REVIEW

Traumatic experiences in childhood and adolescence: a meta-analysis of prospective studies assessing risk for psychosis

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Abstract

Evidence of the association between traumatic experiences and psychosis are uncertain with respect to temporal order, clinical outcomes and the role of the age and genetic liability. The aim of the present meta-analysis was to explore the temporal relationship between the development of psychosis and traumatic exposure using prospective studies and to examine the role of moderation factors on overall effect sizes. Studies were identified by searching Embase-Ovid, PsycINFO (EBSCO), Pubmed, Scopus, Web of Science databases, and yielded an initial total of 9016 papers, leaving finally 23 after the screening process. Three sets of meta-analyses estimated the risk of developing psychotic experiences or full clinical psychosis by having experienced maltreatment by an adult or bullying by peers or parental death, using the random-effects model. Bullying by peers (OR = 2.28 [1.64, 4.34]), maltreatment by an adult (OR = 2.20 [1.72, 2.81]) and parental death (OR = 1.24 [1.06, 1.44]) all increased the risk of psychosis. Moderator analysis showed that negative effects of bullying were detected especially in those with genetic liability for psychosis and exposure to multiple trauma types; studies with higher prevalence of males showed a stronger risk for those exposed to parental death. No significant meta-regression was found between the risk of developing a full clinical psychosis or a psychotic experience. Lack of studies hampered the results about the age of trauma occurrence. The cumulative effect of being bullied from peers and experiencing other adversities during childhood and/or adolescence, together with genetic liability for psychosis, appears to confer the highest risk for developing psychotic symptoms later in life.

Keywords Maltreatment · Bullying · Parental death · Trauma · Longitudinal studies · Psychosis

Introduction

A growing body of literature over the past decades has shown that consequences of childhood trauma include the increasing in risk of psychotic outcomes [1–5]. A recent meta-analysis focusing on the effect of specific traumas including maltreatment, bullying and parental death during childhood, revealed that, with the exception of parental death, none of specific type of trauma is a stronger predictor of psychosis than any other, suggesting that other adversity-related variables such as age of exposure and multi-victimization might be more strongly related to psychosis risk than exposure type [2]. There is actually some evidence that critical periods exist in which certain brain regions are particularly sensitive for the effects of stressors, and that regions most sensitive differ between time frames in which the abuse occurred [6]. Arseneault et al. [4] tested if key element such as the perception of threat may suggest causal pathways to later psychosis in a birth cohort. They found that the intention to harm, in the form of maltreatment by adults and bullying by peers, was strongly associated with children's reports of psychotic symptoms compared to having experienced an accident. Furthermore, the findings suggest that an element of threat, or a perception of threat, could trigger psychotic symptoms, rather than the form the abuse may take (e.g., physical, sexual, or relational). Research shows that associations were usually stronger with increasing frequency and severity of the trauma experienced [5, 7]. Dose–response effects of trauma on psychosis are

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of particular importance, since childhood traumatic experiences tend to cosegregate, so that being exposed to one type of adversity increases the risk of exposure to another [8]. Findings from longitudinal studies controlling for genetic risk for psychotic symptoms or disorders [9, 10] revealed that trauma is related to risk of psychotic symptoms in a dose-response fashion using a cumulative index of trauma, which is consistent with the findings from other studies [11].

Previous findings reported that early traumatic and stressful experiences are related to the development of psychotic symptoms later in life across the continuum of psychosis, from non-clinical expressions of psychotic symptoms to psychotic disorder [12]. While the results of the population-based non-clinical studies support the role of bullying, sexual or physical abuse in the subsequent development of psychotic symptoms [1, 13, 14], the results from the clinical studies, however, do not allow an unequivocal conclusion, suggesting the need for further research. Scientific literature also showed likely interaction between trauma and genetic liability to psychosis [15], and early adversity was shown to moderate genetic risk of psychosis outcomes in two adoption studies [16, 17]. A high prevalence of trauma has also been reported in individuals at ultra-high risk of developing psychosis [18]. It is, therefore, possible that potentially causal effects of childhood trauma act independently of pre-existing genetic liability to increase risk of psychosis and that type, frequency and severity of the trauma are the crucial factors determining risk [19].

The present meta-analysis aims to systematically collect studies prospective in nature, that have explored the temporal relationship between traumatic experiences during childhood/adolescence and the development of psychosis experiences or full clinical psychosis later in life. To our knowledge, this is the first study that will determine to what degree the following potential moderators could influence the overall effect sizes: the age of exposure, the exposure to multiple trauma types, the role of genetic liability and the development of a later "psychosis experience" compared to "full clinical psychosis". Furthermore, study methodological factors like the length of the interval between data collection waves (follow-up duration), the number of assessments, and the way the exposure has been assessed (referred to a time interval/lifetime/both) will be considered as potential moderators, since they may be source of measurement unreliability [20, 21] and their knowledge may help researchers to plan new data collections aiming to a better risk estimate. For this reason, the quality assessment for longitudinal studies will be tested as moderator too.

Prospective design allows a number of methodological advantages such as the establishment of a temporal order and the avoidance of recall and sampling bias [22, 23]. We aimed to assess the risk of psychosis for traumatic experiences characterized by an intention to harm, such as maltreatment by an adult or bullying by peers and for those not characterized by an intention to harm, such as death of a parent. All such types of trauma have been associated with psychosis [1, 24, 25], yet these findings offer little insight into the mechanisms underlying this association. Disentangling whether the intention to harm is the key element involved in trauma risk may suggest causal pathways from childhood trauma to later psychosis. Three separate meta-analyses will compute effect sizes for each risk factor.

Methods

Eligible studies were identified by searching the literature databases Embase-Ovid, PsycINFO (EBSCO), Pubmed, Scopus, Web of Science. The following set of keywords was considered: TITLE-ABS-KEY (maltreat* OR "child abuse" OR "physical abuse" OR "sexual abuse" OR "psychological abuse" OR "emotional abuse" OR bully* OR bullied OR neglect* OR "parent* death" OR "parent* loss" OR traum* OR advers* OR "peer victim*" OR "peer harassment" OR "peer aggression" OR "peer rejection" OR ostracism OR mobbing) and AND TITLE-ABS-KEY (psychosis OR psychotic OR "psychosis-like" OR prodrom* OR "ultra high risk" OR uhr OR hallucinat* OR delusion* OR schizoaffective OR schizophrenia OR schizophrenic OR depersonali* OR dereali* OR paranoia* OR paranoid OR illusion*) AND TITLE-ABS-KEY ("follow up" OR transition OR conversion OR longitudinal OR incidence OR predict* OR "cohort study" OR prospective*). Queries were limited to those involving human subjects and published in English language and focused solely on articles published in peer-reviewed journals to enhance the methodological rigor of the included studies. Several inclusion criteria were used to select eligible studies: (1) they had to be prospective in nature; (2) psychotic subjects had to be excluded at the study baseline; (3) exposure was specifically measured during childhood or/and adolescence (without additional timing details). Exclusion criteria were the following: (1) retrospective and (2) cross-sectional studies (3) studies focusing on personality disorders (e.g., schizotypical and schizoid personality disorder), (4) previous meta-analysis and (5) literature review without numerical results. (6) Studies published in languages other than English were excluded because of time and resource limitations. (7) Studies conducted on participants with organic, drug-induced or secondary psychoses, or on prodromal samples were excluded.

Extracted data were organized into three domains for risk factors (maltreatment, parental death, bullying) and two domains for outcomes (psychotic experience and full clinical psychosis); within each domain, data were further categorized into specific items (physical abuse, sexual abuse, emotional abuse and neglect for maltreatment risk;

victimization, mobbing, harassment, rejection, aggression, ostracism perpetrated by peers for bullying risk; unusual thought content, hallucinations for psychotic experience outcome; psychotic disorder, schizophrenia, schizoaffective disorder for full clinical psychosis outcome), (Table 1). An outcome or a risk factor was coded as present if any of the specification was investigated. Previous literature on the different type of traumatic experience associated with psychosis onset guided the classification into applicable domains [2, 26–29]. Eligibility was assessed by one researcher and checked independently by two researchers for the 10% of the whole number of studies extracted, following a 3-stage procedure: title screening, abstract screening, and whole article screening. Any intercoder discrepancy in the 10% subsample was resolved during regular consensus meetings. In the first phase, A.P. screened all the titles independently and E.C. screened the 10% subsample. For the subsample, 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 (agreement 93.1%). In the third phase, complete texts were examined to reach final decisions on inclusion with agreement levels of 95% (A.P. and A.T.). 10% of eligible reports were independently coded by 2 researchers. In case of disagreement, the discrepancy was resolved in consensus meetings.

Both diagnostic and dimensional measures of psychosis were considered eligible. Diagnostic outcomes were defined as a diagnosis of: psychotic disorder, schizophrenia, schizoaffective disorder, based on DSM-III, DSM-III-R, DSM-IV, DSM IV-TR, DSM 5, Research Diagnostic Criteria, International Classification of Diseases, Ninth Revision (ICD-9), ICD-10, or psychiatrist evaluation. Dimensional outcomes were defined in terms of individuals in the general population reporting psychotic symptoms, including subclinical psychotic experiences. Different instruments used in primary studies to measure psychotic experiences or full clinical psychosis are shown in Table 1. In the case of studies with overlapping samples or when samples were reported in multiple articles, we selected the most appropriate based on the most large study sample.

We performed three sets of meta-analysis, according to the PRISMA guidelines [30] to estimate effect sizes for exposure to each type of traumatic experiences: maltreatment, bullying, or parental death. In each meta-analysis, we applied the same plan of analyses, as further detailed below. Statistical analyses were performed through the meta-analytic software ProMeta 3. First, we computed an effect size (odds ratio) for each study, coding available data. Values of the odds ratio higher than 1 indicate that experiencing a negative event (maltreatment, bullying, or parental death) increased the risk of psychosis. For each effect size, we also computed its 95% confidence interval and statistical significance. Effect sizes were pooled across studies for obtaining an overall effect size with the inverse-variance method. We used the random-effects model as a conservative approach to account for different sources of variation among studies (i.e., within-study variance and between-studies variance) [31]. To examine heterogeneity across studies, we computed both Q and I^2 statistics. A significant Q value indicates the lack of homogeneity of results among studies. I^2 estimates the proportion of observed variance that reflects real differences in effect sizes, with values of 25, 50, and 75% that can be considered low, moderate, and high, respectively [32]. To explain this heterogeneity, we conducted analyses of moderation factors. We tested continuous moderators: demographics (gender, age of exposure); methodological characteristics of the studies (duration of follow-up, number of assessments, study quality based on the New Castle–Ottawa quality assessment scale [33] for cohort study) by means of meta-regressions. Categorical moderators included: clinical outcomes (full clinical psychosis vs psychotic experience); presence of risk factors (genetic liability, considered present if at least one first-degree parent was affected by a psychotic disease); multiple-trauma-type exposure vs single-trauma-type exposure (due to the heterogeneous methods exhibited by the primary studies for the estimate of a dose–response relationship between traumatic experiences and psychosis, it was possible to extrapolate only such dichotomous variable); methodological characteristics of the studies (risk referred to a time interval vs lifetime risk vs both) that were tested by means of subgroup analyses. We checked for potential outliers, by examining standardized residuals for each study. If there were studies with significant standardized residuals, we conducted sensitivity analyses to check the stability of study findings, computing how the overall effect size would change removing one study at a time. Finally, we performed multiple publication bias analyses to control for the fact that published studies may have a larger mean effect size than

Table 1 Domains for risks and outcomes

Domain	Domain
Risk factors	**Outcomes**
Maltreatment:	**Psychotic experience:**
Sexual abuse,	Unusual thought content
Physical abuse	Hallucinations
Emotional/psychological abuse	
Neglect	
Parental death:	**Full clinical psychosis:**
Death of a parent	Psychotic disorder,
Bullying:	Schizophrenia
Victimization,	Schizoaffective disorder
Mobbing	
Harassment	
Rejection	
Aggression	
Ostracism	

unpublished studies [34, 35]. We examined the funnel plot, and statistically tested its asymmetry employing the Egger's [36] regression method and the Begg and Mazumdar's [37] rank correlation method. To understand more in-depth the potential impact of publication bias, we then used the trim and fill procedure [38].

Results

Our search covered articles that were available in the databases until October 2018 and yielded an initial total of 9016 papers. Comparison of the retrieved titles identifies 2961 studies that were duplicates, thus leaving 6055 abstracts for further evaluation. Then we screened manuscript titles and abstract to examine for relevance. In the final screen, 270 full texts were read to validate inclusion, leaving 23 papers considered (Fig. 1) combining a total of 146,108 participants. Data for analysis were obtained from 15 articles for maltreatment (Abajobir et al. [3]; Cutajar et al. [39]; Ellen De Loore [5]; Elklit and Shevlin [40]; Arseneault et al. [4]; Kelleher et al. [41]; Lataster et al. [42]; Spauwen et al. [43]; Janssen et al. [13]; Fisher et al. [44]; van der Ven et al. [45]; van Nierop et al. [46]; Konings et al. [47]; Kramer et al. [48]; Kuepper et al. [49]), 4 articles for parental death (Alvarez-Jimenez et al. [25]; Lee et al. [50]; Makikyro et al. [51]; Laursen et al. [52]) and 8 articles for bullying (Arseneault et al. [4]; Boden et al. [53]; Catone et al. [54]; Ellen De Loore [5]; Fisher et al. [34]; Kelleher et al. [41]; Shakoor et al. [55]; Wolke et al. [28]). Four studies (Arseneault et al. [4]; Ellen De Loore [5]; Fisher et al. [34]; Kelleher et al. [41]) reported data both for maltreatment and bullying exposures. Table 2 summarizes the characteristics of the eligible studies. As displayed in Fig. 2, studies were consistent in showing that maltreatment, bullying and parental death increased the risk of psychosis and most of them were statistically significant.

Associations between traumatic experiences and psychosis

Overall effect sizes of bullying by peers (OR = 2.28 [1.64, 4.34]), maltreatment (including physical abuse, sexual abuse, emotional abuse and neglect) by an adult (OR = 2.20 [1.72, 2.81]) and parental death (OR = 1.24 [1.06, 1.44]) are reported in Table 3. Results indicate that all such traumatic experiences are associated with development of psychosis later in life.

Heterogeneity, and sensitivity analyses

Results of the meta-analyses on maltreatment and bullying were characterized by significant heterogeneity. We further

explored this by means of moderators analysis reported in the next section. In contrast, results of the meta-analysis on parental death, based on a small number of studies, were more homogeneous (Table 3). In addition, we checked for potential outliers. We found only two potential outliers in the meta-analysis on maltreatment (Elklit and Shelvin [40]; Van Nierop et al. [46]; respectively, OR = 16.98 [5.60, 51.42] and OR = 34.40 [4.40, 267.40]); whereas, no potential outliers were detected in the meta-analyses on bullying and parental death. Sensitivity analyses indicated that results of the meta-analysis on maltreatment did not change substantially excluding such studies. Thus, meta-analytic results were robust and these two studies could be included in the meta-analysis.

Analysis of moderation factors

To explain heterogeneity, we conducted analyses of potential moderation factors. First, we tested continuous moderators by means of meta-regressions as reported in Table 4. Results of most meta-regressions were non-significant. Findings of the two meta-regressions that were statistically significant highlighted that the negative effects of parental death were detected in studies with more risk assessments and with a lower percentage of females.

In a second set of moderators, we tested for categorical moderators through subgroups analyses as reported in Table 5. In the meta-analysis on maltreatment, only one moderator (lifetime risk) was close to statistical significance: results indicated a trend to a lower risk of psychosis when the risk was assessed as lifetime. In the meta-analysis on bullying, the risk of psychosis was mainly detected in studies that included samples with genetic liability and in studies that considered exposure to multiple trauma types, whereas was lower when the risk was assessed as lifetime. For the meta-analyses on parental death, it was not possible to test categorical moderators since the number of studies was not enough to perform the analyses.

Publication bias analyses

Finally, we performed multiple publication bias analyses. Some indication of publication bias was detected in the meta-analysis on maltreatment based on the results of Egger's and Begg and Mazumdar's tests (which were both statistically significant) and of the trim and fill procedure (in which five studies were trimmed) (see Table 6); however, this did not change substantially the final results of the meta-analysis. On the other hand, the meta-analyses on bullying and parental death were not affected by publication bias. Overall, these findings suggested that results of the current set of meta-analyses were robust.
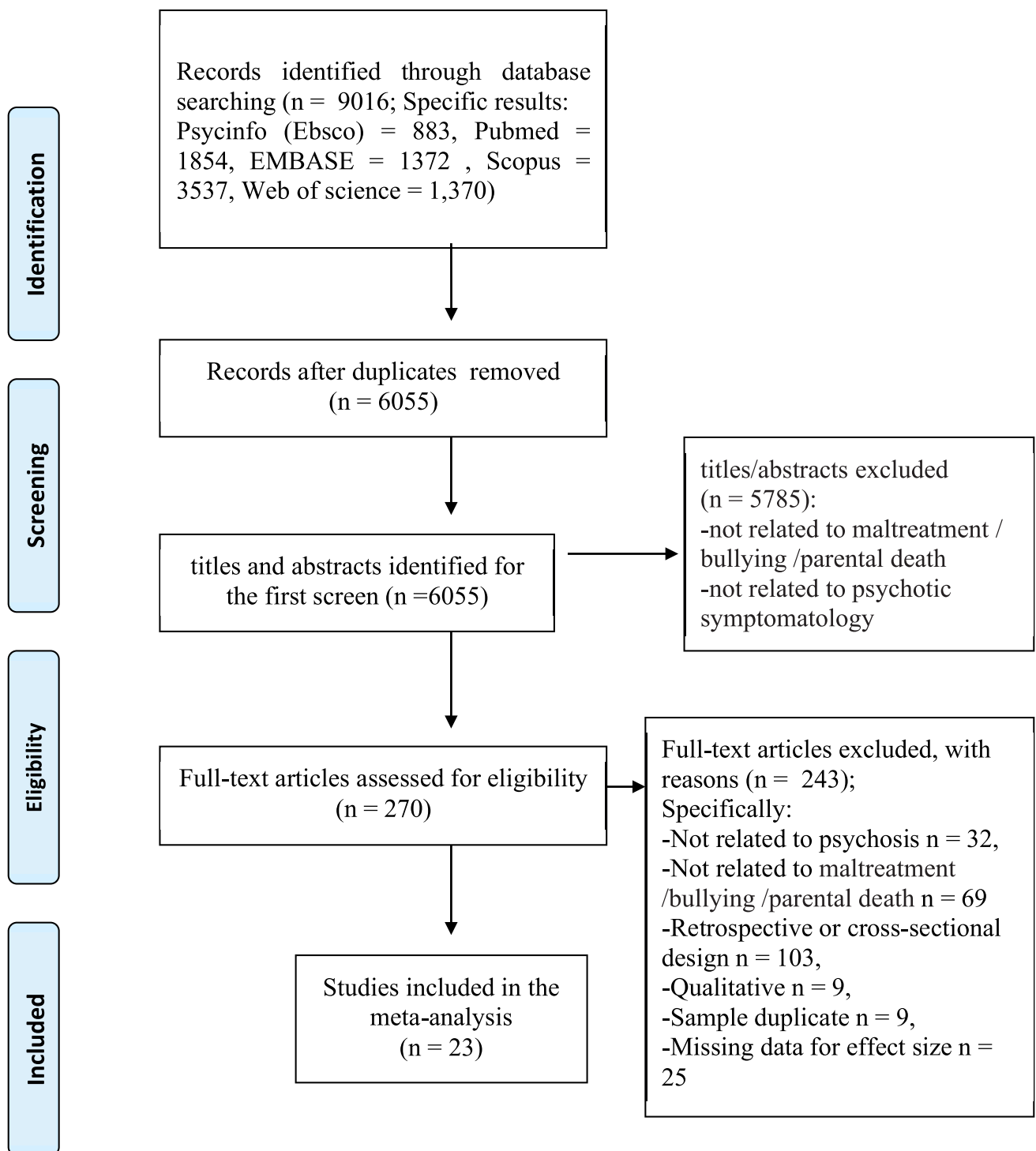
Identification

Records identified through database searching (n = 9016; Specific results: Psycinfo (Ebsco) = 883, Pubmed = 1854, EMBASE = 1372 , Scopus = 3537, Web of science = 1,370)

Screening

Records after duplicates removed (n = 6055)

titles and abstracts identified for the first screen (n =6055)

titles/abstracts excluded (n = 5785):
-not related to maltreatment / bullying /parental death
-not related to psychotic symptomatology

Eligibility

Full-text articles assessed for eligibility (n = 270)

Full-text articles excluded, with reasons (n = 243);
Specifically:
-Not related to psychosis n = 32,
-Not related to maltreatment /bullying /parental death n = 69
-Retrospective or cross-sectional design n = 103,
-Qualitative n = 9,
-Sample duplicate n = 9,
-Missing data for effect size n = 25

Included

Studies included in the meta-analysis (n = 23)

Fig. 1 Prisma flow diagram

Discussion

Results show that traumatic experiences in childhood/adolescence such as bullying by peers (OR = 2.28 [1.64, 4.34]), maltreatment by an adult (OR = 2.20 [1.72, 2.81]) and parental death (OR = 1.24 [1.06, 1.44]) are strongly associated with development of psychosis later in life; those traumas characterized by an intention to harm, like maltreatment and bullying, show a strong and consistent overall risk for psychosis, whereas experiencing a parental death is

Table 2 Characteristic of the eligible studies

Author	Name—country	Sample size	Gender (female %)	Risk factors 1. Maltreatment by adult 2. Bullied by peers 3. Death of parent	Cumulative risk assessment 1. Single risk 2. Multiple risk	Outcome 1. Psychotic experience 2. Full Clinical Psychosis	Age at baseline (y)	Age of trauma exposure (y)	Duration of study follow-up (y)	Genetic liability of the sample	New Castle Ottawa Quality Scale (score)	Instruments measuring risk	Instruments measuring psychosis outcome
Abajobir et al. 2017	Mater-University of Queensland Study of Pregnancy (MUSP)—Australia	3752	NA	1	2	1.2	0–14	< 14	7	NA	8	YASR; PDI	CIDI
Arseneault et al. 2011	Environmental Risk Longitudinal Twin Study (E-Risk)—United Kingdom	2127	51	1.2	2	1	7	< 7	< 5	YES	8	Interview; LHC	Interview
Alvarez-Jimenez et al. 2011	Early Psychosis Prevention and Intervention Centre (EPPIC)—Australia	274	29.9	3	1	2	24	< 24	12	NA	5	Questionnaire	RPMIP
Boden et al. 2016	Christchurch Health and Development Study (CHDS)—New Zealand	1018	45.2	2	1	1	14.5	13–16	20.5	NA	7	Questionnaire	SCL-90; DIS
Catone et al. 2015	British Adult Psychiatric Morbidity Surveys—United Kingdom	4220	NA	2	1	1	NA	NA	1.5	NA	7	Interview	SCAN
Cutajar et al. 2010	Victorian Psychiatric Case Register—Australia	5365	80.1	1	1	2	10.17	0.27–16.99	23.65	NA	8	National Register	National Register

Table 2 (continued)

Author	Name—country	Sample size	Gender (female %)	Risk factors 1. Maltreatment by adult 2. Bullied by peers 3. Death of parent	Cumulative risk assessment 1. Single risk 2. Multiple risk	Outcome 1. Psychotic experience 2. Full Clinical Psychosis	Age at baseline (y)	Age of trauma exposure (y)	Duration of study follow-up (y)	Genetic liability of the sample	New Castle Ottawa Quality Scale (score)	Instruments measuring risk	Instruments measuring psychosis outcome
De Loore et al. 2007	The Netherlands	1129	53.4	1.2	1	1	13.7	< 12	2	NA	7	Questionnaire	DISC-C
Elklit and Shelvin 2010	Denmark	2156	100	1	1	2	26	> 12	15	NA	8	National Register	National Register
Fisher et al. 2013	Avon Longitudinal Study of Parents and Children—United Kingdom	6692	50.9	1.2	1	1	2.75	< 6	10.15	NA	6	BFIS	PLIKSi; SCAN (v.2.0)
Janssen et al. 2004	The Netherlands Mental Health Survey and Incidence Study (NEMESIS)—The Netherland	3876	52.6	1	1	1	41.2	< 16	3	NA	8	Interview	CIDI
Kelleher et al. 2013	Saving and Empowering Young Lives in Europe (SEYLE) study—Ireland	979	45	1.2	1	1	13.72	≤13	1	NA	5	Questionnaire	APSS
Konings et al. 2012	The Greek National Perinatal Study—Greece	1636	55	1	1	1	7	< 7	12	NA	6	Questionnaire	CAPE
Kramer et al. 2012	part of East landers Prospective Twin Survey (EFPTS)—Belgium	508	100	1	1	1	27.1	NA	1.2	NA	7	CTQ	CAPE

Table 2 (continued)

Author	Name—country	Sample size	Gender (female %)	Risk factors 1. Maltreatment by adult 2. Bullied by peers 3. Death of parent	Cumulative risk assessment 1. Single risk 2. Multiple risk	Outcome 1. Psychotic experience 2. Full Clinical Psychosis	Age at baseline (y)	Age of trauma exposure (y)	Duration of study follow-up (y)	Genetic liability of the sample	New Castle Ottawa Quality Scale (score)	Instruments measuring risk	Instruments measuring psychosis outcome
Kuepper et al. 2011	German Early Developmental Stages of Psychopathology (EDSP)—Germany	1923	51.8	1	2	1	18.3	NA	8.4	NA	6	DIA-X/M-CIDI	DIA-X/M-CIDI
Lataster et al. 2012	Early Developmental Stages of Psychopathology (EDSP)—Germany	1722	48.5	1	2	2	8.4	< 24	8.4	NA	6	MIALEC	DIA-X/M-CIDI
Laursen et al. 2007	Denmark	31,752	NA	3	1	2	NA	< 17	16.2	Yes	6	National register	National register
Lee et al. 2012	National Survey of Health and Development—United Kingdom	3275	50	3	1	2	24	< 24	12	NA	5	Interview	PSE
Makykiro et al. 1998	Northern Finland Birth Cohort—Finland	11,017	49	3	1	2	14	< 14	14	NA	9	Interview	National register
Shakoor et al. 2015	Twins Early Development Study (TEDS) and Longitudinal Experiences And Perceptions (LEAP) study—United Kingdom	4826	55	2	1	1	11.56	11–12	4	Yes	9	MPVS	SPEQ

Table 2 (continued)

Author	Name—country	Sample size	Gender (female %)	Risk factors 1. Maltreatment by adult 2. Bullied by peers 3. Death of parent	Cumulative risk assessment 1. Single risk 2. Multiple risk	Outcome 1. Psychotic experience 2. Full Clinical Psychosis	Age at baseline (y)	Age of trauma exposure (y)	Duration of study follow-up (y)	Genetic liability of the sample	New Castle Ottawa Quality Scale (score)	Instruments measuring risk	Instruments measuring psychosis outcome
Spauwen et al. 2006	The Early Developmental Stages of Psychopathology (EDSP) study—Germany	2548	49	1	2	1	15.5	<13	3.5	NA	6	DIA-X/M–CIDI	SCL-90 Revised
van der Ven et al. 2015	Sweden	49,321	NA	1	2	2	19	<19	34	Yes	8	Questionnaire	National register
van Nierop et al. 2013	(Genetic Risk Outcome of Psychosis) GROUP—The Netherland and Belgium	1272	20. 56	1	2	2	28.9	NA	3	Yes	8	Dutch version of CTQ	CASH; SCAN (v.2.1)
Wolke et al. 2014	Avon Longitudinal Study of Parents and Children (ALSPAC)—United Kingdom	4720	56.5	2	1	1	7	NA	11	NA	6	BFIS	PLIKSi

APSS adolescent psychotic symptom screener, *BFIS* bullying and friendship interview schedule, *CAPE* community assessment of psychic experiences, *CASH* comprehensive assessment of symptoms and history, *CIDI* composite international diagnostic interview, *CTQ* Childhood Trauma Questionnaire, *DIA-X/M-CIDI* Munich-Composite International Diagnostic Interview, *DIS* diagnostic interview schedule, *DISC-C* diagnostic interview schedule for children (for DSM-III), *LHC* life history calendar tool, *MIALEC* Munich interview for the assessment of life events and conditions, *MPVS* Multidimensional Peer Victimization Scale, *NA* not available, *PDI* Peter's Delusions Inventory, *PLIKSi* psychosis-like symptoms semi-structured interview, *PSE* present state examination, *RPMIP* Royal Park multidiagnostic instrument for psychosis, *SCAN* schedules for clinical assessment neuropsychiatry, *SCL-90* symptom checklist 90, *SPEQ* Specific Psychotic Experiences Questionnaire, *YASR* young adult self-report
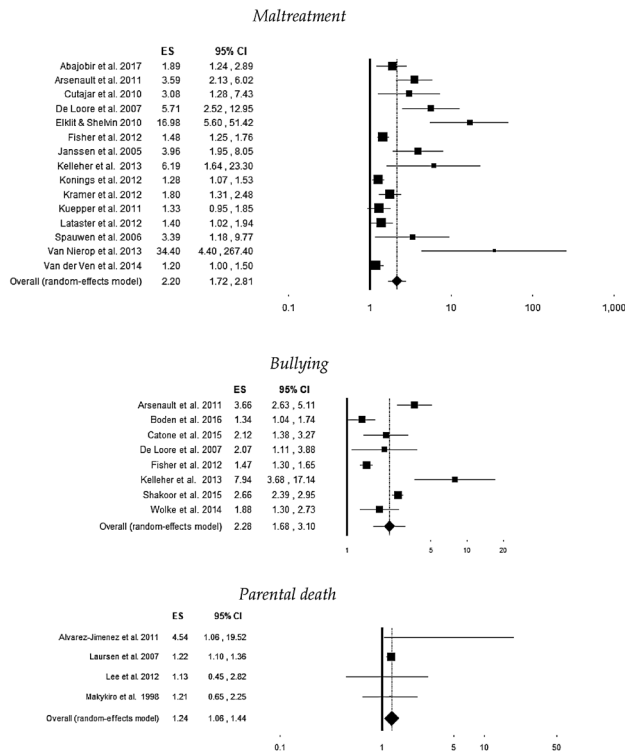
Fig. 2 Forest plots (stratified by risk factor) for the meta-analysis examining the overall association between childhood traumatic experiences and psychosis. *ES* effect size, *CI* confidence interval

Table 3 Overall effect size for each meta-analysis

Risk of psychosis related to:	Overall effect sizes		Heterogeneity	
	k	OR [95% CI]	Q	I^2
Maltreatment	15	2.20*** [1.72, 2.81]	75.56***	81.47
Bullying	8	2.28*** [1.68, 3.10]	86.98***	91.95
Parental death	4	1.24** [1.06, 1.44]	3.12	0

k total number of studies, *OR* odds ratio, *CI* confidence interval

***$p < 0.001$; **$p < 0.01$

associated with a lower risk. Furthermore, genetic liability for psychosis and exposure to multiple traumatic experiences positively moderate the overall association between bullying by peers and psychosis. Male gender and a greater number of assessments in the study design positively moderate the overall association between parental death and risk for psychosis. When the risk was assessed as lifetime, association with psychosis is significantly weaker for bullying and only shows a negative trend for maltreatment ($p = 0.056$). No significant moderation effect on the association between maltreatment and psychosis was found between developing a psychotic experience or a full clinical psychosis. As regards bullying and parental death, it was impossible to test whether their effects were different for participants who reported only psychotic experiences or who received a full clinical psychotic diagnosis since the literature provided only articles that have addressed the association between bullying and psychotic experience and none with full clinical psychosis; whereas, the parental death risk has been studied only in relationship with full clinical psychosis diagnosis. This is an area that needs further research attention, since early traumatic and stressful experiences are related to the development of psychotic symptoms later in life, across the continuum of psychosis, from non-clinical expressions of psychotic symptoms to psychotic disorder [12].

We could not test age of exposure to traumas as a moderator factor because most studies did not report a specific age but intervals, e.g., before age 14, from which it was impossible to create non-overlapping time frames. Previous findings [4] have shown consistency of the risk associated to traumatic events in developing psychosis across timing, but in contrast evidence of effect modification by age has been detected in some studies [43]. Parental death has been previously described as a relevant risk factor for all severe mental disorders, irrespective of age of the proband at the time of risk [52]. Recently, Croft et al. [56] found that adolescence is the age period at highest risk for association with psychosis developed in young adulthood, but temporal proximity to the outcome and the natural resolution of trauma-related psychopathological status that occurs over time [41, 57] could

Table 4 Results of meta-regressions for continuous moderators

Moderators	Meta-analysis on:					
	Maltreatment		Bullying		Parental death	
	k	Slope	k	Slope	k	Slope
Duration of follow-up	15	− 0.02	8	− 0.05	4	− 0.07
Number of assessments	14	− 0.30	8	− 0.06	3	1.31*
% females	13	0.01	7	− 0.02	3	− 0.07***
Study quality[a]	15	0.25	8	0.00	4	−0.00

k total number of studies included in the meta-regression

[a] Based on the New Castle–Ottawa quality assessment scale for cohort study [33]

*$p < 0.05$; ***$p < 0.001$

Table 5 Results of meta-regressions for categorical moderators

Moderators	Meta-analysis on:					
	Maltreatment			Bullying		
	k	OR [95% CI]	Contrast	k	OR [95% CI]	Contrast
Diagnosis			1.08			Na
Full clinical psychosis	5	3.12** [1.54, 6.30]				
Psychotic experience	10	2.09*** [1.61, 2.72]				
Sample with genetical liability			0.60			3.90*
Yes	3	3.43* [1.06, 11.10]		2	3.00*** [2.21, 4.07]	
No	12	2.14*** [1.65, 2.76]		6	1.95*** [1.45, 2.63]	
Cumulative risk			1.67			5.45*
Single trauma type	8	2.68*** [1.83, 3.92]		7	2.12*** [1.54, 2.91]	
Multiple trauma types	7	1.90*** [1.33, 2.72]		1	3.66*** [2.63, 5.11]	
Risk assessment			5.78[a]			12.65**
Referred to a time interval	5	5.98** [1.98, 18.10]		4	2.42*** [1.50, 3.92]	
Lifetime	7	1.62*** [1.31, 2.02]		3	1.69*** [1.29, 2.21]	
Both	3	2.34* [1.12, 4.93]		1	3.66*** [2.63, 5.11]	

[a]$p = 0.056$. Na = result not available since there were not enough studies to perform the analysis

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$

affect risk more than age of exposure. The risk for psychotic experiences has been found stronger after exposure to multiple types of traumas or repeated episodes of trauma at multiple age periods, which is consistent with a dose–response relationship and findings from other studies [58].

Meta-regression analysis revealed that the exposure to other types of trauma, in addition to the bullying exposure, influenced the observed overall effect size between bullying exposure and development of psychosis later in life. The finding suggests that multi-victimization might be related to psychosis risk and that dose–response effect of trauma on psychosis is of particular importance. This is consistent with previous literature, which suggested that other adversity-related variables should be investigated, rather than the exact nature of the exposure [29, 56]. A possible explanation

Table 6 Publication bias analyses

Risk of psychosis related to:	Egger's test	Begg and Mazumdar's test	Trim and fill	Fail safe N
Maltreatment	6.92***	2.72***	5 OR = 1.69*** [1.30, 2.19]	583
Bullying	0.42	0.49	0	607
Parental death	0.90	1.36	0	7[a]

In the trim and fill method, results indicate the number of trimmed studies and the estimated effect size

[a]This value is below Rosenthal's rule of thumb

***$p < 0.001$

of the early and recent adversity roles in predicting psychotic symptoms could be found in the diathesis–stress model of psychosis [59]: the experience of psychosocial stress early in life may also contribute to the diathesis for psychosis by accentuating the vulnerability state, whereas the cumulative impact of stressors occurring later in life may subsequently trigger psychotic expression [60].

Gender does not moderate results, except for the parental death, where males might show a higher probability for developing psychosis. This is in line with previous literature, where female gender has been associated with a greater tendency to express their distress in terms of recognizable depression rather than psychosis [39] although an earlier study [61] found an increased rate of psychotic disorders in child sexual abuse victims that was largely accounted for by schizophrenic disorders among female victims.

Our results show that genetic liability for psychosis positively moderates the bullying risk and not the other risks. Interpretation of interaction of risk factors has been shown before in depression: the genetic liability for depression acts in part by increasing the sensitivity to stressful life events [62] but the same genes also influence the probability that individuals will experience stressful life events in the first place (one environmental factor controlling exposure to the other) [63]. Being bullied by peers during childhood and adolescence seems to have an important role in the interplay of gene–environment interaction.

Two methodological characteristics showed a significant moderation role of the overall effect sizes: the assessment of risk exposure as a lifetime questions (compared to the risk exposure assessment as questions referred to a time interval,

or both), and the number of risk assessments: the risk of psychosis related to bullying was detected to a lesser extent in studies that included samples with lifetime exposure assessment and the risk of psychosis related to parental death was mainly detected in studies that included samples with more than one assessments. For further research, this would suggest that if the study is planned for having multiple assessments of exposure to traumas and asking for an age interval of exposure, the risk for psychosis might be better estimated. Interval length between data collections has been previously associated with the stability of a developmental dimension, showing that the latter decreases as time intervals increase [64]. In this study, such methodological characteristic did not affect the overall association between traumas and later psychosis, neither the methodological quality of longitudinal studies has been found to moderate the risk estimate.

Strengths and limitations

The present meta-analysis included only prospective studies where victimization exposures were assessed prior to the psychotic phenomena onset, allowing the establishment of a temporal order and the avoidance of recall and sampling bias. To our knowledge, this is the first meta-analysis that addressed the role of methodological characteristics of studies, clinical outcomes and genetic liability as potential moderators of overall effect sizes. Limitations encompass: (1) the overall effect size calculation based on the collection of rough effect sizes from each study included, thus excluding the possibility of controlling for potentially confounding factors such as intelligence quotient and social background (2) the impossibility of testing potential moderation factors like age of exposure to trauma and type of outcome with respect to bullying exposure (psychotic experience or full clinical psychosis) due to lack of studies reporting such information. (3) Finally, we could suppose that results of most meta-regressions were non-significant due to a power issue, caused by the small number of studies available for each analysis.

Conclusion

The cumulative effect of being bullied from peers and experiencing other adversities during childhood and/or adolescence, rather than its timing, together with having a first degree family affected from psychosis, appears to confer the highest risk for developing psychotic symptoms later in life. Maltreatment and parental death are also associated with later psychosis, the latter especially in males. Planning a longitudinal study with multiple assessments of exposure

to traumas and information about exposure age interval may better estimate the risk for psychosis.

Future directions

Clinical implications for those known to have been a victim of traumatic experiences in childhood or adolescence regard the psychopathology assessment, commonly related to disorders like depression and PTSD, that may not consider and identify other treatment needs, particularly for low prevalence disorders like psychosis and especially when genetic liability for psychosis is present. Research implications encompass some methodological suggestions: the planning of multiple assessments of exposure to traumas, so that the risk for psychosis might be better estimated; the assessment of the number and duration of traumatic episodes and the age interval of exposure, since previous research findings are still inconsistent in relation to the role of the age on the association with later development of psychosis; the assessment of psychosis later in life across the continuum of its manifestations, both as non-clinical expressions and as psychotic disorders.

Lastly, other traumas may be considered in the future as risk factors for developing psychosis, such as sibling bullying [65].

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest. The study does not contain clinical studies or patient data.

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