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Childhood adversities in people at ultra-high risk (UHR) for psychosis: a systematic review and meta-analysis

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Review Article

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Abstract

Childhood adversities have been reported to be more common among individuals at ultra-high risk (UHR) for psychosis. This paper systematically reviewed and meta-analysed (i) the severity and prevalence of childhood adversities (childhood trauma exposure, bullying victimisation and parental separation or loss) among the UHR, and (ii) the association between adversities and transition to psychosis (TTP). PsycINFO, PubMed and Embase databases were searched for studies reporting childhood adversities among UHR individuals. Only published articles were included. Risk of bias was assessed using Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline (von Elm *et al.*, 2007) and the tool developed by Hoy *et al.* (2012). Seventeen case–control, cross-sectional and longitudinal studies were included. UHR individuals experienced significantly more severe trauma than controls, regardless of trauma subtype. UHR were 5.5, 2.5 and 3.1 times as likely to report emotional abuse, physical abuse and bullying victimisation, respectively. There was no association with parental separation. However, childhood trauma was not significantly associated with TTP (follow-up periods: 6 months to 15 years), suggesting that trauma alone may not be a sufficient risk factor. Sexual abuse was associated with TTP but this may have been driven by a single large study. Potential confounders and low rates of TTP among UHR are limitations of this review. This is the first meta-analysis that quantitatively summarises the associations between childhood adversities and TTP among UHR, and between specific abuse subtypes and TTP. Specific recommendations have been made to increase the quality of future research. PROSPERO registration no. CRD42017054884.

In recent years, growing research interest and clinical focus have been placed on individuals at ultra-high risk (UHR) for psychosis. This is because 6–17% of UHR individuals develop psychosis during the observational window (Cannon *et al.*, 2016; Carrión *et al.*, 2016), and this risk is significantly higher when individuals are not identified early to receive intervention services (Simon and Umbricht, 2010; Fusar-Poli *et al.*, 2015). Furthermore, psychiatric comorbidities are highly prevalent within this population (73% had comorbid axis I diagnoses; 40% had comorbid depressive disorders (Fusar-Poli *et al.*, 2014)). Thus, it is important to understand what predisposes these vulnerable individuals to psychosis.

There are two validated criteria used to identify UHR individuals: the clinical high risk (CHR) criteria, assessed using the Structured Interview for Prodromal Syndromes Criteria (SIPS) (Miller *et al.*, 2002) and the UHR criteria assessed using the Comprehensive Assessment of At-Risk Mental States (CAARMS) (Yung *et al.*, 2005). These individuals are identified if they meet criteria for any of the three categories of risk: Attenuated Psychotic Symptoms (APS) refer to the onset or worsening of subthreshold psychotic symptoms in the prior 12 months; Brief Limited Intermittent Psychotic Symptoms (BLIPS) refer to the onset of transient psychotic symptoms for less than 1 week; Genetic Risk and Deterioration (GRD) refers to genetic risk conferred by present schizotypal personality disorder or having a first-degree relative with a psychotic disorder, accompanied with a decrease in functioning within the past year.

Multiple genetic and environmental factors have been found to be linked to an increased risk of psychosis (Matheson *et al.*, 2011). Exposure to childhood adversities and environmental factors have been found to be associated with an increased risk of psychosis (Matheson *et al.*, 2013; Fusar-Poli *et al.*, 2016). These childhood adversities typically include childhood trauma (emotional abuse, physical abuse, sexual abuse, emotional neglect and physical neglect), peer bullying and parental separation or loss.

The evidence surrounding the association between childhood adversities and psychosis has been consistent. According to a recent meta-analysis, 86.8% of UHR individuals reported having prior exposure to childhood trauma (Kraan *et al.*, 2015*b*). Individuals exposed to various adversity subtypes had 2–4 times increased odds of psychosis (Morgan and Gayer-Anderson, 2016). Patients with psychosis were 2.38–3.40 more likely to have been exposed to sexual

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abuse, physical abuse, emotional abuse, bullying or neglect than controls (Varese *et al.*, 2012). Victims of bullying had more than two times the odds of developing psychotic symptoms (Cunningham *et al.*, 2016).

A better understanding of how specific childhood adversities are associated with psychosis can improve the prediction algorithms for risk stratification among UHR individuals (Gee and Cannon, 2011), as well as improve the effectiveness of interventions in reducing the transition to psychosis (TTP) risk. In addition, a pertinent and unanswered question to address is how much childhood adversities influence the risk of TTP. Most systematic reviews were conducted on individuals with psychotic disorders (Read *et al.*, 2003; Morgan and Fisher, 2007; Bonoldi *et al.*, 2013; de Sousa *et al.*, 2014), or specifically in people with schizophrenia (Matheson *et al.*, 2013). Some reviews broadened the scope to include both psychotic disorders and any psychotic experiences (Varese *et al.*, 2012), while others included studies that report only the severity of psychotic experiences in the general population (van Dam *et al.*, 2012; Trotta *et al.*, 2015) or the UHR population (Fusar-Poli *et al.*, 2013, 2016; Kraan *et al.*, 2015*b*; Brew *et al.*, 2017).

A systematic review by Brew *et al.* (2017) narratively summarised significant associations between sexual abuse and TTP among those at high risk based on one study site in Melbourne; however, more recent studies not included in their review did not find any associations between all subtypes of childhood abuse and TTP (Kraan *et al.*, 2015*a*; Stowkowy *et al.*, 2016). To date, no meta-analyses have investigated childhood adversities and TTP among the UHR population.

The present systematic review and meta-analysis seek to update the literature linking childhood adversities to the development of psychosis. The aims are twofold; to investigate (a) the severity and prevalence of childhood adversities among UHR individuals as compared with controls, and (b) whether childhood adversities increase the risk of TTP among UHR individuals. Whenever possible, meta-analyses were conducted.

Methods

This review followed the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) statement (Liberati *et al.*, 2009). The protocol was registered in PROSPERO (https://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42017054884; registration number: CRD42017054884).

Search strategy

Three databases were searched: PsycINFO, EMBASE and PubMed. The first search was on 16 November 2016 and the final re-run was on 25 September 2018. The following search themes were used: (1) populations which were at UHR or CHR ('ultra-high risk', 'clinically high risk', 'high clinical risk', 'prodromal psychosis', 'basic symptoms', 'at risk mental state', 'prodrome', 'UHR', 'CHR', 'attenuated symptoms', 'psychosis risk syndrome', 'psychosis risk symptoms', 'prodromal' or 'clinical high risk'); (2) exposure to childhood adversities ('trauma', 'life event', 'abuse', maltreat*, bully*, 'bullied', 'parental loss' OR 'parental death'); and (3) schizophrenia ('psychosis', 'psychotic disorder', 'psychotic', schizo* OR schizophren*). The Boolean operator 'and' was used to join these search themes within a single search. Medical Subject Heading (MeSH) terms were also utilised to expand the database search. Publication types were restricted to published articles and articles in press whenever possible, i.e. abstracts were excluded.

The titles and the abstracts of publications were screened concurrently. Next, relevant full articles were screened by two independent authors, one of whom is a content expert in the field. Reference lists of eligible articles were hand-searched for any additional articles. Disagreements about the inclusion of a study were resolved through discussions with the third author.

Inclusion and validity

Population

All studies must have recruited individuals at high risk of psychosis, as determined by the following criteria: (i) CHR, as assessed by SIPS (Miller *et al.*, 2002), or (ii) UHR, as assessed by the CAARMS (Yung *et al.*, 2005). Participants could have been identified in early intervention clinics, hospitals or detected in a cohort recruitment from a geographical region. Individuals with current or previous psychotic disorder, intellectual disability, history of substance dependence or neurological disorders were excluded. Studies that only measured the levels of psychotic experiences among participants but did not use the above-mentioned criteria to define UHR were also excluded.

Measures of childhood adversity

Types of childhood adversities include (i) childhood trauma, (ii) bullying victimisation and (iii) parental separation or loss. An eligible study would have measured any of these three types of adversities before the age of 18. Studies that only reported adversities after childhood were excluded. Prevalence was measured by the percentage of individuals who reported the adversity, while severity was measured by the magnitude of quantitative scores (i.e. higher scores suggest higher severity of exposure).

Types of studies

Observational studies (case–control, cross-sectional and cohort designs) were included. The prevalence of childhood adversities among participants was measured retrospectively in a cross-sectional design or prospectively in a longitudinal study. The reported statistic could be dichotomous (exposed to adversity or not) or continuous (scores rating the severity of exposure). Only longitudinal studies were able to capture the TTP among UHR over at least two assessment time points. Studies were published from January 1990 onwards. There were no language restrictions. Only published journal articles were included.

Critical appraisal

The risk of bias (RoB) in case–control and longitudinal studies was assessed using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) as a guideline (von Elm *et al.*, 2007); the RoB in cross-sectional prevalence studies was assessed using the tool developed by Hoy *et al.* (2012). Each study was assigned a score to determine if there was 'low', 'moderate' or 'high' RoB at the outcome level. This rating process was performed independently by two authors and inter-rater reliability was calculated using Cohen's κ ($\kappa > 0.80$). Discrepancies were discussed between the authors and a consensus rating was assigned. These ratings were used to evaluate if the study quality substantially modified some of our findings. Studies with high RoB were not included in this review.

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Data extraction and analysis

Relevant data were extracted from each publication (see Supplementary Materials S1 for the data extraction form). Comparisons were made between UHR and healthy controls: the exposure to (a) childhood trauma and trauma subtypes, (b) bullying victimisation and (c) parental separation or loss. A second set of analyses was conducted to investigate the effect of childhood adversities on TTP.

In the case of overlapping samples being reported in multiple publications, one publication was selected for a meta-analysis based on its sample size, relevance of findings, and the availability of a control group.

Odds ratios (OR) and hazard ratios (HR) were meta-analysed using random effects (DerSimonian and Laird), inverse-variance methods. When raw data were presented, Hedges' g and ORs were computed for continuous data and dichotomous data, respectively.

Heterogeneity among effect size estimates was assessed using the I^2 statistics obtained from a χ^2 test. Sensitivity and subgroup analyses were conducted when the studies within each meta-analytic calculation differed widely in their RoB ratings, when a group of studies used a specific trauma instrument, or when there were obvious outliers. Publication biases were calculated when there were at least ten studies in a particular meta-analytic calculation. All meta-analyses were conducted in Review Manager 5.3 (http://community.cochrane.org/tools/review-production-tools/revman-5).

Other information associating childhood adversities with positive symptoms and with social and occupational functioning among the UHR were also summarised qualitatively. Any mediating variables linking adversities with UHR was also reported.

Effort was made to contact some authors when more information was required; only 30.7% of them replied with clarifications. However, all authors did not have the requested data. Contact details of some authors were not available or updated. Details can be available upon request.

Results

Search results

Figure 1 shows the PRISMA flowchart of the search results. Duplicates and abstracts were excluded from the 852 records found. Out of the 474 unique publications found, 17 studies (28 publications) were included in the systematic review (Table 1). Of the 17 studies, 10 recruited control groups and were eligible for meta-analytic calculations. Other studies were summarised qualitatively. Forest plots of all meta-analyses are presented in Supplementary Materials (S2–S6). There was a high average inter-rater reliability for RoB among the two authors (95% agreement, $\kappa = 0.89$, 95% CI 0.85–0.93). None of the studies had high RoB ratings (Table 1).

Childhood trauma

Sixteen studies retrospectively measured childhood trauma using the Childhood Trauma Questionnaire (CTQ), Trauma and Distress Scale (TADS), Childhood Trauma & Abuse Scale, Early Trauma Inventory (ETI), or Childhood Experience of Care and Abuse Questionnaire (CECA-Q).

Severity of childhood trauma

Higher total trauma scores suggested more severe childhood trauma exposure. In studies that administered the CTQ to UHR individuals only, moderate-to-severe levels of childhood trauma were reported in South England (Allen *et al.*, 2017), London (Appiah-Kusi *et al.*, 2017) and Australia (Cotter *et al.*, 2016).

UHR participants reported significantly higher total trauma scores than controls (Hedges' $g = 1.38$; 95% CI 0.92–1.84, $Z = 5.92$, $p < 0.001$), suggesting that UHR experienced more severe childhood trauma. In view of the high heterogeneity ($I^2 = 77\%$), a sub-group analysis was conducted by separating studies into their RoB scores. Although studies with moderate-risk tend to produce larger effect sizes (Hedges' $g = 1.95$, 95% CI 1.43–2.46, $p < 0.001$, $I^2 = 33\%$) than studies with low-risk (Hedges' $g = 1.06$, 95% CI 0.74−1.38, $p < 0.001$, $I^2 = 44\%$), both reported similar findings (supplementary materials S2).

A sensitivity analysis comprising only of studies using CTQ was conducted ($n = 4$). The overall effect size did not change substantially (Hedges' $g = 1.40$, CI 0.74–2.16, $p < 0.001$), which suggests that across-study differences were not likely due to the choice of instruments.

Prevalence of childhood trauma

Childhood trauma exposure among UHR ranged from 54% (Kraan *et al.*, 2017*b*) to more than 90% (Thompson *et al.*, 2009; Falukozi and Addington, 2012; Tikka *et al.*, 2013).

Childhood trauma subtypes

Severity of trauma subtypes exposure

UHR individuals reported significantly higher scores for emotional abuse and physical abuse in all three studies (Sahin *et al.*, 2013; Tikka *et al.*, 2013; Reininghaus *et al.*, 2016). However, only Tikka *et al.* (2013) reported significantly higher scores for sexual abuse and emotional neglect among UHR individuals. Both Sahin *et al.* (2013) and Tikka *et al.* (2013) reported higher scores for physical neglect among UHR individuals as compared with controls.

Prevalence of trauma subtypes exposure

UHR were 5.06 times as likely to report emotional abuse (OR = 5.06, 95% CI = 1.55–16.58, $p = 0.007$), and 3.19 times as likely to report physical abuse (OR = 3.19, 95% CI = 1.05–9.75, $p = 0.04$) (Table 2). Emotional neglect was the most prevalent trauma subtype reported in Turkey (Ucok *et al.*, 2015), and this finding was consistent among both genders in a six-site study in Europe (Salokangas *et al.*, 2018). However, in our meta-analysis, no significant differences were found in the prevalence of sexual abuse, emotional neglect and physical neglect across participant groups (supplementay materials S3).

High heterogeneity was observed within the abuse subtypes. This may be explained by the different trauma assessments used, which probed slightly different aspects of trauma. For example, the 43-item TADS included questions on bullying and distress items (e.g. self-esteem, guilt) which were not captured in the 28-item CTQ.

Bullying victimisation and psychosis

Bullying victimisation data were collected from the Retrospective Bullying Questionnaire (RBQ), Ostracism Scale, or specific questions that were part of a larger interview (Childhood Trauma and Abuse Scale). The exposure was recorded as a dichotomous measure (ever bullied or never bullied).

In this meta-analysis ($n = 3$, 844 UHR, 448 controls), UHR individuals were 3.09 times as likely to report bullying

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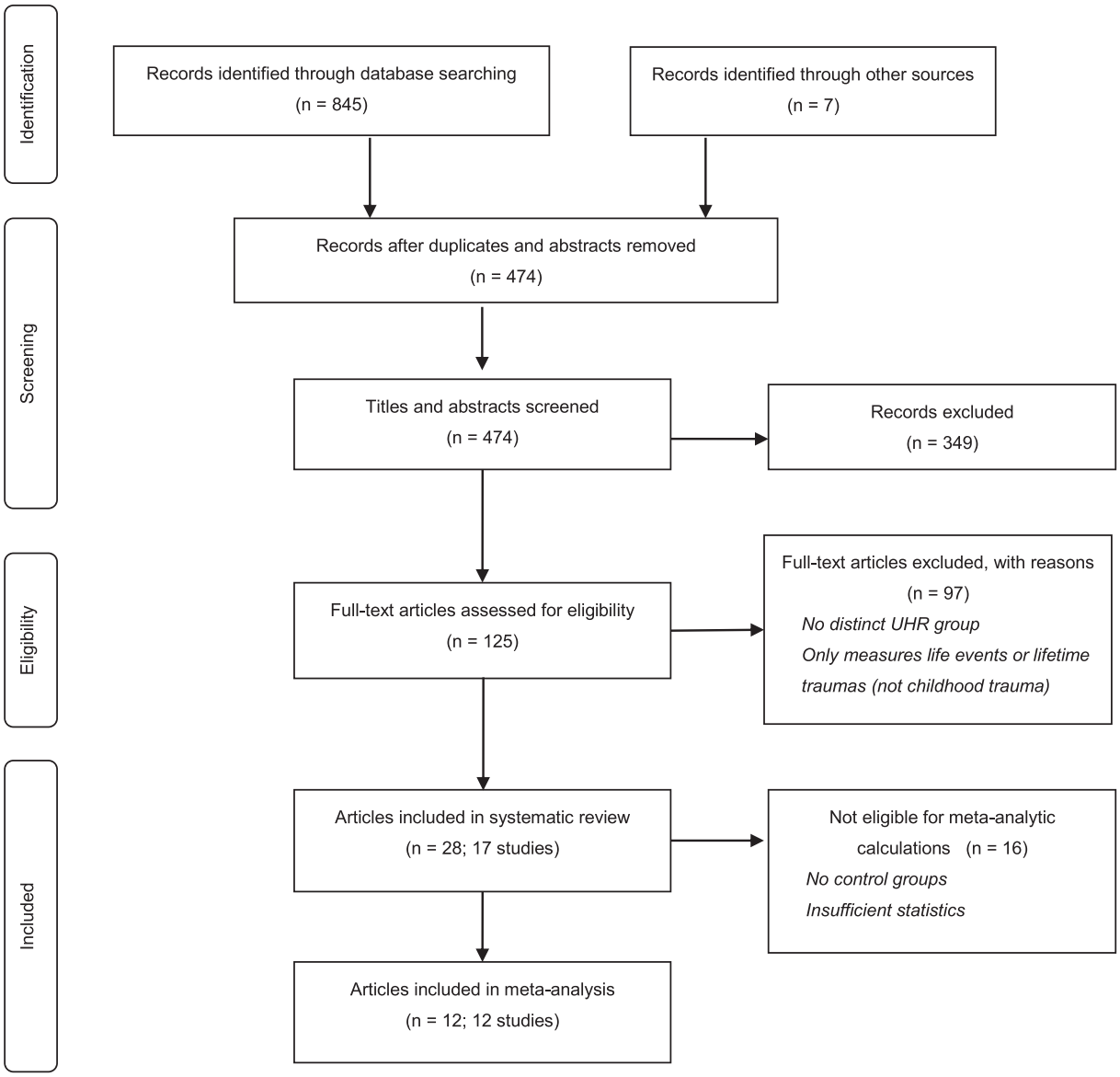

Fig. 1. PRISMA flow chart of search strategy.

victimisation than controls (OR = 3.09, 95% CI = 2.23–4.30; $Z = 6.72$, $p < 0.001$) (supplementary materials S4). There was little evidence of heterogeneity ($I^2 = 7\%$). Across all three countries, the prevalence of bullying among UHR was varied, at 33.3% in South Korea (Kang *et al.*, 2012), 53.3% in America (Stowkowy *et al.*, 2016) and 66.7% in the UK (Valmaggia *et al.*, 2015).

The type of bullying experienced was analysed differently across studies. When bullying was sub-categorised according to the length of exposure, a higher proportion of UHR (42.9%) than controls (27.3%) were prolonged victims (Valmaggia *et al.*, 2015). In the NAPLS-2 study, 60.5% of UHR experienced psychological bullying (*v.* 36.1% in controls), while 29.8% of UHR were physically bullied (*v.* 14.7% of controls) (Addington *et al.*, 2013). Bullying may take place in less traditional forms, such as cyberbullying. Out of 50 UHR participants in Canada, 38% of them experienced cyberbullying, with the most frequent medium being text (30%), followed by Facebook (28%) (Magaud *et al.*, 2013).

Parental loss or separation and psychosis

Data on parental loss or separation were collected from CECA-Q or as a separate additional question. Egerton *et al.* (2016) found that a higher proportion of UHR individuals (67%) reported death of or separation from either parental figure than healthy controls (50%). However, the association between parental loss and UHR state was not significant. Thompson *et al.* (2009) reported that 57% of UHR experienced parental separation but none experienced loss of parents through parental death. It is worthy to note that in both studies, UHR sample sizes were small ($n = 45$ and $n = 30$).

Childhood trauma and TTP

When the association between total childhood trauma and later TTP among UHR individuals was investigated, the effect size was not significant (HR = 1.01, 95% CI 0.99–1.03; $Z = 1.34$, $p = 0.18$).

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Table 1. Study characteristics (sorted according to study site)

No.	Authors	Study (country)	Risk of bias score	*N*	Age, mean (SD)	Gender (% female)	Adversities measured	Adversities instrument	Assessment of UHR status	Follow-up period	Conclusions	Study type	Meta-analysis
1	Addington *et al.* (2013)	NAPLS-2 (8 sites in the USA)	6/18 (moderate)	540 (360 CHR, 180 HC)	CHR: 18.98 (4.18) HC: 19.54 (4.78)	CHR: 41.7% HC: 44.4%	Childhood trauma and bullying	Childhood trauma and abuse scale, single question on bullying	SIPS	NA	Individuals at CHR reported more types of trauma and bullying than HC. The χ^2 comparisons for each type of trauma revealed significant differences (more frequent among CHR than controls)	Longitudinal	Subtypes of trauma
	Cannon *et al.* (2016)	NAPLS-2 (8 sites in the USA)	4/18 (low)	596 CHR	CHR: 18.5 (4.3)	42.3%	Stressful life events and childhood trauma	Childhood trauma and abuse scale	SIPS, SCID	2 years	The 2-year probability of conversion to psychosis was 16%. Family history of psychosis, stressful life events and trauma were not significant predictors of conversion to psychosis	Longitudinal	NA
	Falukozi and Addington (2012)	NAPLS-2 (8 sites in the USA)	4/20 (low)	45 CHR	CHR: 19 (2.83)	CHR: 44.44%	Childhood trauma	Childhood trauma and abuse scale, questions about bullying	SIPS	NA	Almost all participants endorsed at least one type of trauma (91%). 49% had more than half of the types of trauma. 13% experienced all types of trauma	Longitudinal	NA
	Marshall *et al.* (2016)	NAPLS-2 (8 sites in the USA)	4/20 (low)	442 CHR	18.75 (4.16)	42.1%	Childhood trauma and bullying	Childhood trauma and abuse scale	SIPS	NA	Adverse life events, like bullying, may impact the presence of violent content in attenuated positive symptoms	Longitudinal	NA
	Stowkowy and Addington (2013)	NAPLS-2 (8 sites in the USA)	5/18 (low)	75 (25 FHR + CHR, 25 non-CHR, 25 HC)	FHR + CHR: 17.88 (3.24) HC: 19.64 (5.23)	FHR + CHR: 52% HC: 50%	Childhood trauma and bullying	Childhood trauma and abuse scale	Met COPS using SIPS	2 years	Although the two FHR groups did not differ on trauma, they did endorse more trauma than the HC	Case–control	Trauma
	Stowkowy *et al.* (2016)	NAPLS-2 (8 sites in the USA)	6/18 (moderate)	1044 (764 CHR, 280 HC)	UHR: 18.50 (4.23) HC: 19.73 (4.67)	44.7%	Childhood trauma and bullying	Childhood trauma and abuse scale	Met COPS using SIPS	2 years	Individuals at CHR reported significantly more trauma, bullying and perceived discrimination than HC. Neither total bullying nor total trauma contributed to the prediction of psychosis in CHR sample. Only perceived discrimination was a significant predictor	Prospective	Bullying, transition
2	Appiah-Kusi *et al.* (2017))	OASIS (South London, UK)	2/18 (low)	68 (30 UHR, 38HC)	UHR: 23.93 (4.78) HC: 26.14 (4.69)	UHR: 46.7% HC: 47.4%	Childhood trauma	CTQ	PACE criteria	NA	UHR individuals were significantly more likely to report exposure to various types of childhood trauma than HC. Emotional neglect was related with UHR status; other subtypes were not associated with UHR status	Case–control	Trauma, subtypes of trauma
	Egerton *et al.* (2016)	OASIS (South London, UK)	5/18 (low)	67 (47 UHR, 20 HC)	UHR: 23.6 (4.6) HC: 23.8 (4.3) Total: 23.7 (4.5)	UHR: 42.55%, HC: 40.0%, Total: 41.79%	Death/ separation from either parents, abuse, more than 2 family arrangements	CECA-Q	CAARMS	NA	UHR and HC revealed similar incidence of childhood adverse experiences. Severe physical or sexual abuse and unstable family arrangements in childhood were associated with elevated dopamine function in the associative striatum in adulthood	Case–control	NA

(*Continued*)

Table 1. (*Continued.*)

No.	Authors	Study (country)	Risk of bias score	*N*	Age, mean (SD)	Gender (% female)	Adversities measured	Adversities instrument	Assessment of UHR status	Follow-up period	Conclusions	Study type	Meta-analysis
	McDonnell *et al.* (2017)	OASIS (South London, UK)	6/18 (moderate)	65 CHR	CHR: 22.55 (4.01)	40.6%	Childhood bullying	RBQ	CAARMS	NA	Interpersonal sensitivity fully explained the significant association between severe bullying and paranoid ideation. Severity of bullying is likely to be more important than frequency of bullying in explaining the relationship	Cross-sectional	NA
	Valmaggia *et al.* (2015)	OASIS (South London, UK)	6/18 (moderate)	107 (65 UHR, 43 HC)	UHR: 22.55 (4.01) HC: 24.02 (4.01)	54.2%	Childhood bullying	RBQ	CAARMS	NA	UHR described higher levels of childhood bullying than HC. Childhood bullying was associated with paranoid ideation in UHR and HC	Case–control	Bullying
3	Cotter *et al.* (2016)	PACE clinic (Melbourne, Australia)	3/20 (low)	268 UHR	18.60 (3.25)	60.6%	Childhood trauma	CTQ	CAARMS	2.39–14.87 years	At baseline, those who were unemployed at follow-up had longer duration of untreated illness, more severe negative symptoms, lower IQ, poorer functioning, and reported more childhood trauma than employed group	Longitudinal	NA
	Thompson *et al.* (2014)	PACE clinic (Melbourne, Australia)	5/18 (low)	233 UHR	18.5 (3.2)	58.8%	Childhood trauma	CTQ	CAARMS	M = 7.4 years, Range = 2.4–14.9 years	Total CTQ trauma score was not associated with transition to psychosis. Of the individual trauma types, only sexual abuse was associated with transition to psychosis (2–4 times higher risk for those with high sexual abuse scores than those of low scores)	Longitudinal	Transition
	Thompson *et al.* (2016)	PACE clinic (Melbourne, Australia)	3/18 (low)	233 UHR	UHR: 18.5 (3.2)	58.8%	Childhood sexual trauma	CTQ	CAARMS	M = 7.4 years, Range = 2.4–14.9 years	Based on previous report of association between sexual trauma and transition: none of the potential mediators (depression, anxiety, dissociation, mood swings, mania) significantly mediated the total association between sexual abuse scores and transition	Longitudinal	NA
	Yung *et al.* (2015)	PACE clinic (Melbourne, Australia)	3/20 (low)	268 UHR	15–30 years old (no data on mean and SD)	56.7%	Childhood trauma	CTQ	CAARMS, BPRS	2.39–14.87 years	Childhood maltreatment and transition to psychosis independently predicted poor long-term functioning	Longitudinal	NA
4	Allen *et al.* (2017)	(South England, UK)	3/19 (low)	102 (25 HC, 77 UHR)	HC: 23.9 (2.85) UHR: 22.6 (3.64)	HC: 48% UHR: 43%	Childhood trauma	CTQ	CAARMS	NA	The mean CTQ score for UHR participants was 56 (i.e. moderate-to-severe levels of childhood trauma). CTQ was not administered for HC	Case–control	NA

5	Kang *et al.* (2012)	(South Korea)	4/18 (low)	186 (125 HC, 15 TPSS, 46 depressive)	HC: 16.92 (0.27) TPSS: 16.80 (0.41)	HC: 76.0% TPSS: 86.7% Dep: 80.4%	Ostracism	Ostracism Scale	CAARMS	NA	Compared with the normal group, experiences of bullying, suicidal ideation and suicide attempts were significantly higher in depressive and UHR groups	Cross-sectional	Bullying
6	Kraan *et al.* (2015*a*)	DUPS (The Netherlands)	3/18 (low)	125 UHR	UHR: 17.7 (3.9)	32.0%	Childhood trauma	TADS	SIPS	9, 18, 24 months	20.8% of UHR transitioned to psychosis within 24 months. Childhood trauma did not predict transition to psychosis	Longitudinal	Transition
7	Kraan *et al.* (2017*a*)	EDIE-NL (The Netherlands)	4/18 (low)	113 UHR	UHR: 23.5 (5.4)	55.8%	Childhood trauma	CTQ	CAARMS	6, 12, 18, 48 months	There was no evidence that childhood adversity was associated with transition to psychosis.	Longitudinal	Transition
8	Kraan *et al.* (2017*b*)	EU-GEI (11 centres)	5/18 (low)	354 (304 UHR, 50 UHR-)	UHR: 22.7 (4.5) UHR-: 23.98 (4.33)	UHR: 46.1% Controls: 45.0%	Childhood maltreatment	CTQ	CAARMS	12, 24 months	Emotional abuse was associated with an increased risk for transition to psychosis (OR = 3.78, CI = 1.17–12.39, $p = 0.027$). A history of physical abuse was associated with depressive disorder, PTSD, panic disorder and social phobia at follow-up	Longitudinal	Subtypes of trauma, transition
9	Magaud *et al.* (2013)	(Canada)	5/20 (low)	50 CHR	CHR: 16.7 (3.3)	50.0%	Childhood trauma and cyberbullying	CTQ, questions on cyberbullying	Met COPS using SIPS	NA	Cyberbullying was reported in 38% of sample, with most frequent forms being text, Facebook and instant messages. Cyberbullying was significantly associated with childhood trauma	Cross-sectional	NA
10	Palmier-Claus *et al.* (2016)	(Northwest England, UK)	9/18 (moderate)	174 (20 chronic, 20 FE, 14 UHR, 120 HC)	UHR: 22.6 (5.2) HC: 20.1 (2.5)	UHR: 58.1% HC: 71.8%	Childhood trauma	CTQ	CAARMS	NA	Childhood adversity acts on social functioning by increasing levels of depression	Case–control	Trauma
11	Reininghaus *et al.* (2016)	CAPsy (South London, UK)	8/18 (moderate)	146 (50 FEP, 44 ARMS, 52 HC)	ARMS: 23.8 (4.7) HC: 34.4 (12.0)	ARMS: 54.6% HC: 53.9%	Childhood trauma	CTQ	CAARMS, SPI/A	NA	Associations of minor daily stress with negative affect and psychotic experiences were modified by sexual abuse and group. These associations were greater in ARMS exposed to high levels of sexual abuse	Case–control	Trauma, subtypes of trauma
12	Sahin *et al.* (2013)	(Istanbul, Turkey)	5/18 (low)	193 (83 FES, 41 UHR, 69 HC)	FES: 23.1 UHR: 20.5 HC: 23.9	FES: 27.7% UHR: 31.7% HC: 58.0%	Childhood trauma	CTQ	PACE criteria	NA	CTQ total scores and subscale scores were higher in UHR and FES than controls. However, they did not differ between UHR and FES. Childhood trauma was related to the severity of psychotic symptoms in both FES and UHR groups	Case–control	Trauma
13	Salokangas *et al.* (2018)	EPOS (6 centres in Germany, Amsterdam and the UK)	3/20 (low)	245 UHR	22.4 (range 15–35)	45.0%	Childhood trauma	TADS	SIPS	9, 18 months	For CHR females, the effect of childhood adversities and trauma on adult suicidality is mediated via depression. For males, there is a direct effect of childhood adversities and trauma on maintaining adult suicidality	Longitudinal	NA
14	Tikka *et al.* (2013)	Detection of Early Psychosis Project (Turku, Finland)	4/18 (low)	50 (20 CHR, 30 HC)	CHR: 22.2 (5.4) HC: 23.6 (5.1)	CHR: 75% HC: 63.6%	Childhood trauma	TADS	Met COPS using SIPS	NA	CHR patients reported more childhood trauma experiences and poorer premorbid adjustment than HCs. Among CHR: traumatic childhood experiences were	Case–control	Trauma, subtypes of trauma

(*Continued*)

Table 1. (*Continued.*)

No.	Authors	Study (country)	Risk of bias score	*N*	Age, mean (SD)	Gender (% female)	Adversities measured	Adversities instrument	Assessment of UHR status	Follow-up period	Conclusions	Study type	Meta-analysis
											associated with poor general pre-morbid adjustment		
15	Thompson *et al.* (2009)	(New York, USA)	3/20 (low)	30 CHR	18.8 (3.7)	17.0%	Childhood trauma and parental loss	ETI and single question for parental loss and/or separation	SIPS/SOPS	NA	97% of CHR participants endorsed at least one general trauma experience, 83% reported history of physical punishment or abuse, 67% endorsed childhood emotional abuse, 27% reported childhood sexual abuse, 57% experienced parental separation, none experienced parental loss through parental death. Total trauma was positively associated with the severity of APS	Cross-sectional	NA
16	Ücok *et al.* (2015)	Psychotic Disorders Research Program (Istanbul, Turkey)	4/20 (low)	53 UHR	21.1 (4.8)	26.4%	Childhood trauma	CTQ	BPRS, GAF	NA	41.5% of UHR experienced physical abuse; 57.7% experienced emotional abuse; 24.4% experienced sexual abuse; 59.6% experienced emotional neglect; and 0% experienced physical neglect. A history of physical trauma had a negative impact on cognitive function in individuals at UHR for psychosis	Cross-sectional	NA
17	Zuschlag *et al.* (2018)	(South Carolina, USA)	5/20 (low)	152 APS	20.6 (5.7)	34%	Childhood trauma	Did not specify	Clinical assessment of APS	NA	Suicidality is a prominent feature of APS; total trauma and sexual trauma were significant predictors of lifetime suicide attempts after race, sex and age were controlled for	Cross-sectional	NA

APSS, attenuated psychotic symptom syndrome; APS, attenuated psychotic symptoms; CAPsy, Childhood Adversity and Psychosis; CHR, clinical high risk; COPS, Criteria of Prodromal Symptoms; DUPS, Dutch Prediction of Psychosis Study; EDIE-NL, Early Detection and Intervention Evaluation; EPOS, European Prediction of Psychosis Study; ETI, Early Trauma Inventory; EU-GEI, EUropean network of national schizophrenia networks studying Gene-Environment Interactions; FHR, family high risk; FES, first episode schizophrenia; HC, healthy controls; OASIS, Outreach and Support in South London; PACE, Personal Assessment and Crisis Evaluation; SIPS, Structured Interview for Prodromal Symptoms; TADS, Trauma and Distress Scale; TPSS, Thought Perception-Sensitivity Symptoms.

Table 2. Results of separate meta-analyses comparing the prevalence of childhood trauma subtypes between UHR and controls

Childhood trauma	No. of studies	n_{UHR}	$n_{controls}$	OR	95% CI	p Value	I^2 (%)
Emotional abuse	5	758	350	5.06	1.55–16.58	0.007*	94
Physical abuse	5	758	350	3.19	1.05–9.75	0.04*	89
Sexual abuse	5	758	350	1.95	0.99–3.84	0.05	69
Emotional neglect	4	714	298	2.62	0.80–8.58	0.11	94
Physical neglect	2	334	88	0.90	0.68–1.19	0.45	0

*Significant at 0.05 level.

All trauma subtypes did not reveal significant associations with TTP, except for sexual abuse (HR = 1.05, 95% CI = 1.01–1.09, $Z = 2.62$, $p = 0.010$) (Table 3). There was no evidence for heterogeneity ($I^2 = 0\%$) (supplementary materials S5). The follow-up times ranged from 6 months to 14.9 years. The follow-up rates ranged from 36.9% to 80.2%; all studies except for one had at least 50% follow-up rate.

Sensitivity analysis revealed that the association between sexual abuse and TTP became non-significant when Thompson *et al.* (2014)'s study was removed from the analysis, which suggests that the significant relationship was mainly driven by a single large study. When the association between sexual trauma and TTP was adjusted for mood, anxiety and dissociation, it remained significant (Thompson *et al.*, 2016).

Notably, the effect size reported here is HR, which is a time-to-event estimate. A non-significant finding suggests that childhood trauma and its subtypes do not significantly affect the time taken for TTP to occur. In the only study that reported ORs, UHR individuals with a history of emotional abuse had 3.78 times increased risk for TTP (OR = 3.78, 95% CI = 1.17–12.39, $p = 0.027$) (Kraan *et al.*, 2017*b*). However, the increased psychiatric risk of abuse was not specific to psychosis – physical abuse was linked with 2–5 times increased risk of transition to depressive disorder, post-traumatic stress disorder, panic disorder and social phobia.

When the contribution of several predictors (social functioning, verbal learning, cognition, age, stressful life events, family history of psychosis, traumas) were analysed in multivariate cox regressions, childhood trauma and family history of psychosis were not significant in predicting TTP (Cannon *et al.*, 2016).

Bullying and TTP

Total bullying did not significantly contribute to TTP among CHR individuals in Stowkowy *et al.* (2016)'s study. No significant associations were found between psychological bullying and TTP, and between physical bullying and TTP.

Childhood adversities and symptoms or functioning

Multiple studies reported links between childhood adversities and the severity of psychotic symptoms among the UHR. First, greater childhood trauma exposure was positively associated with the severity of APS in UHR samples in various regions of America and the Netherlands (Thompson *et al.*, 2009; Falukozi and Addington, 2012; Kraan *et al.*, 2015*a*; Marshall *et al.*, 2016). Second, severe bullying victimisation was found to be significantly associated with paranoid ideation (Valmaggia *et al.*, 2015), and this relationship was fully explained by heightened interpersonal sensitivity (McDonnell *et al.*, 2017).

Childhood trauma predicted poorer social and occupational functioning outcomes among UHR in Australia and the Netherlands (Kraan *et al.*, 2015*a*, 2017*a*; Yung *et al.*, 2015). The severity of childhood trauma was significantly associated with employment status at baseline and 2–14 years later (Cotter *et al.*, 2016). Total childhood trauma and sexual trauma were significant predictors of adult suicide attempts (Zuschlag *et al.*, 2018).

Affective variables may have a mediating role in the relationship between childhood adversities and functioning. Among UHR, the relationship between childhood adversity and social functioning was mediated by more severe depression (Palmier-Claus *et al.*, 2016). Worse depression was more common among those with greater exposure to childhood abuse (Addington *et al.*, 2013), particularly physical abuse and emotional neglect (Kraan *et al.*, 2017*a*). Childhood adversities were associated with lower self-esteem, which mediated the relationship between emotional neglect and the UHR state (Appiah-Kusi *et al.*, 2017).

Publication bias

There were insufficient studies in each meta-analysis to formally assess publication bias.

Discussion

This review had two aims. The first aim was to compare the severity and prevalence of childhood adversities between UHRs and controls. Generally, UHR individuals reported more severe and more prevalent childhood adversities than controls. The second aim was to investigate the link between childhood trauma and subsequent TTP among the UHR population. There was no evidence of an association between childhood trauma and TTP; however, a link was found between childhood sexual trauma and TTP.

Prevalence and severity of childhood adversities

UHR individuals reported significantly more frequent and severe childhood trauma than controls. Emotional and physical abuse were significantly more prevalent among UHR individuals; UHR experienced more severe exposure across all abuse subtypes. Bullying victimisation was also significantly associated with the UHR state.

The traumagenic neurodevelopmental model is one of the many theories explaining the relationship between childhood adversities and psychosis. The model integrates the evidence on the psychological processes triggered by childhood adversities (e.g. formation of negative schemas about the self) with the evidence on stress dysregulation, memory impairment and

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Table 3. Results of separate meta-analyses investigating the association between trauma and TTP among UHR

Childhood trauma subtype	No. of studies	Sample size	HR	95% CI	*p* Value	I^2 (%)
Total trauma	4	1617	1.01	0.99–1.03	0.18	0
Emotional abuse	5	1730	1.00	0.96–1.05	0.91	0
Physical abuse	5	1730	1.04	0.99–1.09	0.11	0
Sexual abuse	5	1730	1.05	1.01–1.09	0.009*	0
Emotional neglect	5	1730	1.02	0.98–1.07	0.31	0
Physical neglect	4	966	1.01	0.93–1.08	0.89	0

*Significant at 0.05 level.

prefrontal/hippocampal structural changes that have been observed in patients with psychosis (Read *et al.*, 2001, 2014).

The differential effects of childhood trauma subtypes reported here corroborate previous findings. Compared with other types of abuse, emotional abuse had the strongest associations with negative psychiatric outcomes (Barbosa *et al.*, 2014; de Araujo and Lara, 2016; Schmidt *et al.*, 2017), hypothalamic–adrenal–pituitary axis dysregulation (Braehler *et al.*, 2018) and suicidality (Anestis and Joiner, 2011; Schmidt *et al.*, 2017). It seems that emotional trauma amplifies the negative feelings of perceived burdensome and the lack of sense of belonging, more so than other types of adversities (Anestis and Joiner, 2011). Our findings emphasise the importance of analysing specific relationships between trauma subtypes and psychosis.

Relationship between childhood trauma and TTP

Total childhood trauma was not significantly related to increased risk of TTP. When the overall trauma was stratified into its subtypes, the results revealed that sexual abuse was significantly associated with TTP; however, the finding was largely driven by a single study. Overall, the current findings suggest that exposure to childhood adversities alone may not be sufficient to bring about a higher TTP rate among UHR individuals.

This non-significant relationship may be due to the non-specific effects of childhood trauma. Adverse childhood experiences can predispose individuals to develop a range of mental health problems, including depression, anxiety, self-harm (Lereya *et al.*, 2015) or a combination of symptoms from various domains (van Nierop *et al.*, 2015). It is likely that childhood trauma interacts with or contributes additively with other risk factors [such as cannabis use (Harley *et al.*, 2010)] to increase the risk of TTP.

However, there are several caveats to take note of. First, the overall effect size was small because it was computed based on the change HR for a one-point difference in the trauma scores. When Thompson *et al.* (2014) recomputed the HRs such that comparisons were made between a high-exposure (to sexual abuse) or moderate-exposure group with a low-exposure group (CTQ scores of 25 or 15 *v.* 5), the HRs of TTP were four and two times, respectively. This method may be more useful clinically than the regular cox regression, and future studies might consider reporting it for more interpretable results.

Second, the tracking of TTP may not be accurate. Most studies recruited individuals who were <35 years old; however, late-onset psychosis is found to be more prevalent than previously expected (Simon *et al.*, 2017): age of onset was beyond the age of 40 in more than 22% of schizophrenia patients (Selvendra *et al.*, 2014). Thus, psychosis may have developed after the maximum follow-up duration of 2 years, causing TTP rate to be under-reported.

Limitations

Potential confounders

Most studies did not match participants on key variables during recruitment as it was difficult to control them in clinical research. These variables included cannabis use, gender, education level, comorbid psychiatric disorders and age – variables previously found to be significant moderators or mediators of psychosis (Sideli *et al.*, 2012).

These factors were also not statistically adjusted in most of the studies. It could therefore explain the differential findings of lower risk studies and moderate-risk studies in the meta-analysis of the severity of childhood trauma. The larger effect sizes observed by moderate-risk studies were likely influenced by uncontrolled variables like gender, unemployment and education levels (Palmier-Claus *et al.*, 2016; Reininghaus *et al.*, 2016). Thus, this constitutes a bias in the UHR literature, which could be addressed in the future through multivariate analyses.

When confounds were statistically controlled for, unadjusted and adjusted estimates did not differ in their conclusions: three studies reporting the association between childhood trauma and TTP statistically controlled for cannabis use, gender and age (Kraan *et al.*, 2015*a*, 2017*a*, 2017*b*); comorbid psychiatric problems (Thompson *et al.*, 2016) or functioning, age, gender and educational level (Thompson *et al.*, 2014) were controlled for in the Personal Assessment and Crisis Evaluation (PACE) study.

Other limitations

As the actual rates of TTP are low among UHR (Cannon *et al.*, 2016), and the sample sizes of UHR who eventually experience psychosis are small, it becomes more difficult to detect statistical associations between childhood adversities and TTP. Furthermore, many studies recruited UHR individuals from prodromal or early-intervention services, which have been found to capture only a small proportion of individuals who are at high risk of psychosis (Ajnakina *et al.*, 2016). Thus, findings constrained to the UHR population may only be generalisable to a small proportion of individuals at high risk for psychosis.

The range of instruments reporting the prevalence of adversities may have contributed to more heterogeneity among studies. Synthesising the findings became difficult as each instrument consisted of slightly different assessment criteria for the specific type of adversity being investigated.

The exclusion of unpublished studies may introduce a publication bias. However, the inclusion criteria for articles in this

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meta-analysis aimed to prioritise the rigorousness of the review at the expense of exhaustiveness.

Other considerations for future research

There are some important considerations to be made in future analyses. First, the length of exposure to childhood adversities is an important variable as it could directly affect the extent of neurodevelopmental or psychological changes experienced by UHR individuals. Reporting and analysing this information could reveal dose–response relationships. For example, frequent bullying typically has more severe impact on a child's well-being than short-term bullying, and should be analysed as separate categories of exposure.

Second, it is worthwhile to consider the severity and frequency of negative symptoms during risk assessment, as the CHR and UHR assessment criteria largely focus on positive symptoms. Significant associations between childhood neglect and the severity of negative symptoms were found among schizophrenia patients (Bailey *et al*., 2018). It would be interesting to further explore relationships between childhood adversities and negative symptoms among the UHR.

Third, the cross-sectional nature of data collection does not eliminate the possibility that UHR individuals may become more susceptible to adversities after illness onset or cognitive and functional declines. Thus, longitudinal designs can help establish the direction of causality.

Implications and future directions

To date, this is the first meta-analysis that has quantitatively summarised the associations between childhood adversities and TTP among UHR individuals, and between specific abuse subtypes and the UHR state. As many studies in this field are small in nature, with the exception of a few, this meta-analysis seeks to overcome the problem of small samples.

Overall, our findings support the association between childhood adversities and the UHR state; however, these adversities alone may not be sufficient to cause UHR to convert into psychosis. There is a need to investigate the role of childhood adversities in relation to other risk factors, in order to elucidate any additive effects, gene–environment or environment–environment interactions.

Nevertheless, our review supports the need to screen for childhood adversities among the UHR population in early intervention services. It is important to assess any previous trauma which may predispose or perpetuate current symptoms. Targeted and individualised therapy can therefore be provided more effectively for better clinical outcomes.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S003329171800394X.

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