

Childhood Adversities Increase the Risk of Psychosis: A Meta-analysis of Patient-Control, Prospective- and Cross-sectional Cohort Studies

Filippo Varese^{†,1,2}, Feikje Smeets^{†,3}, Marjan Drukker³, Ritsaert Lieverse³, Tineke Lataster³, Wolfgang Viechtbauer³, John Read⁵, Jim van Os^{*,3,4}, and Richard P. Bentall¹

¹Institute of Psychology, Health and Society; University of Liverpool, UK; ²School of Psychological Sciences, University of Manchester, UK; ³Department of Psychiatry and Psychology, Maastricht University, The Netherlands; ⁴King's College London, King's Health Partners, Department of Psychosis Studies, Institute of Psychiatry, London, UK; ⁵Department of Psychology, University of Auckland, New Zealand

†Shared first authorship.

*To whom correspondence should be addressed; PO Box 616 (DRT10), 6200 MD Maastricht, The Netherlands; tel: +31-43-3688683, fax: +31-43-3688689, e-mail: j.vanos@maastrichtuniversity.nl

Evidence suggests that adverse experiences in childhood are associated with psychosis. To examine the association between childhood adversity and trauma (sexual abuse, physical abuse, emotional/psychological abuse, neglect, parental death, and bullying) and psychosis outcome, MEDLINE, EMBASE, PsychINFO, and Web of Science were searched from January 1980 through November 2011. We included prospective cohort studies, large-scale cross-sectional studies investigating the association between childhood adversity and psychotic symptoms or illness, case-control studies comparing the prevalence of adverse events between psychotic patients and controls using dichotomous or continuous measures, and case-control studies comparing the prevalence of psychotic symptoms between exposed and nonexposed subjects using dichotomous or continuous measures of adversity and psychosis. The analysis included 18 case-control studies ($n = 2048$ psychotic patients and 1856 nonpsychiatric controls), 10 prospective and quasi-prospective studies ($n = 41\ 803$) and 8 population-based cross-sectional studies ($n = 35\ 546$). There were significant associations between adversity and psychosis across all research designs, with an overall effect of $OR = 2.78$ (95% $CI = 2.34-3.31$). The integration of the case-control studies indicated that patients with psychosis were 2.72 times more likely to have been exposed to childhood adversity than controls (95% $CI = 1.90-3.88$). The association between childhood adversity and psychosis was also significant in population-based cross-sectional studies ($OR = 2.99$ [95% $CI = 2.12-4.20$]) as well as in prospective and quasi-prospective studies ($OR = 2.75$ [95% $CI = 2.17-3.47$]). The estimated population attributable risk was 33% (16%–47%). These findings indicate that childhood adversity is strongly associated with increased risk for psychosis.

Key words: psychosis/adversity/trauma/meta-analysis/abuse/neglect

Introduction

Adverse childhood events including trauma is a common experience worldwide, with some estimates suggesting that about a third of the general population may be affected.¹ Evidence suggests that its effects in adulthood may include a range of negative social outcomes, including higher criminality,² a lower educational level³ and lower general health and well-being. Adverse childhood events have also been related to a greater risk of psychiatric disorder^{1,4,5} and, especially given its high prevalence, it is likely that it is an important determinant of mental ill-health.⁶

A growing number of methodologically sound studies have examined child maltreatment (eg, sexual abuse, physical abuse, emotional/psychological abuse and neglect), peer victimization (eg, bullying), and experiences of parental loss and separation as risk factors for psychosis and schizophrenia. Nevertheless, the association between adverse childhood events and psychosis has been a topic of enduring controversy. Only narrative reviews have so far attempted to synthesize these findings, with inconsistent conclusions.⁷⁻⁹ Therefore, a systematic quantitative synthesis of the existing data is required.

The present study presents a quantitative review and meta-analysis of the available empirical literature, examining the magnitude and consistency of the effects of different, widely-examined types of adversity and trauma observed in: (i) prospective cohort studies, (ii) large population-based cross-sectional studies, and (iii) case-control studies.

Methods

Search Strategy

We followed the Meta-analysis of Observational Studies in Epidemiology guidelines (see supplementary table S1).¹⁰ Search terms regarding exposure to adversity were chosen based on the most widely studied types of traumatic experiences in the psychosis literature and represented overall exposure, physical, emotional and sexual abuse, physical and emotional neglect, bullying, and parental death. A systematic database search from 1906 up to 2011 was performed on PsychINFO, PubMed, EMBASE, and Web of Science using the following search themes: (“child abuse”; “physical abuse”; “sexual abuse”; “psychological abuse”; “emotional abuse”; neglect*; trauma*; advers*; maltreat*; bully*; bullied; victim*; “expressed emotion”; “communication deviance”; “parental loss”; separate*; discrimination) combined with psychosis-related search terms (ie, psychosis; psychoti*; schizo*; hallucinat*; delusion*; paranoi*) using the Boolean operator “and.” Medical Subject Headings (MeSH) were used to further expand the results of the database search, to identify all relevant studies (table 1 and supplementary table S2). The present analysis focused exclusively on childhood trauma (defined as sexual abuse, physical abuse, emotional/psychological abuse, neglect, parental death, and bullying). Other psychosocial adversities included in the original search (parental communication deviance, expressed emotion and discrimination) were not eligible for the present analysis.

The following steps were taken to identify all relevant studies and reduce file drawer effects (publication bias due to the likelihood of studies being published depending on the statistical significance of their results): (1) electronic databases were searched for relevant unpublished material (eg, conference articles) from the year 2000 onward; (2) the database search was extended to reports published in Dutch, French, German, Italian, Portuguese, and Spanish; (3) the authors of all eligible reports were contacted and invited to send any relevant unpublished reports (see supplementary table S3); and (4) the reference lists and citations of eligible articles were examined to identify any eligible report not previously located through the database search (forward- and backward tracking of literature).

Inclusion and Validity

Only reports published after January 1980 were included because the first known empirical study on adverse childhood events and psychosis was published at this time¹¹ and the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition (DSM-III)*, was released in 1980, improving diagnostic consistency. Eligible studies employed the following methodologies: (1) prospective cohort studies and (2) large-scale cross-sectional studies investigating the association between childhood trauma and psychotic

symptoms or illness; (3) case-control studies comparing the prevalence of adverse events between psychotic patients and controls using dichotomous or continuous measures; and (4) case-control studies comparing the prevalence of psychotic symptoms between exposed and nonexposed subjects using dichotomous or continuous measures for adverse childhood events and psychosis. Only reports with sufficient statistical information for the computation of effects comparable to other reported studies were included. When this information was not available (and was not provided by the authors contacted), the study was deemed ineligible.

Measures of childhood adversity and trauma were considered eligible if: (1) the adverse events were assessed at the individual level and (2) exposure was specifically measured prior to the age of 18 (including measures assessing trauma in childhood and adolescence without additional timing details). Types of trauma included in the current meta-analysis were defined as: childhood sexual abuse (sexual acts toward a child, including intercourse, touching, etc.), childhood physical abuse (violent acts leading to physical injury or harm, such as harsh physical punishment), childhood emotional abuse (exposure to behaviour that might result in trauma, such as harshness, name calling by parents during childhood), childhood physical neglect (failure of those who are responsible for physical care to provide this care during childhood, eg, by failing to provide food or clothes), childhood emotional neglect (failure of those who are responsible to provide emotional care to provide this care during childhood, eg, by being unresponsive to a child’s emotional needs), and bullying (an act of repetitively aggressive behavior by a peer with the intention to hurt the child, such as physical assault or intimidation or repeated name-calling). Parental death was defined as death of one of the parents before the age of 18. Parental loss or separation was deemed only eligible if this was equal to parental death due to the high heterogeneity in the definition of separation (varying between being separated from one of the parents for a period of 2 weeks to parental death).

Both diagnostic as well as dimensional measures of psychosis were considered eligible. Diagnostic outcomes were defined as a diagnosis of: psychotic disorder, schizophrenia, or schizoaffective disorder, based on *DSM-III*, *DSM-III-R*, *DSM-IV*, *DSM IV-TR*, Research Diagnostic Criteria, *International Classification of Diseases, Ninth Revision (ICD-9)*, *ICD-10*, or psychiatrist or psychologist evaluation. Dimensional outcomes were defined in terms of individuals in the general population reporting psychotic symptoms, including subclinical psychotic experiences. Studies conducted on heterogeneous psychiatric samples, on participants with organic, drug-induced or secondary psychoses, or on prodromal samples were excluded. Similarly, studies using schizotypal personality measures were considered ineligible. In the case of studies with overlapping samples or when samples were reported

Table 1. Characteristics of Studies Reporting Adverse Childhood Events in Psychosis included in the Meta-Analysis

Source	Project	Sample Size	Age (y)	No. of Cases	No. of Controls	Cases Age	Controls Age
Case-control studies ^a							
Friedman and Harrison ¹¹ (United States)		35		20	15	30.8	31.9
Convoy et al ¹² (Czech Republic)		200		100	100	33.3(m); 43.4 (f)	36.4 (m); 38.1 (f)
Furukawa et al ¹³ (Japan)	GLADS	337		225	112		
Agid et al ¹⁴ (Israel)		152		76	76	42.5	41.7
Dell' Erba et al ¹⁵ (Italy)		114		54	60	32.7	33.4
Giblin et al ⁴⁶ (UK)		32		14	18	77.7	73.4
Fennig et al ¹⁷ (Israel)		60		40	20	18.1	18.1
Morgan et al ¹⁸ (UK)	AESOP	781		390	391	30.5	37.3
Weber et al ¹⁹ (Germany)		63		42	31	32.6	40.3
Rubino et al ²⁰ (Italy)		484		174	310	43.1	37.4
Cohen et al ²¹ (United States)		302		198	113	61.5	63.0
Fisher et al ²² (UK)	AESOP	428		182	246	31	39
Husted et al ²³ (Canada)		147		79	68	51.8	49.6
Bartels-Velthuis et al ²⁴ (The Netherlands)		212		60	152		
Evans ²⁵ (UK)		60		29	31	27.7	23.7
Heins et al ²⁶ (The Netherlands)	GROUP	499		272	227	28.1	32.3
Varese et al ²⁷ (UK)		65		45	20	42.7	39.5
Daalman et al ²⁸ (personal communication)				100	124		
McCabe et al ²⁹ (Australia)	ASRB	675		408	267	40.7	39.27
Prospective cohort studies ^a							
Mäkikyrö et al ³⁰ (Finland)	NFBC	11017					
Janssen et al ³¹ (The Netherlands)	NEMESIS	4045	41.4				
Spauwen et al ³² (Germany)	EDSP	2524	21.7				
De Loore et al ³³ (The Netherlands)	YHCSL	1129	15.1				
Schreier et al ³⁴ (UK)	ALSPAC	6437	12.9				
Arseneault et al ³⁵ (UK)	E-RISK	2127					
Cutajar et al ³⁶ (Australia)	VPCR	5436	33.7	2759	2677		
Wigman et al ³⁷ (The Netherlands)	TRAILS	2149	13.6	217	1834		
Cross-sectional studies ^a							
Murphy et al ³⁸ (United States)		391					
Ross and Joshi ³⁹ (United States)		502	45.2				
Whitfield et al ⁴⁰ (United States)	ACE	17337	57				
Kim and Kim ⁴¹ (Republic of Korea)		1672	15.7				
Shevlin et al ⁴² (United States)	NCS	5877	32.2				
Shevlin et al ⁴³ (United States)	NCS	5782					
Houston et al ⁴⁴ (United States)	NCS	5877	32.02				
Kelleher et al ⁴⁵ (Ireland)	Challenging Times	211		14	197		
Nishida et al ⁴⁶ (Japan)	ESPAT	4894	13.3				
Shevlin et al ⁴⁷ (United States)	NCS-repl	2353	44.35				
Harley et al ⁴⁸ (Ireland)	Challenging Times	211					
Bebbington et al ⁴⁹ (UK)	APMS	7298					
Van Nierop et al ⁵⁰ (The Netherlands)	NEMESIS-II	6250		384	5866		

Note: ACE, Adverse Childhood Experiences Study; AESOP, Aetiology and Ethnicity in Schizophrenia and Other Psychoses; ALSPAC, Avon Longitudinal Study of Parents and Children⁵¹; APMS, Adult Psychiatric Morbidity Survey; ASRB, Australian Schizophrenia Research Bank; EDSP, The Early Developmental Stages of Psychopathology; E-RISK, Environmental Risk Longitudinal Twin Study; ESPAT, Epidemiological Study of Psychopathology of Adolescents in Tsu; GLADS, Group for Longitudinal Affective Disorders Study; GROUP, Genetic Risk and Outcome in Psychosis; NCS, National Comorbidity Survey; NEMESIS, The Netherlands Mental Health Survey and Incidence Study; NFBC, Northern Finland 1966 Birth Cohort; TRAILS, Tracking Adolescents' Individual Life Survey⁵²; VPCR, Victoria Psychiatric case register, Police Surgeon's Office and Victorian Institute of Forensic Medicine Institute; YHCSL, Youth Health Care Division of South Limburg (Maastricht).

^aPlease note study type was defined on the base of how the included articles analyzed the data; for instance, a longitudinal study analyzing data in a cross-sectional manner was deemed as 'cross-sectional'.

in multiple articles, we selected the most appropriate based on the following criteria: (1) a definition of adversity exposure that most closely resembled the search terms used, (2) whether the articles had a specific focus on adversity as a main variable, and (3) (for longitudinal studies) duration of the follow-up period (supplementary table S4).

Eligibility was assessed independently by 2 researchers following a 3-stage procedure: title screening, abstract screening, and whole article screening. Any intercoder discrepancy was resolved during regular consensus meetings. In the first phase, F.S. and F.V. screened all the titles independently. If one or both deemed a title to be eligible for further screening, this was included in the second phase (abstract screening) for further examination (F.S. and F.V. independently; agreement 93.4%). In the third phase, complete texts were examined to reach final decisions on inclusion (F.S. and F.V. or F.V. and R.L. independently) with agreement levels of 96.6% (FV and FS) and 97.6% (FV and RL). All eligible reports were independently coded by 2 researchers. In case of disagreement, a third coder was consulted.

Effect Size Computation and Statistical Analyses

All analyses were carried out using the meta-analysis commands of Stata 11.⁵³ We choose ORs as the main outcome metric. When not reported in the primary studies, ORs and their associated variance component were estimated from available descriptive statistics (ie 2×2 tables) using standard computational techniques for dichotomous data.^{54,55} In the case of studies reporting chi-square analysis for 2×2 data, the reported chi-square value and sample size were used to estimate effects of the r-family and were then converted to ORs using the computational methods described by Borenstein and colleagues.⁵⁵ Risk ratios were treated as ORs without further adjustment as the incidence of psychosis in the studied populations was low (ie, <10%).⁵⁶

To examine the global association between adverse childhood events and psychosis, a meta-analysis was carried out on the effects extracted from (1) studies exclusively focusing on single types of adversity (ie, any type of adverse experience considered in this review), as well as (2) studies providing a summary measure of exposure to multiple types of childhood adversity. In the absence of a summary measure of childhood adversity, the authors of studies reporting multiple effects (eg, separate effects for sexual abuse and physical abuse, but no global measure of trauma) were asked to provide additional information for computing summary effects. A similar procedure was employed for studies reporting multiple effects for the associations between adverse events and specific psychotic symptoms. When this information was not available, reports were excluded to avoid bias stemming from the violation of statistical independence. Furthermore, all analyses were also stratified by research design in order to assess whether findings

differed across designs. Finally, for studies reporting unadjusted effects as well as effects adjusted for potential confounding, only unadjusted effects were included to improve comparability between studies.

The computation of summary effects was carried out under the random-effects model using the DerSimonian-Laird estimator. Heterogeneity analyses were carried out using the Q and I^2 statistics to examine and quantify the amount of observed variance accounted for by true heterogeneity rather than sampling error.⁵⁷ Meta-regression analysis was subsequently used to determine whether (1) differences in study design and (2) inclusion of adjusted or unadjusted effect sizes influenced the observed association between childhood adverse events and psychosis.

Additional analyses were carried out to test the effect of exposure to the specific types of adversity considered in this review (ie, sexual abuse, physical abuse, emotional/psychological abuse, neglect, bullying, and parental death). Due to the large overlap between the studies which examined these adversity-specific effects, these corollary analyses were treated as independent research syntheses and no attempt was made to statistically compare these effects using meta-regression or subgroup analyses.

Ancillary analyses consisted of (1) publication bias assessment⁵⁸ and implementation of the “trim and fill” method of Duval and Tweedie⁵⁹ (to assess and adjust for the potential influence of publication bias), (2) influence analyses (to identify potential outliers and investigate the influence of single studies on the present findings), and (3) sensitivity analyses for the effect of influential cases and the inclusion of studies controlling for clinical-demographic covariates.

Furthermore, the population attributable risk (PAR) was calculated, using the ORs obtained from the main analyses and the prevalence of childhood trauma. This prevalence was obtained by performing a meta-analysis using all studies included in the main analysis, with the exclusion of the case-control studies. A meta-analysis of these proportions and their SEs was carried out to get a weighted estimate of the proportion. We calculated the PAR 3 times in which we used the values of successively the lowerbound of the 95% confidence interval, the mean and the upperbound of the 95% confidence interval for both the weighted estimates of the proportion, and of the OR obtained from the main analyses.

Results

The search strategy resulted in 27 898 articles. After title screening, 2721 articles were screened by abstract reading; 736 articles were included in the final screening phase, yielding 41 included articles (the study selection process is detailed in figure 1). Table 1 summarizes the characteristics of the eligible studies. Additional details about study design and outcome definitions are displayed in supplementary tables S2 and S4.

Overall Association Between Adverse Childhood Events and Psychosis

As meta-regression revealed that the type of outcome measured in the primary studies (ie, diagnostic vs dimensional) did not influence the observed effect sizes ($\beta = -.15$, $SE = .22$, $p = .50$), all analyses were carried on the aggregated sample of effects. The results of the aggregated analysis are presented in figure 2. The analysis comprised 18 case-control studies (with a total of 2048 psychotic patients and 1856 nonpsychiatric controls), 10 prospective and quasi-prospective studies (with a total of 41 803 respondents), and 8 population-based cross-sectional studies (with a total of 35 546 respondents). Trauma was significantly associated with an increased risk for psychosis with an $OR = 2.78$ (95% $CI = 2.34\text{--}3.31$). The magnitude of the summary effects of adversity on psychosis was largely comparable across different study designs ($OR = 2.72$ [95% $CI = 1.90\text{--}3.88$] for case-control studies; $OR = 2.99$ [95% $CI = 2.12\text{--}4.20$] for population-based cross-sectional studies; $OR = 2.75$ [95% $CI = 2.17\text{--}3.47$] for prospective studies), as indicated by the results of meta-regression analysis for the effect of study type (all $ps > .05$). The Q and I^2 tests indicated that the association between adverse events and psychosis was statistically heterogeneous in all analyses (all $ps < .01$), with high estimated proportions of true heterogeneity.

The PAR was calculated using the weighted proportion and the ORs obtained from the main analysis. The mean value of the weighted proportion over all studies was 0.27 (95% $CI = 0.14, 0.4$). The estimated PAR using the mean values of the calculated weighted proportion and the OR was 33%, with a lowest estimate of 16% (PAR calculation using the lowerbound of the 95% confidence interval for both the proportion and the OR) and a highest estimate of 47% (PAR calculation using the upperbound of the 95% confidence interval for both the proportion and the OR).

Associations Between Specific Types of Adversity and Psychosis

The results of separate meta-analyses which examined the effect of specific adverse experiences (sexual abuse, physical abuse, emotional/psychological abuse, neglect, bullying, and parental death) are presented in table 2 (forest plots are available as electronic supplementary material, supplementary figures S1 and S2). With the exception of parental death, statistically significant associations were observed between all types of childhood adversity and psychosis.

Sensitivity Analyses

Egger's test ($B = 0.65$, $SE = 0.63$, $p = .31$) indicated that the findings were not significantly influenced by small studies effects or other selection biases. Similarly, when the analysis was stratified by research design, the results of the

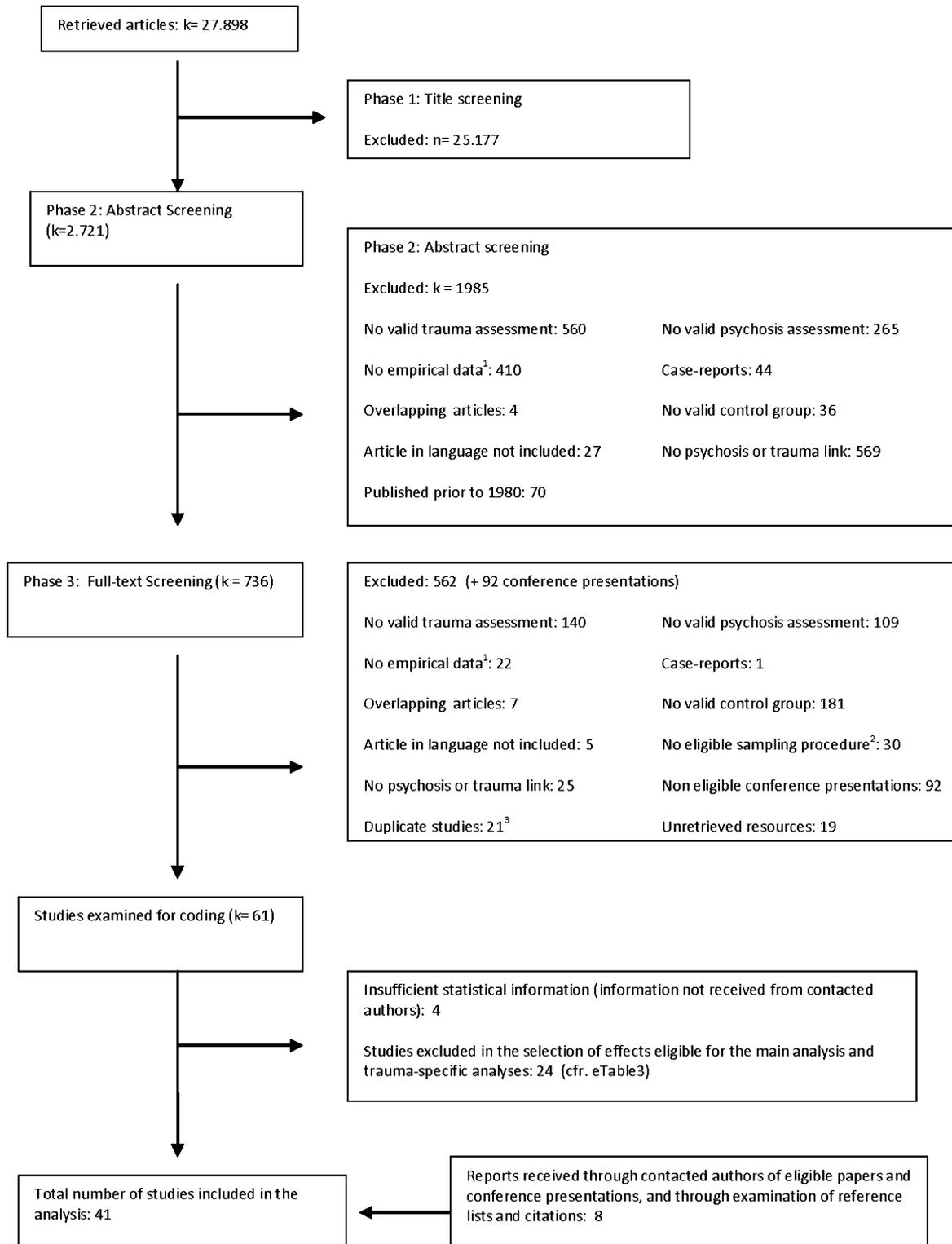
Egger's test were not significant for all analyses: population-based cross-sectional studies ($B = 2.36$, $SE = 1.33$, $p = .13$), prospective cohort ($B = 0.44$, $SE = 1.26$, $p = .73$) and patient-control studies ($B = 0.52$, $SE = 1.25$, $p = .66$) were unaffected by publication bias. In the aggregated analysis, the application of the trim and fill method identified 9 missing studies. When the estimated missing effects were included in the analysis, the global association between adversity and psychosis remained highly significant, $k = 45$; $OR = 2.29$ (95% $CI = 1.91\text{--}2.74$), $p < .001$. For the analyses stratified by research design, the application of the Duval and Tweedie method led to the identification of 7 hypothetically missing effects for the analysis of the patient-control studies, whereas no missing effects were evident for the analyses of epidemiological cross-sectional studies and prospective studies. In the analysis of the patient-control studies, the association between adverse childhood events and psychosis remained significant after the inclusion of these hypothetically missing effects, $k = 25$; $OR = 1.85$ (95% $CI = 1.29\text{--}2.63$), $p < .001$.

Influence analyses indicated that no study exerted undue influence on the main results of this research synthesis. As an additional sensitivity analysis, we excluded the effect extracted from Furuuwa et al,¹³ the only eligible study for which a significant negative association between childhood trauma (death of one or both parents) and psychosis was estimated. The exclusion of this study did not alter the pattern of findings for the analyses focusing in the overall association between adversity and psychosis. However, the previously statistically nonsignificant association between parental death and psychosis was found to be significant after the exclusion of this potential outlier, $k = 7$, $OR = 2.3$ (95% $CI = 1.63\text{--}3.24$), $p < .001$.

Sensitivity analyses were carried out to examine the association between childhood adversity and psychosis in a subgroup of studies reporting adjusted ORs for confounding factors. The association between adversity and psychosis was significant in studies that controlled for the effect of gender ($k = 10$, $OR = 2.52$ [95% $CI = 2.00\text{--}3.19$], $p < .001$), age ($k = 9$, $OR = 2.57$ [95% $CI = 2.00\text{--}3.31$], $p < .001$), and socioeconomic status ($k = 6$, $OR = 3.01$ [95% $CI = 1.98\text{--}4.58$], $p < .001$). When only studies which adjusted for any confound (ie, not limited to the 3 above) in their original analyses were considered, the association between adverse childhood events and psychosis remained significant; $k = 12$, $OR = 2.72$ (95% $CI = 2.08\text{--}3.68$), $p < .001$.

Discussion

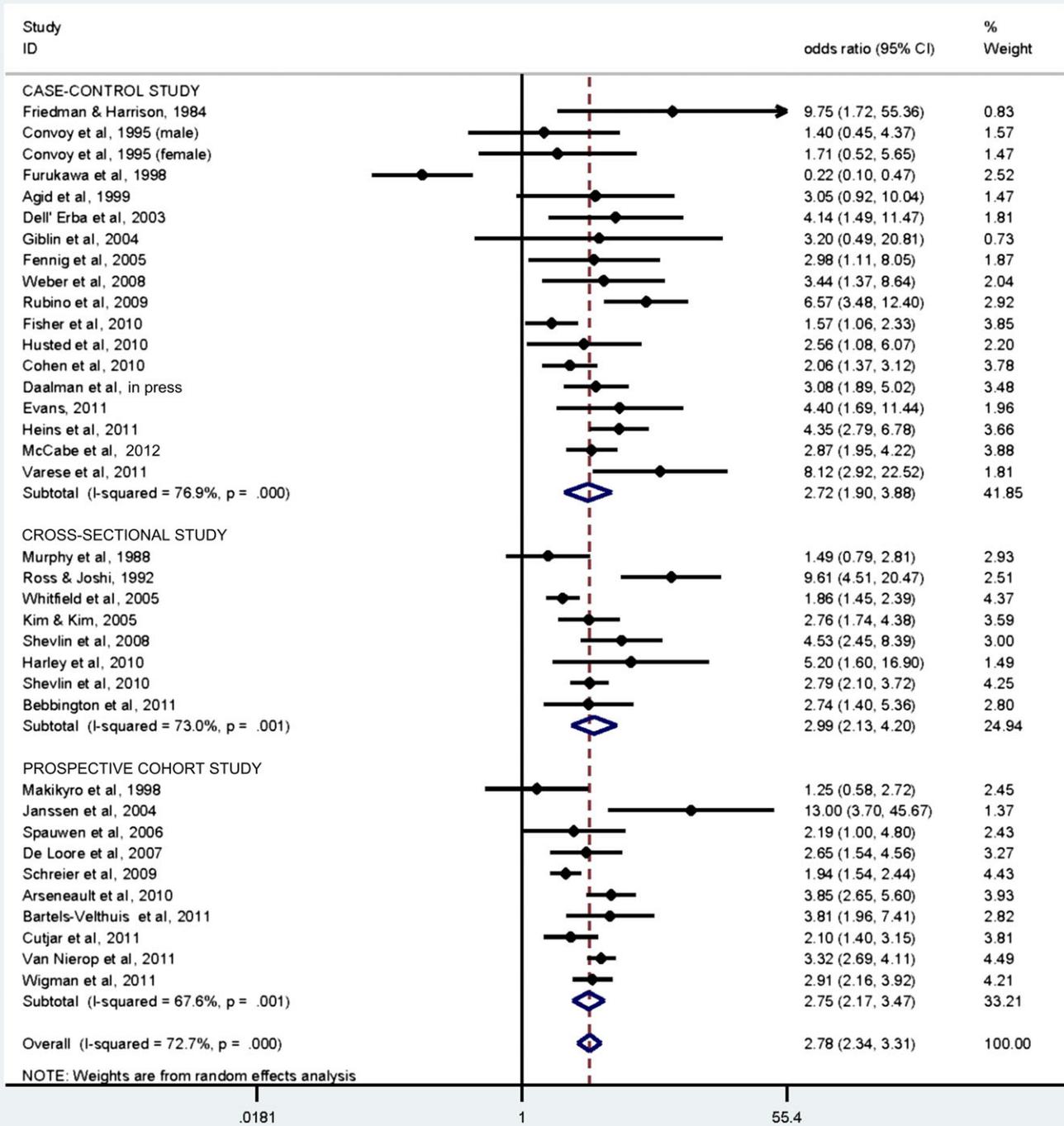
This review finds that childhood adversity and trauma substantially increases the risk of psychosis with an OR of 2.8. Furthermore, our findings suggest that if the adversities we examined as risk factors were entirely removed from the population (with the assumption that the pattern of the other risk factors remained unchanged), and



¹e.g. book chapters, reviews, other meta-analyses, letters, theoretical papers. ²e.g. convenience samples,

³ Titles occurring in the Endnote file twice, articles published under two titles

Fig. 1. Flowchart of studies included in meta-analysis.



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Fig. 2. Forest plot (stratified by research design) for the meta-analysis examining the overall association between childhood adverse experiences and psychosis.

assuming causality, the number of people with psychosis would be reduced by 33%. The association between childhood adversity and psychosis held for the occurrence of psychotic symptoms in the general population, as well as for the development of psychotic disorder in prospective studies; the association remained significant when studies

were included that corrected for possible demographic and clinical confounders. The analyses focusing on the effect of specific traumas revealed that, with the exception of parental death (although this association became significant after the exclusion of a potential outlier), all types of adversity were related to an increased risk of psychosis,

Table 2. Results of the separate meta-analyses focusing on specific adverse experiences

	<i>k</i>	OR (95% CI), <i>p</i> value	<i>Q</i> test	<i>I</i> ² (%)
Sexual abuse	20	2.38 (1.98–2.87), <i>p</i> < .001	<i>Q</i> = 34.5, <i>p</i> < .05	44.9
Physical abuse	13	2.95 (2.25–3.88), <i>p</i> < .001	<i>Q</i> = 47.8, <i>p</i> < .001	74.9
Emotional abuse	6	3.40 (2.06–5.62), <i>p</i> < .001	<i>Q</i> = 23.1, <i>p</i> < .001	78.3
Bullying	6	2.39 (1.83–3.11), <i>p</i> < .001	<i>Q</i> = 19.1, <i>p</i> < .01	73.9
Parental death	8	1.70 (0.82–3.53), <i>p</i> = .154	<i>Q</i> = 35.4, <i>p</i> < .001	80.2
Neglect	7	2.90 (1.71–4.92), <i>p</i> < .001	<i>Q</i> = 32.9, <i>p</i> < .001	81.8

indicating that exposure to adverse experiences in general increases psychosis risk, regardless of the exact nature of the exposure. This meta-analysis found no evidence that any specific type of trauma is a stronger predictor of psychosis than any other. These findings suggest that other adversity-related variables such as age of exposure and multi-victimization might be more strongly related to psychosis risk than exposure type, which, it has been argued,⁶⁰ might affect the specific psychotic symptoms experienced.

The findings imply that exposure to adverse childhood events should be regarded as an important determinant of psychotic disorders. Although the reviewed cross-sectional studies did not allow us to ascertain the direction of causality, the included prospective studies provide evidence for temporal causality. Since childhood traumatic experiences tends to cosegregate so that being exposed to one type of adversity increases the risk of exposure to another,⁴ dose-response effects of trauma on psychosis are of particular importance. However, most studies have not tested for dose-response relationships, and due to the heterogeneous methods in which dose-response effects were defined in those primary studies which did consider this issue, it was not possible to include a synthesis of these data in the current review. However, 9 out of 10 of the studies which tested for these associations were positive for a dose-response relation (see supplementary table S5).

Although several studies included in this meta-analysis used self-reported retrospective measures of childhood experiences, associations with psychosis were also observed in studies which employed other methods to assess trauma exposure. There is also evidence that the retrospective assessment of childhood trauma tends to underestimate rather than overreport real incidence rates⁶¹ and studies have demonstrated the validity and reliability of retrospective reports of trauma in psychotic samples, showing that they are stable across time, unaffected by current symptoms, and are generally concordant with other sources of information.⁶²

Several limitations should be considered when interpreting these findings. First, there was substantial statistical heterogeneity for all outcomes and exposures of interest as the primary studies varied considerably in terms of their

assessment of childhood adverse experiences (eg, in terms of severity, frequency, timing, duration etc) and assessment of psychosis outcomes. Heterogeneity in the data could also be a result of differences in the methodological quality of studies. However, exploration of the data showed that, even when only studies that controlled for confounders were included and regardless of study design, the effect of childhood adversity on psychosis remained, indicating that these parameters of methodological quality did not obscure the main effect found in the current meta-analysis. Moreover, studies included in this review controlled for other general demographic and clinical confounds such as comorbid psychopathology,^{60,63–67} ethnicity,^{63,68} educational attainment,^{28,63,65,66,69,70} and IQ.^{60,67} Other studies also controlled for variables which have been specifically linked to increased risk for psychosis such as drugs and cannabis use,^{63,64,66} genetic liability (eg, family history of psychosis or other psychiatric disorder),^{22,63,67,68} and urbanicity.^{63,66} It is also worth nothing that studies which examined the interaction between childhood trauma and cannabis use have revealed that the risk of developing psychosis following childhood trauma is (at least partially) independent from that conveyed by cannabis exposure.^{71,72} Similar results have been observed in studies which examined the relative contribution of childhood trauma while controlling for genetic vulnerability to psychotic symptoms or disorders.^{73,74} Therefore, the quality of all included studies and the sensitivity analyses support the conclusion that childhood trauma is substantially associated with an increased risk for psychosis.

We cannot rule out the effect of proximal and distal interactions of adversity with other factors (eg, cannabis use, genes, urbanicity) in the current meta-analysis because most studies did not correct for these interactions or corrected for only a subset of these factors as possible moderators. However, since the analysis which included only adjusted ORs still showed a significant association it appears that there is a substantial true effect of childhood experience on psychosis. Additionally, due to a lack of studies focusing on specific age of trauma occurrence, it was not possible to address issues regarding the influence of age of exposure to psychosis outcome. Finally, the psychosis literature has tended to focus exclusively on

hallucinatory and delusional symptoms and not on other symptoms. Therefore, the existing data did not allow us to test whether adversity was specifically associated with the development of specific symptoms.

In conclusion, our review of 41 studies found evidence that childhood adversity is substantially associated with an increased risk for psychosis. This finding, combined with other findings on the impact of traumatic experiences in childhood on both general health⁶ and mental health^{1,4,5} stress the importance of these disruptive experiences early in development on subsequent functioning in the adult. The implications of our findings for primary prevention are obvious and urgently in need of greater attention.^{75,76} A range of psychosocial treatment approaches to psychosis, which are more likely to address the sequelae of adverse childhood events, have been found to be effective for many patients and should be made more available.⁷⁷

Our findings suggest that clinicians should routinely inquire about adverse events in childhood in order to develop comprehensive formulations and treatment plans when working with patients with schizophrenia or similar diagnoses.⁷⁸ Psychosocial interventions which have been used for patients affected by trauma might be considered among the treatment options for patients with psychosis. The current review focused on specific types of adverse events (abuse, neglect, parental death, and bullying). Nevertheless, adversity is a heterogeneous concept (including types of exposure not considered here, for instance medical illness, exposure to war, natural disasters, parental separation). Future studies should focus on differentiating adversity type, as well as consider the possible interaction between trauma and other risk factors (eg, cannabis, genetic risk), the developmental stage of exposure to trauma, and mechanisms linking adversity to specific positive and negative symptoms.^{79,80}

Supplementary Material

Supplementary material is available at <http://schizophreniabulletin.oxfordjournals.org>.

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