was found. No additive interaction between PRS and childhood adversities (*adj.* *B* = −0.20, S.E. = 0.41, $p = 0.632$)	16

(*Continued*)

Table 1. (*Continued.*)

Authors, year, study name, country	Sample	Type of childhood adversity	Measure of childhood adversity	Other exposures	Measure of other exposures	Outcome definition and measure	Confounders	Main findings	Quality score
(Trotta et al., 2019) Genetic And Psychosis (GAP) study ENGLAND	*N* = 285 patients with ICD-10 FEP *N* = 256 healthy controls	Parental separation and loss, physical and sexual abuse, being taken in institutional care and multiple family arrangement before age of 17	CECA-Q (Bifulco et al., 2005)	*COMT Val158Met*, *AKT1 rs2494732*, and *DRD2 rs1076560* polymorphisms		Diagnosis of ICD-10 psychotic disorders SCAN (World Health Organization, 1992a; 1992b)	Population stratification, gender, age, ethnicity, and education	Childhood adversity was associated with case status, but none of the three polymorphisms was. No evidence of rGE was found. No additive interaction was found either for *COMT Val158Met* (*adj.* RD −0.03, 95% CI −0.09, −0.04), or *AKT1 rs2494732* (*adj.* RD −0.05, 95% CI −0.13, to −0.03), or *DRD2 rs1076560* (*adj. RD* −0.05, 95% CI −0.18–0.07)	15
(Fisher et al., 2014) Aetiology and Ethnicity of Schizophrenia and Other Psychoses (AESOP) study ENGLAND	*N* = 172 patients with ICD-10 FEP *N* = 246 healthy controls	Maternal physical abuse (cases: *n* = 22; controls: *n* = 9)	CECA-Q (Bifulco et al., 2005)	Family and parental history of psychosis, depression, or mania (cases: *n* = 54, 31.4%; controls: *n* = 32, 13.0%)	FIGS (NIMH Genetics Initiative, 1992)	Diagnosis of ICD-10 psychotic disorders SCAN (World Health Organization, 1992a; 1992b)	Gender, age, ethnicity, study centre, and higher paternal social class	Evidence of rGE between maternal physical abuse and family and parental psychosis was found. Furthermore, no interaction was found between maternal physical abuse and either family (*ICR* = 3.51, 95% CI −16.16–23.18, *p* = 0.726) or parental (*ICR* = 1.98, 95% CI −19.48–23.43, *p* = 0.857) history of mental diseases	15
Substance use									
General population samples									
(Houston et al., 2008) National Comorbidity Survey (NCS) USA	*N* = 5,877	Sexual molestation and rape before 16 years of age (*n* = 543, 9.2%)	PTSD module of the CIDI (World Health Organization, 1990)	Any cannabis use before 16 years of age (*n* = 643, 10.9%)	Medication and drugs module of the CIDI (World Health Organization, 1990)	Diagnosis of non-affective psychosis according to DSM-III-R criteria (*n* = 42) SCID-I (First et al., 1996)	Gender, age, lifetime depression, urbanicity, ethnicity, years in education, employment status, and living arrangement	Evidence of both additive (RD 0.025, 95% CI 0.021–0.030, *p* < 0.001) and multiplicative interaction (χ^2 = 100.43, *p* < 0.001) between cannabis and sexual abuse was found	15
(Konings et al., 2012) The Netherlands Mental Health Survey and Incidence Study (NEMESIS-1), NETHERLANDS	*N* = 4,842	Emotional, psychological, physical or sexual abuse before 16 years of age (*range*: 0–3, moderate to severe maltreatment: *n* = 412, 8.5%)	Ad hoc semi-structured interview	Lifetime cannabis use (*n* = 462, 9.5%)	CIDI-L section on substance use (Smeets, 1993)	Any lifetime psychotic symptom assessed using the Psychosis section of the CIDI-L (Smeets, 1993)	Gender, urbanicity, other drug use, age, ethnicity, urbanicity, single marital status, discrimination, and unemployment	Child abuse increased risk for psychotic symptoms in cannabis users (χ^2 = 8.08, *p* = 0.04). Evidence of rEE was found (OR 1.57, 95% CI 1.33–1.86, *p* < 0.001)	16
(Morgan et al., 2014b) South East London Community Health Study (SELCoH) ENGLAND	*N* = 1,680	Childhood physical (*n* = 402, 22.7%) or sexual abuse (*n* = 79, 5.2%)	Ad hoc interview	Lifetime and past year cannabis use	Ad hoc interview	Lifetime psychotic experiences (*n* = 315, 17.9%) PSQ (Bebbington & Nayani, 1995)	Gender, age, ethnicity, education, social class	Evidence of rEE between child abuse and cannabis use was found. Additive interaction with past year cannabis was not significant (*ICR* = 2.40, 95% CI −0.17–4.97, *p* = 0.07)	16
(Vinkers et al., 2013) Genetic Risk and Outcome of Psychosis (GROUP) study NETHERLANDS and BELGIUM	*N* = 339	Emotional, physical, and sexual abuse, and physical and emotional neglect (*mean* = 1.33, *range*: 1.0–2.95)	CTQ-SF (Bernstein et al., 2003)	Past year cannabis use (none: *n* = 292, 86%; less than weekly: *n* = 27, 8%; weekly *n* = 14, 4%; daily: *n* = 7, 2%)	Past year cannabis use assessed using the CIDI (World Health Organization, 1990)	Positive, negative and depressive PLEs (*mean* = 0.38, *range*: 0.0–1.29) CAPE (Konings et al., 2006)	Gender, age, ethnicity, and family relatedness	Neither rEE nor interaction between cannabis and childhood adversities was found	16

(*Continued*)

Table 1. (*Continued.*)

Authors, year, study name, country	Sample	Type of childhood adversity	Measure of childhood adversity	Other exposures	Measure of other exposures	Outcome definition and measure	Confounders	Main findings	Quality score
First-Episode Psychosis (FEP) or ultra-high risk or genetic high-risk clinical samples									
(Ajnakina et al., 2014) Genetic And Psychosis (GAP) study ENGLAND	*N* = 291 patients with ICD-10 FEP *N* = 218 healthy controls	Parental separation (cases: *n* = 153, 55.4%; controls: *n* = 79, 36.4%), physical (cases: *n* = 63, 22.7%; controls: *n* = 34, 15.7%) and sexual abuse (cases: *n* = 42, 15.0%; controls: *n* = 25, 11.5%) before age of 17	CECA-Q (Bifulco et al., 2005)	Lifetime cannabis use, frequency of cannabis use, and type of cannabis used	CEQ (Barkus et al., 2006) and CEQmv (Di Forti et al., 2009)	Diagnosis of ICD-10 non-organic psychotic disorders SCAN (World Health Organization, 1992a; 1992b)	Gender, age, and genetic ancestry	No E × E was found between any of the childhood adversities and any of the cannabis measures	18
(Sideli et al., 2018) Genetic And Psychosis (GAP) study ENGLAND	*N* = 231 patients with FEP *N* = 214 healthy controls	Severe sexual abuse or severe physical abuse before 16 years of age (cases: *n* = 65; controls: *n* = 33)	CECA-Q (Bifulco et al., 2005)	Lifetime cannabis use (cases: *n* = 161; controls: *n* = 124), frequency of cannabis use, and type of cannabis used	CEQ (Barkus et al., 2006) and CEQmv (Di Forti et al., 2009)	Diagnosis of ICD-10 non-organic psychotic disorders OPCRIT (McGuffin, Farmer, & Harvey, 1991)	Gender, ethnicity, education, and family history of mental disorders	Neither rEE nor additive interaction between childhood adversity and lifetime cannabis use (ICR = 1.46, 95% CI −0.54 to 3.46, *p* = 0.152) was found. The specific effect of type and frequency of cannabis use could not be tested due to small frequencies, but there was a suggestion that EE interaction was mainly driven by low potency and low-frequency cannabis	13
Stressful life events and social risk factors									
General population samples									
(Lataster et al., 2012) Developmental Stages of Psychopathology Study (EDSP)	*N* = 3,021	Childhood physical and sexual abuse, parental separation or death, exposure to war, kidnap, imprisonment, natural catastrophe (*n* = 605, 35.1%)	CIDI (World Health Organization, 1990)	Recent life events (>10 life events: *n* = 433, 25.1%)	MEL (Maier-Diewald et al., 1983) CIDI (World Health Organization, 1990)	Psychotic symptoms (*n* = 170, 9.9%) CIDI (World Health Organization, 1990)	Gender, age, cannabis use, urbanicity	rEE between early and recent events was found. Additive interaction was found between childhood adversity and being exposed to more than 10 recent adversities (Wald test $\chi^2 = 4.59$, *p* = 0.032), while for fewer life events the interaction was not significant	17
(Morgan et al., 2014b) South East London Community Health Study (SELCoH) ENGLAND	*N* = 1,680	Childhood physical (*n* = 402, 22.7%) or sexual abuse (*n* = 79, 5.2%)	Ad hoc interview	Cumulative exposure to past year or lifetime life event (*range*: 0–9)	Ad hoc interview	Lifetime psychotic experiences (*n* = 315, 17.9%) PSQ (Bebbington & Nayani, 1995)	Gender, age, ethnicity, education, social class	Evidence of rEE between child abuse and stressful events. Additive interaction was found between any child abuse and lifetime exposure to life events (*ICR* = 0.21, 95% CI 0.05–0.38, *p* = 0.01), with a stronger interaction with past year life events (ICR = 0.56, 95% CI 0.08–1.05, *p* = 0.02)	16
(Newbury et al., 2018a, 2018b) Environmental Risk (E-Risk) Longitudinal Twin Study ENGLAND & WALES	*N* = 2,063	Personal experiences of violent crime victimization before age of 18 (*n* = 398, 19.3%)	JVQ-R2 (Finkelhor, Hamby, Turner, & Ormod, 2011)	Neighbourhood social adversity (neighbourhood characterized by both low social cohesion and high neighbourhood disorder, *n* = 772, 35.9%)	Ad hoc interview (Odgers et al., 2009)	Any psychotic symptom (*n* = 59, 2.9%) PQ-B (Loewy, Pearson, Vinogradov, Bearden, & Cannon, 2011) and ad hoc interview (Polanczyk et al., 2010)	Family psychiatric history, family SES, maternal psychotic symptoms, adolescent alcohol and cannabis dependence, childhood psychotic symptoms, and neighbourhood – level deprivation	Evidence of rEE between exposure to violent crime and neighbourhood social adversity was found. The cumulative risk associated with violent crime victimisation and neighbourhood social adversity was greater than the risk related to either type of events (*adj.* OR 4.86, 95% CI 3.28–7.20, *p* < 0.001), but the E × E interaction was not significant (*ICR* = 1.81, 95% CI = −0.03 to 3.65, *p* = 0.054)	16

(*Continued*)

Table 1. (*Continued.*)

Authors, year, study name, country	Sample	Type of childhood adversity	Measure of childhood adversity	Other exposures	Measure of other exposures	Outcome definition and measure	Confounders	Main findings	Quality score
(Ouellet-Morin et al., 2015) Environmental Risk (E-Risk) Longitudinal Twin Study ENGLAND & WALES	*N* = 1,052	Emotional, physical, and sexual abuse and emotional and physical neglect (*n* = 235, 24.9%)	CTQ-SF (Bernstein et al., 2003)	Intimate partner violence (*n* = 389, 39.8%)	CTS-R (Straus, 1990)	Any psychotic symptom (*n* = 45, 4.7%) in context of DSM-IV depressive disorder (*n* = 94, 9.8%) DIS (Robins, Cottler, & Buckolz, 1996) and PSQ (Bebbington & Nayani, 1995)	Socio-economic deprivation (composite index of family income, education, and social class), young motherhood, substance abuse, and antisocial personality	Evidence of rEE between child abuse and partner violence was found. The cumulative risk associated with childhood maltreatment and partner violence was greater than the risk related to either type of events (*adj.* OR 0.31, 95% CI 0.16–0.62)	14
(Räikkönen et al., 2011) Helsinki Birth Cohort Study FINLAND	*N* = 12747	Separation from parents (*n* = 1719)	Finnish National Archives' register	Socio-economic status (SES)	Finnish National Archives' register	ICD-10 non-affective psychoses (*n* = 311) Finnish Hospital Discharge and Causes of Death Registers	Gender, year of birth	rEE was found between parental separation and low SES ($p < 0.001$). Neither parental separation, nor low SES was associated to psychotic disorders. The parental separation × low SES interaction was not significant (*adj.* HR = 1.05, 95% CI 0.69–1.61, $p = 0.81$), but separated children were at higher risk for psychosis if belonging from an upper SES (adj. HR = 2.64, 95% CI 1.13–6.13, $p = 0.025$)	14
First-Episode Psychosis (FEP) or ultra-high risk or genetic high-risk clinical samples									
(Gayer-Anderson et al., 2015) Aetiology and Ethnicity of Schizophrenia and Other Psychoses (AESOP) study ENGLAND	*N* = 202 patient with FEP *N* = 266 healthy controls	Severe sexual and physical abuse before 16 years of age (*v.* non-severe or none)	CECA-Q (Bifulco et al., 2005)	Ideal and perceived levels of practical (cases: *mean* = 9.92, S.D. = 2.36; controls: *mean* = 10.83, S.D. = 2.02) and emotional support (cases: *mean* = 10.61, S.D. 2.57; controls: *mean* = 11.48, S.D. = 1.93) Number of significant others (6–7 significant others (SO): cases: *n* = 68, 33.6%; controls: *n* = 109, 41%) Discrepancy score between ideal and perceived support	SOS (Power, Champion, & Aris, 1988)	ICD-10 diagnosis of psychotic disorders (*n* = 202) SCAN (World Health Organization, 1992a; 1992b)	Gender, age ethnicity, education, current employment, parental history of mental illness, study centre	The impact of physical abuse on odds of psychosis was modified by the number of significant others, with a higher risk for those with poor social network (5 or more SO: *adj.* OR 0.99, 95% CI 0.42–2.36; less than 5 SO: *adj.* OR 3.24, 95% CI 1.42–7.38, LR test $\chi^2 = 3.90$, $p = 0.048$)	13
(Morgan et al., 2014a) Aetiology and Ethnicity of Schizophrenia and Other Psychoses (AESOP) study ENGLAND	*N* = 390 patients with FEP *N* = 391 healthy controls	Parental separation (cases: *n* = 160, 41%; controls: *n* = 80, 20.4%) or death (cases: *n* = 30, 7.7%; controls: *n* = 14, 3.6%) before age of 16	MRC Socio demographic schedule (Mallett, 1997)	Adult disadvantage (five indicators (i.e. unemployment, living alone, no relationship, and limited social network, renting house): cases: *n* = 39, 10.1%; controls *n* = 4, 1%) No education (cases: *n* = 24, 32%; controls: *n* = 71, 18.3%)	MRC Socio-demographic schedule (Mallett, 1997) RSES (Rosenberg, 1989)	ICD-10 diagnosis of psychotic disorders (*n* = 390) SCAN (World Health Organization, 1992a; 1992b)	Gender, age, ethnicity, study centre, and parental history of psychosis.	Additive interaction was found between early separation and adult disadvantage (*ICR* = 4.30, 95% CI 0.66–7.94, $p = 0.021$), but not between early separation and no education	15

(*Continued*)

Table 1. (*Continued.*)

Authors, year, study name, country	Sample	Type of childhood adversity	Measure of childhood adversity	Other exposures	Measure of other exposures	Outcome definition and measure	Confounders	Main findings	Quality score
Psychological and psychopathological mechanisms									
Non- First-Episode Psychosis (FEP), mixed, or unspecified clinical samples									
(Mansueto et al., 2019) Genetic Risk and Outcome of Psychosis (GROUP) study NETHERLANDS	*N* = 1,119 patients with non-affective psychotic disorder	Childhood neglect (*mean* = 1.86, S.D. = 0.63) and abuse (*mean* = 1.43, S.D. = 0.52)	CTQ-SF (Bernstein et al., 2003)	Mentalizing abilities (*mean* = 17.71, S.D. = 2.73)	Hinting task (Corcoran et al., 1995)	Positive (*mean* = 13.62, S.D. = 6.58), negative (*mean* = 14.19, S.D. = 6.19), disorganization (*mean* = 16.16, S.D. = 6.29), excitement (*mean* = 11.70, S.D. = 3.89), and emotional distress symptoms (*mean* = 15.49, S.D. = 5.63) PANSS (Kay et al., 1987)	Gender, age, and cannabis use	Mentalizing abilities did not moderate the effect of either childhood neglect or abuse on psychotic symptoms	13

Adj, adjusted; AVH, Auditory Verbal Hallucinations; BDNF, Brain-Derived Neurotrophic Factor; CI, confidence interval; COMT, Catechol O-methyltransferase; DIS, Diagnostic Interview Schedule; EPP, Extended Psychosis Phenotype; DRD, Dopamine Receptor D; DSM, Diagnostic and Statistical Manual of mental disorders; E × E, Environment × Environment interaction; FEP, First Episode of Psychosis; FKBP5, Binding protein 5; G × E, Gene × Environment interaction; ICD, International Classification of Disease; ICR, Interaction Contrast Ratio; IQ, Intellectual Quotient; JVQ, Juvenile Victimization Questionnaire; LR, Likelihood Ratio; MRC, Medical Research Council; MTHFR, methylenetetrahydrofolate reductase; OR, odds ratio; PD, Psychotic Disorder; PLEs, Psychotic-Like Experiences; PRS, polygenic risk score; PTSD, Post-Traumatic Stress Disorder; RD, Risk Difference; rEE, Environment–Environment correlation; rGE, Gene–Environment correlation; S.D., Standard Deviation; S.E., Standard Error; SES, Socio-economic status.

AAQ, Adult Attachment Questionnaire; ASI, Attachment Style Interview; BPRS, Brief Psychiatric Rating Scale; CAARMS, Comprehensive Assessment of At-Risk Mental States; CAPE, Community Assessment of Psychic Experiences; CAPPS, Current and Past Psychopathology Scale; CECA, Childhood Experience of Care and Abuse; CECA-Q, Childhood Experience of Care and Abuse Questionnaire; CEQ, Cannabis Experiences Questionnaire; CEQmv, Cannabis Experiences Questionnaire modified version; CIDI, Composite International Diagnostic Interview; CIS-R, Clinical Interview Schedule – Revised; CRS, Danish Civil Registration System; CTQ, Childhood Trauma Questionnaire; CTQ-SF, Childhood Trauma Questionnaire – short form; CTS-R, Conflict Tactics Scale-Form R; FIGS, Family Interview for Genetic Studies; K-SADS, Schedule for Affective Disorders and Schizophrenia for School-Age Children; MEL, Munich Interview for the Assessment of Life Events and Conditions; OPCRIT, Operational Criteria System; PANSS, Positive and Negative Syndrome Scale; PBI, Parental Bonding Instrument; PSE, Present State Examination; PQ-B Prodromal Questionnaire – Brief version; PSQ, Psychosis Screening Questionnaire; RSES, Rosenberg self-esteem scale; SCAN, Schedule for Assessment in Neuropsychiatry; SCID-I, Structured Clinical Interview for the DSM Axis I disorder; SOS, Significant Others Scale; UM-CIDI, University of Michigan Composite International Diagnostic Interview.

Note: when not reported in the paper, frequencies were calculated from percentages. References of measurement instruments are provided in the Supplementary Materials.

Table 2. Summary of the findings of methodologically robust mediation studies by type of exposure and population

Authors, year, study name, country	Sample	Type of childhood adversity	Measure of childhood adversity	Other exposures	Measure of other exposures	Outcome definition and measure	Confounders	Main findings	Quality score
Substance use									
General population samples									
(van Nierop et al., 2014) The Netherlands Mental Health Survey and Incidence Study 2 (NEMESIS-2) NETHERLANDS	*N* = 6,646	Emotional neglect, bullying, psychological, physical, or sexual abuse before age 16 years of age (cumulative score: controls: *mean* = 1.4, S.D. = 2.9; EPP: *mean* = 3.9, S.D. = 4.75; PD: *mean* = 5.8, S.D. = 4.8)	Ad hoc interview	Frequency of lifetime cannabis use (controls: *mean* = 0.4, S.D. = 1.0; EPP: *mean* = 0.7, S.D. = 1.6; PD: *mean* = 1.2, S.D. = 2.0)	CIDI 3.0 (Kessler, 1994)	Severity of psychotic experiences in individuals with lifetime psychotic symptoms (EPP: *n* = 384; PD: *n* = 43) Ad hoc interview SCID-I for DSM-IV (First et al., 1996)	Gender, age	Childhood adversity predicted cannabis use ($\beta = 0.13$, $p < 0.001$). Cannabis use did not show any mediation effect	16
Stressful life events and social risk factors									
General population samples									
(Shevlin et al., 2015) Adult Psychiatric Morbidity Survey (APMS) ENGLAND	*N* = 7,403	Physical abuse (*n* = 254, 3.4%), sexual touching and intercourse, (*n* = 561, 7.6%), or both (*n* = 97, 1.3%) before 16 years of age	Ad hoc questionnaire (Domestic violence and abuse questionnaire)	Loneliness (*mean* = 1.64, S.D. = 0.90)	Single item from the Social Functioning Questionnaire (Tyrer et al., 2005)	Diagnosis of psychotic disorders according to ICD-10 (definite psychosis *n* = 23). PSQ (Bebbington & Nayani, 1995) and SCAN (World Health Organization, 1992a; 1992b)	Gender, age, education, ethnicity, cannabis use, and adult victimization	Loneliness partially mediated the effect of combined physical and sexual abuse on psychosis (OR 3.81 95% CI 1.07–13.61; indirect effect: $\beta = 0.722$, S.E. = 0.24, $p < 0.001$)	14
(Bhavsar et al., 2019) South East London Community Health Study (SELCoH) ENGLAND	*N* = 1,698	Childhood physical or sexual abuse (*n* = 429)	Ad hoc interview	Cumulative exposure to past year violent (range 0–4) and non-violent life event (0–3)	Ad hoc interview	Lifetime psychotic experiences (*n* = 306, 17.9%) PSQ (Bebbington & Nayani, 1995)	Gender, age ethnicity, education, social class	Childhood abuse showed both a direct (*adj.* OR 1.58, 95% CI 1.19–2.1) and indirect effect via life events (*adj.* OR 1.51, 95% CI 1.32–1.72). Partial mediation explained 47% of the total effect (33% via violent life events)	16
(van Nierop et al., 2014) The Netherlands Mental Health Survey and Incidence Study 2 (NEMESIS-2) NETHERLANDS	*N* = 6,646	Emotional neglect, bullying, psychological, physical, or sexual abuse before age 16 years of age (cumulative score: controls: *mean* = 1.4, S.D. = 2.9; EPP: *mean* = 3.9, S.D. = 4.75; PD: *mean* = 5.8, S.D. = 4.8)	Ad hoc interview	Social defeat (controls: *mean* = 0.8, S.D. = 1.8; EPP: *mean* = 2.0, S.D. = 2.6; PD: *mean* = 4.3, S.D. = 2.9) Affect dysregulation (controls: *mean* = 2.7, S.D. = 5.3; EPP: mean = 6.5, S.D. = 7.3; PD: *mean* = 12.4, S.D. = 7.4)	CIDI 3.0 (Kessler, 1994)	Severity of psychotic experiences in individuals with lifetime psychotic symptoms (EPP: *n* = 384; PD: *n* = 43) Ad hoc interview SCID-I for DSM-IV (First et al., 1996)	Gender, age, and cannabis use	Childhood adversity predicted social defeat ($\beta = 0.33$, $p < 0.001$) and affective dysregulation ($\beta = 0.30$, $p < 0.001$). Social defeat mediated 86.6% of the effect of childhood adversity on psychotic experiences in individuals with psychotic disorders (indirect effect: $\beta = 0.04$, $p = 0.004$). Social defeat and affect dysregulation together mediated 80.4% of the effect of childhood adversity on psychotic experiences in individuals with EPP. Specifically, social defeat alone mediated 30.7% of the effect ($\beta = 0.03$, $p = 0.081$), while the remaining 49.7% was mediated by social defeat via affective dysregulation ($\beta = 0.04$, $p = 0.002$).	16

(*Continued*)

Table 2. (*Continued.*)

Authors, year, study name, country	Sample	Type of childhood adversity	Measure of childhood adversity	Other exposures	Measure of other exposures	Outcome definition and measure	Confounders	Main findings	Quality score
First-Episode Psychosis (FEP) or ultra-high risk or genetic high-risk clinical samples									
(Morgan et al., 2014a) Aetiology and Ethnicity of Schizophrenia and Other Psychoses (AESOP) study ENGLAND	*N* = 390 patients with FEP *N* = 391 healthy controls	Parental separation (cases: *n* = 160, 41%; controls: *n* = 80, 20.4%) or death (cases: *n* = 30, 7.7%; controls: *n* = 14, 3.6%) before age of 16	MRC Socio demographic Schedule (Mallett, 1997)	Adult disadvantage (i.e. unemployment, living alone, no relationship and limited social network, renting house) (five indicators: cases: *n* = 39, 10.1%; controls *n* = 4, 1%) No education (cases: *n* = 24, 32%; controls: *n* = 71, 18.3%)	MRC Socio demographic Schedule (Mallett, 1997)	ICD-10 diagnosis of psychotic disorders (*n* = 390) SCAN (World Health Organization, 1992a; 1992b)	Gender, age, ethnicity, study centre, and parental history of psychosis.	Adult social disadvantages (indirect effect: *adj.* OR 1.16, 95% CI 0.99–1.37), no qualification (adj. OR 2.38, 95% CI 1.34–4.20), and both (*adj.* OR 1.57, 95% CI 1.20–2.06) mediated the effect of parental separation on case status, accounting all together for 75% of the variance.	15
Psychological and psychopathological mechanisms									
General population samples									
(McCarthy-Jones 2018) Adult Psychiatric Morbidity Survey (APMS) ENGLAND	*N* = 7403	Penetrative sexual abuse (*n* = 126, 2.2%) and physical abuse (*n* = 207, 3.6%)	Ad hoc questionnaire (Domestic violence and abuse questionnaire)	Anxiety (*mean* = 0.86, S.D. = 1.56) Depression (*mean* = 0.63, S.D. = 1.49) Obsessions (*mean* = 0.16, S.D. 0.66) and compulsions (*mean* = 0.11, S.D. = 0.56) PTSD (*mean* = 0.50, S.D. = 1.43)	CIS-R (Lewis et al., 1992) Trauma Screening Questionnaire (Brewin et al., 2002)	AVH (*n* = 49, 0.8%) PSQ (Bebbington & Nayani, 1995)	Gender, age, ethnicity, education, IQ, childhood physical abuse, and depression	No effect of physical abuse on AVH was found. Sexual abuse had both a direct effect (*adj.* OR 5.81, 95% CI 2.53–13.33) on AVH and indirect effects via PTSD symptoms (*adj.* OR 1.11, 95% CI 1.00–1.29) and compulsions (adj. OR 1.10, 95% CI 1.01–1.28). No mediation via depression was found when anxiety was included as a covariate	13
(Janssen et al., 2005) The Netherlands Mental Health Survey and Incidence Study (NEMESIS) NETHERLANDS	*N* = 4,045	Emotional, psychological, physical or sexual abuse before 16 years of age (*n* = 369, 10%)	Ad hoc semi-structured interview (Janssen et al., 2004)	T0 mother's and father's care (range: 0–36) and overprotection (range 0–36)	PBI (Parker, Tupling & Brown, 1979)	Any T2 psychotic symptom (broad psychosis, *n* = 38) and pathology-level psychotic symptoms (narrow psychosis: *n* = 10) BPRS (Overall & Gorham, 1962)	For broad psychosis: age and any drug use; for narrow psychosis: age, any drug use and any baseline DSM-III-R diagnosis	Childhood adversity was associated with parental care and overprotection. The effect of lower care on broad (*adj.* OR 1.36, 95% CI 0.87–2.12) and narrow psychosis (*adj.* OR 1.59, 95% CI 0.54–4.62) became non-significant when childhood adversity was included in the model (broad: OR 3.40, 95% CI 1.53–7.56; narrow: OR 8.50, 95% CI 1.85–39.02)	15
(van Nierop et al., 2014) The Netherlands Mental Health Survey and Incidence Study 2 (NEMESIS-2) NETHERLANDS	*N* = 6,646	Emotional neglect, bullying, psychological, physical, or sexual abuse before age 16 years of age (cumulative score: controls: *mean* = 1.4, S.D. = 2.9; EPP: *mean* = 3.9, S.D. = 4.75; PD: *mean* = 5.8, S.D. = 4.8)	Ad hoc interview	Social defeat (controls: *mean* = 0.8, S.D. = 1.8; EPP: *mean* = 2.0, S.D. = 2.6; PD: *mean* = 4.3, S.D. = 2.9) Affect dysregulation (controls: *mean* = 2.7, S.D. = 5.3; EPP: mean = 6.5, S.D. = 7.3; PD: *mean* = 12.4, S.D. = 7.4)	CIDI 3.0 (Kessler, 1994)	Severity of psychotic experiences in individuals with lifetime psychotic symptoms (EPP: *n* = 384; PD: *n* = 43) Ad hoc interview SCID-I for DSM-IV(First et al., 1996)	Gender, age, and cannabis use	Childhood adversity predicted social defeat ($\beta = 0.33$, $p < 0.001$) and affective dysregulation ($\beta = 0.30$, $p < 0.001$). Social defeat mediated 86.6% of the effect of childhood adversity on severity of psychotic experiences in individuals with psychotic disorders (indirect effect: $\beta = 0.04$, $p = 0.004$). Social defeat and affect dysregulation together mediated 80.4% of the effect of childhood adversity on the severity of	16

								psychotic experiences in individuals with EPP. Specifically, social defeat alone mediated 30.7% of the effect on psychosis ($\beta = 0.03$, $p = 0.081$), while the remaining 49.7% was mediated by social defeat via affective dysregulation ($\beta = 0.04$, $p = 0.002$).	
(Sitko et al., 2014) National Comorbidity Survey (NCS) USA	$N = 5{,}877$	Witnessing injury or killing ($n = 519$, 8.8%), rape ($n = 148$, 2.5%), sexual molestation ($n = 371$, 6.3%), physical assault ($n = 178$, 3.0%), physical abuse ($n = 246$, 4.2%), neglect ($n = 164$, 2.8%), and being held or threatened with a weapon ($n = 236$, 4.0%) before age of 16	Life events history module of the UM-CIDI (Wittchen & Kessler, 1994)	Current attachment stile: secure, avoidant or anxious (*range:* 0–4) Severity of lifetime major depression (*range*: 0–9)	AAQ (Hazan & Shaver, 1987) Sadness module of the UM – CIDI (Wittchen & Kessler, 1994)	Lifetime paranoia (*range*: 0–3) and hallucinations (*range*: 0–4) Belief and experience module of the UM-CIDI (Wittchen & Kessler, 1994)	Gender, age	Effect of neglect on paranoia was mediated by anxious and avoidant attachment ($\beta = 0.047$, 95% CI 0.010–0.252). Effect of being held or threaten with a weapon on paranoia was partially mediated by avoidant attachment ($\beta = 0.083$, 95% CI 0.101–0.257). Indirect effect of rape on paranoia ($\beta = 0.020$, 95% CI 0.053–0.15) and hallucinations ($\beta = 0.088$, 95% CI 0.171–0.523) was mediated by anxious attachment. Depression decreased the mediating effect of attachment insecurity on the relationship between childhood abuse and paranoia and hallucinations	15
(Sheinbaum et al., 2015) SPAIN	$N = 214$	Parental antipathy (*mean* = 1.57, S.D. = 0.91) and role reversal (*mean* = 1.59, S.D. = 0.87)	CECA (Bifulco et al., 1994)	Attachment insecurity (enmeshed: $n = 12$, 5.6%; fearful: $n = 34$, 15.9%; angry-dismissive: $n = 14$, 6.5%; withdrawn: $n = 31$, 14.5%)	ASI (Bifulco, Moran, Ball, & Lillie, 2002)	Positive (*mean* = 1.21, S.D. = 2.69) and negative subclinical symptoms (*mean* = 1.51, S.D. = 2.39) CAARMS (Yung et al., 2005)	Depressive symptoms	Angry-dismissive attachment partially mediated the effect of parental antipathy on positive symptoms (*Raw Parameter Estimate* = 0.126, S.E. = 0.076, $p < 0.05$)	13
Non- First-Episode Psychosis (FEP), mixed, or unspecified clinical samples									
(Mansueto et al., 2019) Genetic Risk and Outcome of Psychosis (GROUP) study NETHERLANDS	$N = 1$, 119 patients with non-affective psychotic disorders	Childhood neglect (*mean* = 1.86, S.D. = 0.63) and abuse (*mean* = 1.43, S.D. = 0.52)	CTQ-SF (Bernstein et al., 2003)	Mentalizing abilities (*mean* = 17.71, S.D. = 2.73)	Hinting Task (Corcoran, Mercer, & Frith, 1995)	Positive (*mean* = 13.62, S.D. = 6.58), negative (*mean* = 14.19, S.D. = 6.19), disorganization (*mean* = 16.16, S.D. = 6.29), excitement (*mean* = 11.70, S.D. = 3.89), and emotional distress (*mean* = 15.49, S.D. = 5.63) PANSS (Kay et al., 1987)	Gender, age, and cannabis use	Mentalizing abilities were negatively associated with childhood neglect (but not abuse) and with psychotic symptoms. Mentalization partially mediated the effect of childhood neglect on negative symptoms (total effect: 1.01, 95% CI 0.27–0.75; indirect effect: 0.17, 95% CI 0.02–0.40; *adj.* $R^2 = 0.07$, $p < 0.001$), disorganization (total effect: 1.29, 95% CI 0.46–1.95; indirect effect: 0.23, 95% CI 0.03–0.49; *adj.* $R^2 = 0.11$, $p < 0.001$); and excitement (total effect: 0.76, 95% CI 0.32–1.21; indirect effect: 0.05, 95% CI 0.009–0.14; *adj.* $R^2 = 0.55$, $p < 0.001$). When the analyses were run separately for men and women, the mediation was only evident in the men sample	13

(*Continued*)

Table 2. (*Continued.*)

Authors, year, study name, country	Sample	Type of childhood adversity	Measure of childhood adversity	Other exposures	Measure of other exposures	Outcome definition and measure	Confounders	Main findings	Quality score
First-Episode Psychosis (FEP) or ultra-high risk or genetic high-risk clinical samples									
(Morgan et al., 2014a) etiology and Ethnicity of Schizophrenia and Other Psychoses (AESOP) study ENGLAND	*N* = 390 patients with FEP *N* = 391 healthy controls	Parental separation (cases: *n* = 160, 41%; controls: *n* = 80, 20.4%) or death (cases: *n* = 30, 7.7%; controls: *n* = 14, 3.6%) before age of 16	MRC Socio demographic Schedule (Mallett, 1997)	Self-esteem (cases: mean 36.2, s.d. 7.8; controls: mean 39.2, s.d. 7.6)	RSES (Rosenberg, 1989)	ICD-10 diagnosis of psychotic disorders (*n* = 390) SCAN (World Health Organization, 1992a; 1992b)	Gender, age, ethnicity, study centre, and parental history of psychosis.	Self-esteem did not mediate the effect of parental separation on psychosis	15
(Walker et al., 1981) Danish high-risk project DENMARK	*N* = 207 individuals at CHR for schizophrenia (*n* = 15 affected with schizophrenia)	Parental separation before age of 10	Ad hoc interview (Schulsinger, 1976) and Danish population register	Being under institutional care before age of 10	Ad hoc interview (Schulsinger, 1976) and Danish population register	Paranoia/ autistic traits, thought disorders, hebephrenic traits, and borderline delusions or hallucinations CAPPS (Endicott & Spitzer, 1972) and PSE (Wing & Cooper, 1974)	None	Among males, maternal separation was directly related to lower levels of hebephrenic traits. Maternal separation was related to institutional care in both genders, but paternal separation only in males. Furthermore, only among males there was a significant path from parental separation to institutional care to thought disorders (*path coefficient* = 0.80, $p < 0.01$), hebephrenic traits (*path coefficient* = 0.55, $p < 0.01$), and borderline delusions or hallucinations (*path coefficient* = 0.55, $p < 0.01$). No relation was found with paranoia/autistic traits	16

Adj, adjusted; AVH, Auditory Verbal Hallucinations; BDNF, Brain-Derived Neurotrophic Factor; CI, confidence interval; COMT, Catechol O-methyltransferase; DIS, Diagnostic Interview Schedule; EPP, Extended Psychosis Phenotype; DRD, Dopamine Receptor D; DSM, Diagnostic and Statistical Manual of mental disorders; E × E, Environment × Environment interaction; FEP, First Episode of Psychosis; FKBP5, Binding protein 5; G × E, Gene × Environment interaction; ICD, International Classification of Disease; ICR, Interaction Contrast Ratio; IQ, Intellectual Quotient; JVQ, Juvenile Victimization Questionnaire; LR, Likelihood Ratio; MRC, Medical Research Council; MTHFR, methylenetetrahydrofolate reductase; OR, odds ratio; PD, Psychotic Disorder; PLEs, Psychotic-Like Experiences; PRS, polygenic risk score; PTSD, Post-Traumatic Stress Disorder; RD, Risk Difference; rEE, Environment–Environment correlation; rGE, Gene–Environment correlation; s.d., Standard Deviation; s.e., Standard Error; SES, Socio-economic status.

AAQ, Adult Attachment Questionnaire; ASI, Attachment Style Interview; BPRS, Brief Psychiatric Rating Scale; CAARMS, Comprehensive Assessment of At-Risk Mental States; CAPE, Community Assessment of Psychic Experiences; CAPPS, Current and Past Psychopathology Scale; CECA, Childhood Experience of Care and Abuse; CECA-Q, Childhood Experience of Care and Abuse Questionnaire; CEQ, Cannabis Experiences Questionnaire; CEQmv, Cannabis Experiences Questionnaire modified version; CIDI, Composite International Diagnostic Interview; CIS-R, Clinical Interview Schedule – Revised; CRS, Danish Civil Registration System; CTQ, Childhood Trauma Questionnaire; CTQ-SF, Childhood Trauma Questionnaire – short form; CTS-R, Conflict Tactics Scale-Form R; FIGS, Family Interview for Genetic Studies; K-SADS, Schedule for Affective Disorders and Schizophrenia for School-Age Children; MEL, Munich Interview for the Assessment of Life Events and Conditions; OPCRIT, Operational Criteria System; PANSS, Positive and Negative Syndrome Scale; PBI, Parental Bonding Instrument; PSE, Present State Examination; PQ-B, Prodromal Questionnaire – Brief version; PSQ, Psychosis Screening Questionnaire; RSES, Rosenberg self-esteem scale; SCAN, Schedule for Assessment in Neuropsychiatry; SCID-I, Structured Clinical Interview for the DSM Axis I disorder; SOS, Significant Others Scale; UM-CIDI, University of Michigan Composite International Diagnostic Interview.

Note: when not reported in the paper, frequencies were calculated from percentages. References of measurement instruments are provided in the Supplementary Materials.

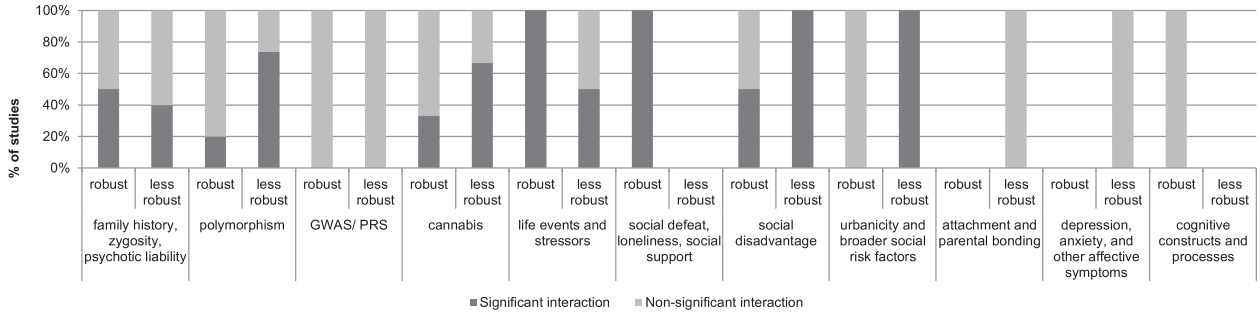

Fig. 2. Findings from robust and less robust moderation/interaction studies. The figure shows the percentage of significant ($p < 0.05$) and non-significant interaction studies reported by more robust and less robust studies, by type of risk factor. GWAS, genome-wide association study. PRS, polygenic risk score.

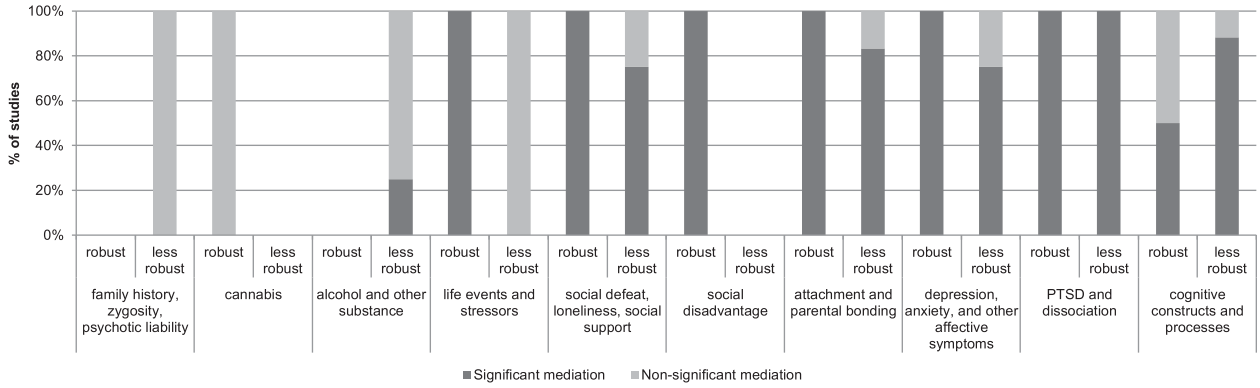

Fig. 3. Findings from robust and less robust mediation studies. The figure shows the percentage of significant ($p < 0.05$) and non-significant mediation studies reported by more robust and less robust studies, by type of risk factor. PTSD, post-traumatic stress disorder.

polymorphisms) genetic measures (Table 1). A total of 34 studies investigated such associations and 10 (29.4%) were considered methodologically robust (see online Supplementary Table S6). Two robust population-based cohort studies showed that parental history of psychosis interacted significantly with parental separation (Paksarian et al., 2015) and parental unemployment (Wicks et al., 2010) in increasing the risk of non-affective psychosis. Two studies on FEP samples found no evidence of gene–environment interaction between CA and familial risk for mental health problems (Fisher et al., 2014; Trotta et al., 2015a), one of which reported a significant association between high genetic risk for psychosis and self-reported severe physical abuse from mother (Fisher et al., 2014), indicating the potential presence of a passive rGE.

Interactions between potential molecular genetic susceptibility and exposure to CA in predicting the development of psychotic symptoms have mainly focused on candidate genes. *COMT* $Val^{158}Met \times$ CA interaction has been associated with psychotic experiences in a non-FEP prospective study (Vinkers et al., 2013). However, such G × E was not replicated by other studies (Debost et al., 2017; Ramsay et al., 2013; Trotta et al., 2019), and no relationship was found with *FKBP5* (Ajnakina et al., 2014), *BDNF* (Ramsay et al., 2013), *MTHFR C677T* (Debost et al., 2017), *DRD2* or *AKT1* risk haplotypes (Trotta et al., 2019). Only one study used genome-wide association and polygenic risk score methods in FEP, with negative findings (Trotta et al., 2016). The less robust studies overall replicated the inconsistent findings regarding the moderating effect of genetic vulnerability, and the sparse findings regarding specific genetic susceptibilities, with the more consistent results for *FKBP5*, *BDNF*, and a suggestion of a three-way interaction between *COMT* $Val^{158}Met$, CA, and cannabis use in individuals carrying the *Val/Val* genotype, which showed an effect on positive (e.g. delusions and hallucinations) and negative (including reduced social drive and volition, blunted emotions, lack of energy, poverty of speech and thoughts) psychotic experiences (see Fig. 2 and online Supplementary Table S6).

Substance use

Out of 12 studies on substance abuse, six were methodologically robust (see online Supplementary Table S6) and all of them explored the relationship with cannabis use. Additive and multiplicative interactions were found in large epidemiological surveys (Houston, Murphy, Adamson, Stringer, & Shevlin, 2008; Konings et al., 2012), but not replicated in other population and case-control studies (Ajnakina et al., 2014; Morgan et al., 2014b; Sideli et al., 2018; Vinkers et al., 2013). Several of these studies (Konings et al., 2012; Morgan et al., 2014b) claimed that the CA × cannabis interaction may be confounded by environment–environment correlation (rEE), but other studies (Sideli et al., 2018; Vinkers et al., 2013) did not confirm this finding. However, the CA–cannabis interaction was also reported by the majority of the less robust studies (see Fig. 2 and online Supplementary Table S6).

Social, psychological and psychopathological mechanisms

Seven out of thirteen studies assessing social risk factors were rated as methodologically robust (see online Supplementary

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Table S6). Two population-based studies reported an additive interaction between CA and life events, particularly when numerous and occurring in the previous 12 months (Lataster et al., 2012; Morgan et al., 2014b). In a prospective cohort study, the experience of both CA and intimate partner violence was related to a more than double risk for psychotic symptoms in major depressive disorder, compared to the exposure to either type of event (Ouellet-Morin et al., 2015). The moderating role of life events was partly confirmed by around half of the less robust studies (see Fig. 2 and online Supplementary Table S6). In a case-control study, the effect of physical abuse on FEP was significantly reduced by the presence of close others (Gayer-Anderson et al., 2015), suggesting a protective role of social support against the psychotogenic effects of CA. Less consistent were the findings on the role of adult disadvantage: while in a case-control study, adult disadvantage interacted with parental separation in the risk for psychosis (Morgan et al., 2014a), in a birth cohort no synergism was found (Räikkönen et al., 2011), and a single less robust study reported negative findings. Among the two studies investigating the role of broader social factors, a robust cohort study found that the interaction between CA and neighbourhood social adversity only approached significance (Newbury et al., 2018a). Of the three studies on psychological mechanisms, only one satisfied criterion for robustness (Mansueto et al., 2019), which reported no evidence of moderation by mentalizing abilities.

Mediation studies

Genetic risk factors, substance use, stressful events, and social risk factors

Neither of the two studies on genetic risk factors was methodologically robust and both reported negative findings. The only robust study (out of five) analysing the mediating role of cannabis use on the relationship between CA and psychotic symptoms led to negative results (van Nierop et al., 2014) and a single less robust study suggested a partial mediating effect of substance abuse. Life events were found to partially mediate the CA-psychosis association (47% of the total effect), with a greater mediation effect for violent (*v.* non-violent) life events (Bhavsar et al., 2019) but the findings have not been replicated by less robust studies. A single mediation study on adult disadvantage found that it mediated the effect of parental separation on psychosis, accounting for 75% of the total effect (Morgan et al., 2014a). In two large population studies, evidence for a mediatory pathway between CA and psychosis was found for social defeat (van Nierop et al., 2014) and for loneliness (Shevlin, McElroy, & Murphy, 2015), and the results were also consistent in less robust studies (see Fig. 3 and online Supplementary Table S7).

Psychological and psychopathological mechanisms

A total of 56 studies focused on psychological mechanisms, and eight (14.3%) were methodologically robust (see online Supplementary Table S7). The most consistent evidence concerned the mediating role of attachment and non-psychotic symptoms. Two prospective studies pointed to the potential mediating role of parental bonding and institutional care (Janssen et al., 2005; Walker et al., 1981). With regards to the role of specific types of attachment insecurity, the NCS study highlighted specific pathways linking different types of CA to psychotic symptoms, via avoidant and anxious attachment (Sitko, Bentall, Shevlin, O'Sullivan, & Sellwood, 2014), and a Spanish study suggested that angry/dismissive attachment specifically mediated the effect of parental antipathy on PLEs (Sheinbaum et al., 2015). The mediating role of insecure attachment was confirmed by five out of six less robust studies (see Fig. 3 and online Supplementary Table S7).

PTSD and anxiety symptoms, but not depression, partially mediated the effect of sexual abuse on auditory verbal hallucinations (McCarthy-Jones, 2018). Moreover, the totality of less robust studies ($n = 22$) reported mediation via dissociation and/or PTSD symptoms. In another study, mood instability lay on the pathway connecting CA to social defeat to PLEs (van Nierop et al., 2014). A single robust study reported that depression decreased the mediating effect of attachment insecurity on the relationship between CA and psychosis (Sitko et al., 2014). The mediating role of depression, mood instability, and other affective symptoms was further confirmed by most of the less robust studies (12 out of 16). Only one robust study investigated the role of self-esteem with negative results (Morgan et al., 2014a). According to a single robust study, mentalization abilities partially mediated the effect of childhood neglect on negative and affective symptoms of psychosis (Mansueto et al., 2019). However, a number of less robust studies (15 out of 17) suggested mediation via mentalization or metacognitive abilities, core beliefs about the self and others, and other cognitive processes (see Fig. 3 and online Supplementary Table S7).

Discussion

This systematic review included 121 studies exploring potential genetic, social, psychological, and psychopathological mediating and moderating factors of the relationship between CA and psychosis (from subclinical psychotic experiences through to clinically diagnosed psychotic disorders). To maximize the comprehensiveness of the review, the search was not limited to mediation studies (Williams, Bucci, Berry, & Varese, 2018) but also included interaction studies. However, only a quarter of the studies satisfied our criteria for methodological robustness. Moreover, due to the large degree of heterogeneity across the studies included and the small number of studies available for each mediating/moderating factor, it was not possible to conduct a quantitative synthesis of the findings. Indeed, caution has been urged when attempting to apply meta-analytical methods to only a few heterogeneous studies, as it can result in biased effect estimates and too narrow or too broad confidence intervals (Debray, Moons, & Riley, 2018; Guolo & Varin, 2017). In order to limit the effect of publication bias, the narrative synthesis was mainly focused on methodologically robust studies. However, Figs 2 and 3, which show the percentage of studies with statistically significant findings among the robust and less robust studies, suggest that findings were largely consistent across studies, regardless of their methodological quality. Furthermore, a visual inspection of the robust interaction studies suggests that studies with negative findings were well represented (online Supplementary Table S8), suggesting a limited effect of reporting bias. Although robust mediation studies led, with few exceptions, to significant results, these mostly came from large population-based studies (online Supplementary Table S9), suggesting that evidence of the mediatory role of social and psychological factors is unlikely to be based on smaller studies. Nevertheless, in this review a statistical estimate of publication bias could not be calculated due to the heterogeneity of the studies.

Overall, non-FEP studies were scarcely represented among the robust studies. The majority of the statistically significant findings regarding moderation and, especially, mediation effects came

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from the general population and, to a lesser extent, FEP/UHR studies focusing on psychotic symptoms and PLEs. This may be related to the phenotypic expression of psychosis according to a continuum model of psychosis (van Os et al., 2009), the greater prevalence of PLEs compared to psychotic disorders (Linscott & van Os, 2013), and/or the greater statistical power of studies using continuous rather than dichotomous outcomes. The latter also suggests that evidence of moderation/mediation between CA and other risk factors may have been underestimated among studies using disorder-level outcomes.

Summary of findings

The existing biological findings from the more robust studies suggest that the effect of CA in increasing the risk for psychosis might be partially independent of pre-existing genetic liability. Interaction between CA and family history for psychosis as well as specific polymorphisms led to inconsistent findings, and the few positive results were related to genes, such as *COMT*, whose role in the pathogenesis of schizophrenia was not confirmed by a recent meta-analysis (Ripke et al., 2014). On the other hand, genes involved in dopaminergic and glutamatergic transmission, as well as in immunity function (e.g. *FKBP5*), whose role in the pathogenesis of schizophrenia has been increasingly recognised (Ripke et al., 2014), were less explored by current interaction studies and should be further investigated in relation to CA by methodologically robust studies. However, the findings should be interpreted in light of the fact that G × E studies had fairly limited sample sizes which may have reduced the likelihood of detecting significant interaction effects. In addition, previous studies suggested that investigating the gene–CA interaction in psychosis would be benefitted by using overall measures of genetic risk derived from GWAS studies, replication across different populations, and statistical models accounting for multiple testing and the confounding effect of rGE (Morgan & Gayer-Anderson, 2016; van Winkel, Stefanis, & Myin-Germeys, 2008). Further, well-powered research addressing these issues is still required.

Consistent with a previous review (Williams et al., 2018), there were contradictory findings regarding the moderating effect of cannabis use, both in robust and less robust studies, and only a negative mediation study, while no robust studies on other substances were found. Evidence of interaction was found in only a few large epidemiological surveys (Houston et al., 2008; Konings et al., 2012), suggesting that lack of interaction may be influenced by insufficient statistical power. An alternative explanation may be that all these studies defined cannabis use in terms of using at least once over the life-course (Ajnakina et al., 2014; Houston et al., 2008; Konings et al., 2012; Morgan et al., 2014b; Sideli et al., 2018), while it is possible that the impact of cannabis exposure may substantially vary depending upon the quantity, type, and age of first use.

The evidence presented in this review supports a role for social risk factors in the pathway between CA and psychosis, particularly the interaction with (Lataster et al., 2012; Morgan et al., 2014a; Ouellet-Morin et al., 2015) and mediation by (Bhavsar et al., 2019) life events. The effect of social support also seemed to be consistent across studies: while having close others reduced the impact of CA on FEP (Gayer-Anderson et al., 2015), loneliness and social defeat mediated the effect on PLEs (van Nierop et al., 2014) and psychosis (Shevlin et al., 2015), a finding also replicated in less robust studies.

According to a few methodologically robust studies examining the role of attachment styles and parental bonding, insecure attachment and institutional care, these factors partially mediated the effect of CA on schizotypal traits (Walker et al., 1981), PLEs (Sheinbaum et al., 2015), and psychotic symptoms (Janssen et al., 2005; Sitko et al., 2014). Furthermore, a few robust studies supported a contribution of mood, anxiety, and PTSD symptoms to the pathway between CA and psychosis (McCarthy-Jones, 2018; van Nierop et al., 2014) but most of the evidence on the mediating role of mood and anxiety symptoms, as well as PTSD and dissociation, came from a number of less robust studies which had potential limitations in terms of selection bias, crude measurement instruments, and (lack of) adjustment for confounders. This suggests that the size of the mediation or moderation effect might not have been accurately estimated and that alternative explanations might be possible. Only two robust studies explored the role of cognitive mediators (Mansueto et al., 2019; Morgan et al., 2014a), among which a single study found evidence of partial mediation of the CA-psychosis association via mentalization (Mansueto et al., 2019).

Pathway specificity

Taken together, the findings regarding the interaction between early and recent adversities and the mediating role of post-traumatic and mood symptoms support the model of the affective pathway to psychosis (Myin-Germeys & van Os, 2007). Cumulative adversity can detrimentally affect emotion regulation processes, through which individuals modulate their emotions to respond to environmental demands (Bargh & Williams, 2007; Rottenberg & Gross, 2003), and thus may represent a mechanism linking repeated exposure to adversity to development of psychosis. Furthermore, early trauma can shape how we interpret interpersonal contexts throughout the lifespan and is associated with the development of attachment insecurity, including worry about relationships, difficulty in trusting others, and social withdrawal (Berry, Barrowclough, & Wearden, 2007). Research suggests this might represent another mechanism through which psychosis develops and is maintained (Bentall et al., 2014; Freeman et al., 2013; Sitko, Varese, Sellwood, Hammond, & Bentall, 2016).

Cumulative adversity can also 'get under the skin,' through stress-sensitization of the dopamine system and hypothalamic-pituitary-adrenal (HPA) axis dysregulation (Davis et al., 2016; Misiak et al., 2017; Ruby et al., 2014), possibly via epigenetic mechanisms (Tomassi & Tosato, 2017). Previous reviews suggested that this pathway may be particularly relevant for positive symptoms, and relatively independent of neurodevelopmental delays and cognitive impairment, which in turn seem more related to negative symptoms (Howes & Murray, 2014; Myin-Germeys & van Os, 2007). However, this postulated model needs to be further explored since only a single robust study found evidence of an effect on positive but not negative psychotic symptoms (Sheinbaum et al., 2015).

Some studies examined the relationship between particular types of CA and specific moderators or mediators, but only a few led to evidence of an effect. Physical abuse was found to interact with social support in FEP (Gayer-Anderson et al., 2015). The effect of sexual abuse on psychotic symptoms was partially mediated by PTSD, compulsions (McCarthy-Jones, 2018), as well as attachment anxiety (Sitko et al., 2014). The effect of neglect on paranoia was found to be mediated by attachment insecurity (Sitko et al., 2014), whereas the association with negative

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symptoms was mediated by metacognitive abilities (Mansueto et al., 2019). Although preliminary and less robust studies further confirmed the pathways from sexual abuse via PTSD and dissociation (Bortolon, Seillé, & Raffard, 2017; Hardy et al., 2016; see online Supplementary Materials) and from neglect via attachment insecurity and cognition (Gawęda, Göritz, & Moritz, 2019; Pilton et al., 2016; see online Supplementary Materials), such a small number of methodologically robust studies does not yet allow for drawing firm conclusions on any specific mediating or moderating pathways.

Compared to the majority of the studies defining CA in terms of parental abuse and/or neglect, only a few of the reviewed studies explored the specific effect of parental separation/death or adoption (Ajnakina et al., 2014; Boyda & McFeeters, 2015; Ierago et al., 2010; Morgan et al., 2014a; Paksarian et al., 2015; Räikkönen et al., 2011; Trotta et al., 2015a; Walker et al., 1981) and more subtle forms of parental difficulties, such as parental antipathy, rejection, emotional invalidation (Akün, Durak Batigün, Devrimci Özgüven, & Baskak, 2018; Fisher et al., 2013; Sheinbaum et al., 2015; Udachina & Bentall, 2014), and vulnerable parental status (Wicks et al., 2010). It is possible that this area was not extensively covered by the search strategy or that studies on these adversities were, in fact, less common. The methodologically robust studies included in this review suggested a possible synergism with social disadvantage and potentially an indirect effect on psychosis via attachment and parental bonding. Less robust studies indicated a further potential mediatory pathway via beliefs about others and the world.

Consistency of findings across community and clinical samples

The more consistent findings on the moderating/mediating effect of adult adversities both on PLEs (Bhavsar et al., 2019) and psychotic symptoms (Lataster et al., 2012; Morgan et al., 2014a; Ouellet-Morin et al., 2015) were consistently replicated in robust population-based studies. Similarly, the mediatory role of loneliness/social defeat was ascertained both at symptom- (van Nierop et al., 2014) and disorder-level both in the population (Shevlin et al., 2015) and clinical FEP samples (Gayer-Anderson et al., 2015). Among psychological mediators, the mediating role of parental bonding and attachment insecurity was consistently observed on PLEs (Sheinbaum et al., 2015) and symptoms (Janssen et al., 2005; Sitko et al., 2014) in population-based studies, as well as in a high-risk for psychosis sample (Walker et al., 1981). Taken together, the findings suggest that large population studies provided more consistent findings for possible pathways (i.e. adult adversities and parental bonding) from CA to psychosis, both at the symptom and disorder levels.

Directions for future research and clinical implications

The present work suggests that recent life events, the experience of loneliness and social defeat, attachment and parental bonding, and, to a lesser extent, mood and PTSD symptoms mediate and/or moderate the impact that CA has on psychotic symptoms across the lifespan. However, most studies were affected by a number of limitations that reduce the potential impact of the findings. Inadequate sampling strategies and lack of information on participation rate may have affected the generalizability of the findings as well as the sensitivity to selection bias. Furthermore, retrospective assessment of CA and mediatory variables may have increased the possibility of recall bias. Moreover, the differential effect of childhood *v.* adolescent exposure to adversity on psychosis in relation to specific mediators and moderators was not investigated by the studies included in this review and warrants exploration. Small sample sizes are likely to be associated with lack of power and risk for type II errors. Moreover, evidence suggests that additive interaction may be more effective than multiplicative interaction in capturing the effect of those exposures – such as CA, substance misuse, or genetic risk factors – that may act either independently or synergistically on the same outcome (van Os et al., 2008; van Winkel et al., 2013) and few studies adopted this approach. In mediation studies, the lack of longitudinal prospective studies and in some cases the likely co-occurrence between CA and possible mediators, which may have also occurred in childhood (Janssen et al., 2005; Räikkönen et al., 2011; Walker et al., 1981), makes it difficult to establish a temporal order between the exposure and the mediator. In both types of studies, robust statistical methods for testing interaction and mediation models are warranted, as well as adjustment for other genetic, social, and psychological risk factors.

We suggest that future research should focus more on prospective cohort studies, including samples at different points along the psychosis spectrum, and employing consistent and validated measures of multiple exposures and outcomes to more robustly study these potential mechanisms. The benefits of conducting methodologically robust studies are multiple: (a) they allow researchers to unravel causal links between the mediators/moderators of the well-established CA-psychosis association; (b) inform public health policies; and (c) facilitate the development of tailored preventative and therapeutic interventions to reduce the 'toxic' effect of CA throughout development at an individual and societal level (Shonkoff et al., 2012).

Psychological mediating and moderating factors in relation to the CA-psychosis association include anxiety, depression, and emotion dysregulation, in a context of relational insecurity, perceived discrimination, and lack of social support. These factors might be linked with the way individuals with CA and psychotic symptoms process internal and external information (Garety, Kuipers, Fowler, Freeman, & Bebbington, 2001). A recent meta-analysis reported that a few studies have focused on interventions for people with psychotic symptoms and developmental trauma, with initial but limited evidence for mindfulness-based acceptance and commitment therapy, skills training in affective and interpersonal regulation, psychodynamic psychotherapy and systemic approaches (Bloomfield et al., 2020). If the findings of this review are replicated in more robust studies, then it would be important for individual and family interventions to focus on such potential treatment targets, including emotion regulation, acceptance, interpersonal skills, trauma re-processing, and the integration of dissociated ego states (Brent, 2009; Louise, Fitzpatrick, Strauss, Rossell, & Thomans, 2018). Such treatment targets would also be crucial for preventive interventions for high-risk children and adolescents who were exposed to CA (Gillies et al., 2016; Macdonald et al., 2012; Mavranezouli et al., 2020).

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