CHAPTER 2

Trauma and recent life events in individuals at ultra high risk for psychosis: Review and meta-analysis

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Schizophrenia Research 2015, 161 (2-3): 143-149
Abstract

Background: Childhood trauma and recent life-events have been related to psychotic disorders. The aim of the present study was to examine whether childhood trauma and recent life-events are significantly more prevalent in patients at Ultra High Risk (UHR) of developing a psychotic disorder compared to healthy controls.

Method: A search of PsychInfo and Embase was conducted, relevant papers were reviewed, and three random effects meta-analyses were performed. One meta-analysis assessed the prevalence rate of childhood trauma in UHR subjects and two meta-analyses were conducted to compare UHR subjects and healthy control subjects on the experience of childhood trauma and recent life-events.

Results: We found 12 studies on the prevalence of (childhood) trauma in UHR populations and 4 studies on recent life-events in UHR populations. We performed a meta-analysis on 6 studies (of which trauma prevalence rates were available) on childhood trauma in UHR populations, yielding a mean prevalence rate of 86.8% (95% CI 77%–93%). Childhood trauma was significantly more prevalent in UHR subjects compared to healthy control groups (Random effects Hedges’ g = 1.09; Z = 4.60, p <.001). In contrast to our hypothesis, life-event rates were significantly lower in UHR subjects compared to healthy controls (Random effects Hedges’ g = −0.53; Z = −2.36, p <.02).

Conclusions: Our meta-analytic results illustrate that childhood trauma is highly prevalent among UHR subjects and that childhood trauma is related to UHR status. These results are in line with studies on childhood trauma in psychotic populations. In contrast to studies on recent life-events in psychotic populations, our results show that recent life-events are not associated with UHR status.
Introduction

A growing body of literature has addressed the role of childhood trauma as one of the risk factors for the development of psychosis [1-4]. Childhood trauma is defined as psychological, physical, emotional or sexual abuse, and emotional neglect, before age 17 years [5]. Higher rates of traumatic events have been found in individuals with psychotic disorders compared to the general population [6, 7]. In a recent meta-analysis examining both retrospective and prospective studies, early childhood trauma was found to increase the odds of psychotic disorder by almost a factor 3 [3].

Although most studies investigating the relationship between trauma and psychosis have focused on childhood adversity before age 17 years, there is growing evidence for a role for recent stressful life events in the pathway to psychosis. Recent stressful life events are defined as events in the last months prior to onset of psychosis that usually involve danger and that cause a substantial change in one’s positive or negative personal circumstances [8]. A recent meta-analysis of 16 studies on the association between recent life events and onset of psychosis reported that individuals with psychotic disorders were three times more likely to have experienced recent life events prior to the onset of psychosis compared to healthy controls [9].

Criteria have been established to identify ultra-high risk (UHR) patients, mainly based on the presence of subthreshold psychotic symptoms in help-seeking individuals for a non-psychotic disorder with a recent decline in social functioning [10-12]. The focus of studies on childhood trauma or recent life events has recently broadened to UHR patients [13-16].

The present study aimed to present all available results on both early childhood trauma and recent stressful life events in UHR populations. The prevalence rate of traumatic events in UHR patients was estimated based on a meta-analysis. Following evidence from studies in clinical samples [4, 9], we hypothesized that childhood trauma and recent life events would be significantly more prevalent in UHR patients than in healthy controls.
Methods

Data collection
Following the PRISMA database search guidelines (www.prisma-statement.org), systematic database searches of publications from 1993 (year of first UHR paper) to April 2014 were conducted in Embase and PsychINFO, including all UHR studies that involved data on trauma or recent life events. We combined the following sets of keywords:

1) ‘ultra high risk’ OR ‘uhr’ OR ‘prodrome’ OR ‘prodromal’ OR ‘at high risk’ OR ‘clinical* at risk’ OR ‘at clinical* risk’ OR ‘clinical high risk’ OR ‘at risk mental state’ OR ‘arms’ OR ‘attenuated symptoms’ OR ‘blips’ OR ‘brief limited intermittent psychotic symptoms’ OR ‘psychosis risk symptoms’ OR ‘HR’ OR ‘CHR’ OR ‘caarms’ OR ‘sips’
2) ‘psychosis’ OR ‘psychotic disorder’ OR ‘schizophreni*’ OR ‘schizo*’ OR ‘psychoti*’ OR ‘halluci*’ OR ‘delusion*’ OR ‘voice*’ OR ‘thought disorder’ OR ‘paranoii*’
3) ‘trauma*’ OR ‘life event*’ OR ‘event*’ OR ‘abuse’ OR ‘victim*’ OR ‘advers*’ OR ‘trauma’ OR ‘bully*’ OR ‘bullying*’ OR ‘cyberbullying’ OR ‘neglect’

The search yielded 1839 studies. Three studies were added after manual searches in PubMed [13, 17, 18] resulting in a total of 1842 studies.

First, the publications were screened by title. In a second screening the abstracts were scrutinized for relevance. Subsequently, a final screening of the full-text was conducted (Figure 1).

Data extraction
Publications were considered eligible, if they:

a) included data on individuals meeting At-Risk Mental State (ARMS) criteria as defined by the Personal Assessment and Crisis Evaluation (PACE) clinic [11] or UHR criteria as defined by the Structured Interview for Prodromal Syndromes criteria (SIPS) [19]

b) reported on early childhood trauma or recent life events in relation to UHR status in a cross-sectional or prospective design. Childhood trauma was defined as physical, psychological, sexual or emotional abuse and emotional neglect before age 17 years. Recent life events were defined as events in the last months prior to assessment that usually involve danger and that cause a marked negative
Figure 1: Flowchart of selected studies

Identification

Records identified through database searching (n = 1839)

Additional records identified through other sources (n = 3)

Records after duplicates removed (n = 1823)

Records screened (n = 1823)

Records excluded (n = 1789)

Full-text articles assessed for eligibility (n = 34)

Full-text articles excluded, with reasons (n = 18)
  Review paper (n=2)
  Not related to UHR (n=8)
  Not related to trauma or life events (n=8)

Studies included in quantitative synthesis (meta-analysis) (n = 11; 16 papers)
or positive emotional reaction.

Publications were excluded if they only reported on stress without specifically referring to recent life events or (childhood) trauma, or if UHR was measured by criteria other than the Comprehensive Assessment of At Risk Mental State (CAARMS) [11] or SIPS [19].

After exclusion, 16 publications remained covering 11 studies reporting on (childhood) trauma or recent life events in 1111 UHR patients and 335 healthy controls.

Of the 16 selected publications, 12 reported on prevalence rates of (childhood) trauma in UHR patients (Table 1). Ten were cross-sectional studies [13, 15, 20-27] and two were prospective follow-up studies [14, 28]. When publications reported findings from overlapping study populations, the study with the largest sample size was selected for the first meta-analysis to estimate the prevalence rate of traumatic events. For instance, of the two studies from the North American Prodrome Longitudinal Study 2 in North America reporting on the same cohort, Addington et al., 2013 [13] was selected rather than Stowkowy and Addington, 2013 [23]. Five publications used overlapping study samples and were therefore excluded from the meta-analysis [15, 20, 22, 23, 27]. One study was excluded from the meta-analysis because no information was available on prevalence rates of individuals who experienced childhood traumatic events [24].

Six studies were used to assess the prevalence of traumatic experiences in UHR patients [13, 14, 21, 25, 26, 28]. Additional data were requested and received from Addington et al., (2013), Thompson et al., (2014) and Zimbrón et al., (2013) [13, 25, 28]. Three studies compared trauma questionnaire scores in UHR and healthy control subjects [21, 23, 24].

Two studies compared recent life event scores in UHR and healthy control subjects [16, 18] (Table 2).

**Data analysis**

We conducted three random effects meta-analyses with Comprehensive Meta-Analysis (CMA; version 1.0.25; Biostat, Englewood, NJ). One meta-analysis assessed the prevalence rate of trauma in UHR patients alone, and two meta-analyses were conducted to compare prevalence rates of trauma and recent life events between UHR patients and healthy control subjects. Heterogeneity is a concern in meta-analysis as it may introduce the problem of
Table 1. Overview studies on childhood trauma in UHR populations

<table>
<thead>
<tr>
<th>Author et al., (Year)</th>
<th>Study</th>
<th>Outcome measure</th>
<th>Instrument measuring trauma</th>
<th>Instrument measuring UHR</th>
<th>Study design</th>
<th>Participants</th>
<th>Gender (Male%)</th>
<th>Mean age (range)</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Bechdolf et al., (2010) [14]</td>
<td>PACE Australia</td>
<td>To investigate whether trauma predicts conversion to psychosis in an UHR population</td>
<td>General Trauma Questionnaire</td>
<td>CAARMS</td>
<td>Follow-up mean in days=615</td>
<td>N=92 UHR 34.80%</td>
<td>18.0 (15-24)</td>
<td>Sexual trauma was the strongest predictor for transition to psychosis in an UHR population</td>
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<tr>
<td>2. Velthorst et al., (2013) [20]</td>
<td>PACE Australia</td>
<td>Examine differences in baseline symptom presentation between UHR patients with and without history of trauma</td>
<td>Trauma was retrieved by case managers as it was documented in medical files</td>
<td>CAARMS</td>
<td>Cross-sectional</td>
<td>N=127 UHR 41.70%</td>
<td>18.2 (14-26)</td>
<td>Of UHR patients who experienced trauma, physical abuse was related to higher rates of paranoid thoughts compared to UHR subjects without a history of trauma</td>
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<tr>
<td>3. Thompson et al., (2010) [15]</td>
<td>PACE Australia</td>
<td>Examine prevalence of attenuated psychotic symptoms with sexual content</td>
<td>12 items that corresponded to items used in the US national comorbidity survey [57] and the Australian National Survey of Mental Health and wellbeing [58] with one item included about childhood emotional abuse</td>
<td>CAARMS</td>
<td>Cross-sectional</td>
<td>N=92 UHR 34.80%</td>
<td>18.0 (15-24)</td>
<td>Presence of attenuated psychotic symptoms with sexual content was related to a history of sexual trauma</td>
<td></td>
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<tr>
<td>Author</td>
<td>Study</td>
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<td>Instrument measuring trauma</td>
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<tr>
<td>4. Falukozi and Addington</td>
<td>NAPLS-2 Canada rod. 2012</td>
<td>Examine the content of attenuated psychotic symptoms and its relationship to a history of childhood trauma</td>
<td>Abuse and Trauma Questionnaire (Janssen et al., 2004) [6]</td>
<td>SIPS</td>
<td>Cross-sectional</td>
<td>N=45 UHR</td>
<td>56%</td>
<td>19 (14-35)</td>
<td>A relationship between the experience of childhood trauma and the content of attenuated positive symptoms was reported in the CHR group.</td>
</tr>
<tr>
<td>5. Addington et al., 2013</td>
<td>NAPLS-2 North America</td>
<td>Prevalence of trauma in UHR and HC and its relationship to current psychopathology, cannabis use and functioning</td>
<td>Childhood Trauma and abuse scale</td>
<td>SIPS</td>
<td>Cross-sectional</td>
<td>N=360 UHR</td>
<td>58.3%</td>
<td>18.98</td>
<td>Individuals at CHR reported significantly more trauma and bullying compared to healthy controls.</td>
</tr>
<tr>
<td>6. Stowkowy and Addington</td>
<td>NAPLS-2 Canada rod. 2013</td>
<td>To compare FHR who also met UHR criteria to FHR who did not meet UHR criteria and HC on various risk factors</td>
<td>Adapted version of the Childhood Trauma and Abuse Scale (Janssen et al., 2004) [6]</td>
<td>SIPS</td>
<td>Cross-sectional</td>
<td>N=25 FHR</td>
<td>40%</td>
<td>20.76</td>
<td>FHR+UHR and FHR-non UHR reported a significant difference in trauma prevalence compared to the HC group.</td>
</tr>
<tr>
<td>7. Sahin et al., 2013</td>
<td>Psychotic Disorder Research Program of Istanbul Turkey</td>
<td>Severity of childhood trauma and its relationship with clinical features in FES, UHR and HC</td>
<td>Childhood Trauma Questionnaire</td>
<td>CAARMS</td>
<td>Cross-sectional</td>
<td>N=83 FES</td>
<td>72.3%</td>
<td>23.1</td>
<td>Childhood trauma is related to the severity of psychotic symptoms in both FES and UHR populations and significantly higher compared to HC.</td>
</tr>
</tbody>
</table>

Table 1.
<table>
<thead>
<tr>
<th>Author</th>
<th>Study</th>
<th>Outcome measure</th>
<th>Instrument measuring trauma</th>
<th>Instrument measuring UHR</th>
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</tr>
</thead>
<tbody>
<tr>
<td>8. Tikka et al., (2013) [21]</td>
<td>Detection of Early Psychosis Project of Turku University Finland</td>
<td>Prevalence of childhood trauma and premorbid adjustment and their association with each other</td>
<td>Trauma and Distress Scale</td>
<td>SIPS</td>
<td>Cross-sectional</td>
<td>N=20 UHR</td>
<td>25%</td>
<td>36,7%</td>
<td>23.1 (14-35) UHR patients reported more childhood trauma experiences compared to the healthy control group</td>
</tr>
<tr>
<td>9. Zimbrón et al., (2013) [25]</td>
<td>Cameo United Kingdom</td>
<td>Determine whether clinical and sociodemographic factors would be more prevalent in FEP compared to UHR</td>
<td>Childhood Trauma Questionnaire/ Trauma History Screen</td>
<td>CAARMS</td>
<td>Cross-sectional</td>
<td>N=30 FEP</td>
<td>60%</td>
<td>22.0 (16-32)</td>
<td>UHR patients were exposed to a higher burden of trauma compared to the FEP group</td>
</tr>
<tr>
<td>10. Thompson et al., (2009) [26]</td>
<td>New York Metropolitan area</td>
<td>Prevalence of childhood trauma and its relationship to attenuated positive symptoms and other symptoms</td>
<td>Early Trauma Inventory</td>
<td>SIPS</td>
<td>Cross-sectional</td>
<td>N=30 UHR</td>
<td>83%</td>
<td>18.8 (13-25)</td>
<td>Childhood abuse was associated to positive symptoms, especially grandiosity. This effect was accounted for by the ethnic minority of the sample</td>
</tr>
</tbody>
</table>

Table 1.↓
<table>
<thead>
<tr>
<th>Author</th>
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<th>Mean age (range)</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>11. Thompson et al., (2014) [28]</td>
<td>PACE Australia</td>
<td>Association between experience of childhood trauma and the development of psychotic disorder</td>
<td>Childhood Trauma Questionnaire</td>
<td>CAARMS</td>
<td>7-year follow-up</td>
<td>N=233 UHR</td>
<td>41.20%</td>
<td>18.9 (15-30)</td>
<td>Sexual trauma was associated with transition to psychosis. Those with highest sexual abuse scores were estimated to have transition risk 2-4 times that of those with low scores.</td>
</tr>
<tr>
<td>12. Magaud et al., 2013) [27]</td>
<td>Study not specified Canada</td>
<td>Examine the prevalence of cyberbullying in UHR</td>
<td>Childhood Trauma Questionnaire, Cyberbullying was assessed by additional questions</td>
<td>SIPS</td>
<td>Cross-sectional</td>
<td>N=50 UHR</td>
<td>50%</td>
<td>16.7 (range not specified)</td>
<td>38% of the UHR sample reported cyberbullying. An association was found between previous trauma and cyberbullying.</td>
</tr>
</tbody>
</table>

CAARMS, Comprehensive Assessment of At-Risk Mental State; SIPS, Structured Interview for Prodromal Syndromes; PACE, Personal Assessment and Crisis Evaluation; NAPLS 2, North American Prodrome Longitudinal Study 2; UHR, Ultra High Risk; FEP, first episode psychosis; FES, first episode schizophrenia; HC, healthy control; FHR, Family High Risk
<table>
<thead>
<tr>
<th>Author</th>
<th>Study</th>
<th>Outcome measure</th>
<th>Instrument measuring life events</th>
<th>Instrument measuring UHR</th>
<th>Study design</th>
<th>Participants</th>
<th>Gender (Male)</th>
<th>Mean age (range)</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. DeVylder et al., (2013) [18]</td>
<td>COPE United States of America</td>
<td>Exposure to major life-events was hypothesized to associate to symptoms at baseline and prospectively</td>
<td>Coddington’s Life Events Record (3 months prior to interview)</td>
<td>SIPS</td>
<td>4-year follow-up</td>
<td>N=65 UHR</td>
<td>76.9% 58.3%</td>
<td>UHR 19.5 HC 20.4 (range not specified)</td>
<td>Life events were unrelated to symptoms and were comparable in UHR patients and HC</td>
</tr>
<tr>
<td>2. Mason et al., (2004) [59]</td>
<td>Psychological Assistance Service United Kingdom</td>
<td>Examine risk factors for transition to psychosis in UHR individuals</td>
<td>The Schedule of Recent Experience (12 months prior to interview)</td>
<td>CAARMS</td>
<td>1-year follow-up</td>
<td>N=74 UHR</td>
<td>52.7% 17.3 (13-20)</td>
<td>Experience of life-events was no predictor for transition to psychosis</td>
<td></td>
</tr>
<tr>
<td>3. Phillips et al., (2012) [16]</td>
<td>PACE Australia</td>
<td>Examine whether UHR individuals experienced more stressful life-events and hassles and higher levels of distress compared to HC</td>
<td>Life Events Interview Schedule (12 months prior to interview)</td>
<td>CAARMS</td>
<td>1-year follow-up</td>
<td>N=143 UHR</td>
<td>46.1% 42.7%</td>
<td>UHR 18.69 HC 21.47 (14-30)</td>
<td>The UHR sample reported significantly fewer life events compared to the HC sample</td>
</tr>
<tr>
<td>Author</td>
<td>Study</td>
<td>Outcome measure</td>
<td>Instrument measuring life events</td>
<td>Instrument measuring UHR</td>
<td>Study design</td>
<td>Participants</td>
<td>Gender (Male)</td>
<td>Mean age (range)</td>
<td>Conclusions</td>
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<tr>
<td>Thompson et al., (2007) [56]</td>
<td>PACE Australia</td>
<td>Examine whether there were positive correlations between experience of stressful events, HPA-axis functioning, hippocampal and pituitary structure and psychotic symptoms in UHR individuals</td>
<td>Life Events Interview Schedule (1 month prior to interview)</td>
<td>CAARMS</td>
<td>1-year follow-up</td>
<td>N=23 UHR</td>
<td>60.9%</td>
<td>18.9 (14-30)</td>
<td>No significant correlation was reported between life-events and psychotic symptoms</td>
</tr>
</tbody>
</table>

CAARMS, Comprehensive Assessment of At-Risk Mental State; SIPS, Structured Interview for Prodromal Syndromes; PACE, Personal Assessment and Crisis Evaluation; UHR, Ultra High Risk; HC, healthy control
‘comparing apples with oranges’. Heterogeneity was tested with a χ² test. We also report the I² statistic. When I² = 0%, 25%, 50% or 75%, then retrospectively no, low, moderate or high heterogeneity must be assumed [29].

Publication bias was evaluated using Duval and Tweedie’s trim and fill procedure, which yields an adjusted estimate of the pooled effect size after publication bias has been taken into account [30, 31].

**Results**

**Prevalence of childhood trauma in UHR patients**

We conducted a meta-analysis including six studies (Figure 2). The mean prevalence rate of trauma was 86.8% (95% CI 77%-93%). Although there was no publication bias, heterogeneity was high $Q(5)=29.386$, $p<0.001$ and $I^2=83.0$.

<table>
<thead>
<tr>
<th>Study name</th>
<th>Event rate</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>Z-Value</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Addington et al., 2013</td>
<td>0.797</td>
<td>0.752</td>
<td>0.835</td>
<td>10.438</td>
<td>0.000</td>
</tr>
<tr>
<td>Bechdof et al., 2010</td>
<td>0.696</td>
<td>0.596</td>
<td>0.781</td>
<td>3.855</td>
<td>0.000</td>
</tr>
<tr>
<td>Thompson et al., 2013</td>
<td>0.901</td>
<td>0.856</td>
<td>0.933</td>
<td>10.068</td>
<td>0.000</td>
</tr>
<tr>
<td>Thompson, J. et al., 2009</td>
<td>0.970</td>
<td>0.799</td>
<td>0.996</td>
<td>3.248</td>
<td>0.001</td>
</tr>
<tr>
<td>Tikka et al., 2013</td>
<td>0.976</td>
<td>0.713</td>
<td>0.999</td>
<td>2.594</td>
<td>0.009</td>
</tr>
<tr>
<td>Zimbron et al., 2013</td>
<td>0.868</td>
<td>0.770</td>
<td>0.928</td>
<td>5.462</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Fig. 2. Meta-analysis of prevalence rate of childhood trauma in UHR samples

**Trauma in UHR patients versus healthy controls**

Three studies compared the prevalence of childhood trauma between UHR patients and healthy controls. Trauma scores were significantly higher in UHR patients than in healthy controls, in which trauma ranged from 42.7-60% [13, 21] (Random effects Hedges’ g=1.09; Z=4.60, p<.001). There were some indications for publication bias, but Trim and Fill corrected the g to 0.74, which still indicates a large difference between groups. There was moderate heterogeneity $Q(2)=4.57$, n.s. and $I^2=56.2$. 
Recent life events in UHR patients versus healthy controls
Only two studies compared the prevalence of recent life events between UHR patients and healthy controls. UHR patients experienced a significantly less number of life events compared with healthy controls (Random effects Hedges’ g=-0.53; Z=-2.36, p<.02). With two studies publication bias could not be assessed and heterogeneity was moderate Q(1)=2.1, n.s. and I²=52.4.

Discussion
Our meta-analysis clearly indicates that prevalence rates of childhood trauma in UHR populations are high. The mean prevalence rate of 86.8% is consistent with the reported prevalence rate of 85% in patients diagnosed with schizophrenia [32]. UHR patients reported higher trauma scores, but seemed to experience less recent life events than healthy controls. In addition, recent life events were not related to transition to psychosis.

Childhood trauma in UHR patients
Our results show that childhood trauma rates in UHR populations are substantially higher than rates in the general population (ranging from 42.7-60%) [13, 21]. The fact that only 10-20% of the UHR population will eventually make a transition to a psychotic disorder [33-35] suggests that childhood trauma may not be specifically related to higher risks of developing a psychotic disorder alone. Instead, childhood trauma may cause a general vulnerability to present to clinical services with distressing subclinical psychotic experiences underlying many psychiatric disorders in early adulthood.

Supporting this idea are the high co-morbidity rates consistently reported in UHR populations [36, 37] Apart from psychotic disorders, trauma during childhood has also been related to higher odds of developing post-traumatic stress disorder (PTSD) [38], addiction [39], and depression and anxiety disorder [40-42].

How to explain the relationship between childhood trauma and UHR status?
One of the explanations for the relationship between childhood trauma and subclinical psychotic symptoms is that childhood trauma leads to negative schemes about self, others and the world. For example, bullying or physical abuse in childhood could lead to suspiciousness of others, which may in turn lead to proneness for distressing paranoid ideas in adolescence [43].
However, this hypothesis does not provide an adequate explanation for what actually happens in the brain in the formation of subclinical psychotic experiences. Research suggests that persistent exposure to traumatic experiences, such as bullying and abuse, may affect the stress regulation system: the hypothalamic-pituitary-adrenal (HPA) axis [44-47]. After experiencing a severe traumatic event, the stress regulation system becomes overactive, causing increased cortisol levels and increased stress and fear responses to normal environmental triggers. Over activation of the HPA-axis has also been found to result in increased dopamine activity in subcortical brain regions. Increased dopamine activity is associated with development of psychotic symptoms, in clinical [45, 48] and in UHR populations [49].

In addition, persistent exposure to childhood trauma is associated with both structural and functional abnormalities in the prefrontal cortex, amygdala and hippocampus [50, 51]. These brain abnormalities have been reported in UHR patients, in which increased pituitary volume and reduced hippocampal volume have been found [49].

Interestingly, traumatic experiences that occur in childhood seem to bridge many years relatively unnoticed before symptoms emerge in adolescence and early adulthood. This delayed effect of childhood trauma on brain alterations is in line with the neurodevelopmental conceptualization of schizophrenia, stating that progressive (disruptive) developments in the brain happen early on, but become more apparent in adolescence, a period of substantial brain maturation [52, 53]. There is 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 [54]. For example, in a study investigating sexual abuse and brain alterations, sexual abuse between age 3 and 5 years showed reduced hippocampal volume, while similar abuse between 9 and 10 years was mainly related to changes in the corpus callosum. Instead, abuse between 14 and 16 years led to changes in the prefrontal cortex [42].

**Recent life events in UHR patients**

In contrast to our hypothesis, the reported number of recent life events in UHR patients was lower than that of healthy controls and recent life events were not related to transition to psychosis. This finding is in contrast to studies on recent life events and psychotic disorders [9].
An explanation for the discrepancy in findings between clinical and UHR studies might be that UHR populations are too heterogeneous to detect the relationship between psychosis and life events since only about 22% will transition to psychosis within 12 months and the prevalence of life events was low [35]. Larger samples may be needed to detect a relationship between life events and transition to psychosis in UHR samples.

Alternatively, it may be that, in order to detect a significant relationship in heterogeneous UHR samples, studies need to address the combination of both childhood trauma and recent life events. It is not unlikely that the combination of trauma during childhood and stressful events later in life cause a ‘double-hit reaction’. Following this hypothesis, childhood trauma leads to a general sensitivity to stress, and the stressful life event later in life may cause someone to eventually cross the psychosis threshold. The combination of childhood trauma and recent life events has not yet been investigated in UHR populations and is recommended for future research.

Our results show that UHR patients experienced less life events compared to healthy controls. This could be explained by an attempt to cope with the emerging subclinical psychotic symptoms, a large part of this sample tends to withdraw from the social environment. Social withdrawal, while predictive of transition in UHR samples [55], may in fact result in a reduced number of recent life experiences in this population.

Although UHR patients experience less life events compared to healthy controls, they were found to experience higher levels of subjective distress in response to these life events [16]. This may be the effect of an overactive HPA-axis, and may indicate that UHR patients are less resilient to recent life events compared to healthy controls. This hypothesis is further supported by the finding that UHR patients have higher cortisol levels and experience more anxiety and depression in response to minor life events or ‘daily hassles’ [56].

**Limitations**

Our findings must be interpreted in light of several limitations. First, the sample size of the included studies (particularly those examining life events) was small and often lacked comparison with a control group. Second, considerable heterogeneity in the studies on childhood trauma makes comparison difficult. Third, most of the reviewed studies have a cross-sectional design, implying that no conclusions can be drawn about causality. In addition, because there were only two prospective studies
on childhood trauma, a meta-analytical approach on the association between childhood trauma and transition to psychosis was not possible.

A limitation of the reviewed studies lies in the measurement of childhood trauma and life events. Trauma was sometimes retrieved from trauma questionnaires completed by case managers based on their knowledge of the patient [15], which may have led to underreporting of traumatic events. In addition, most studies on childhood trauma lacked information about the frequency, duration, timing and impact and distress of childhood trauma.

Studies on recent life events lacked specification about the onset of the UHR symptoms and life events were recorded only over the last month [16, 56], or the last 3 months [18] prior to interview. Ideally, to investigate whether life events preceded UHR symptoms, life events should be measured prior to the onset of UHR symptoms.

**Conclusion**
Overall, our review and meta-analysis show that childhood trauma is highly prevalent in UHR patients. Recent life events are less prevalent in UHR patients than in healthy controls, although the reported stress in response to life events is higher. The high prevalence of childhood trauma in UHR samples emphasizes the need for early detection programs to focus on these traumatic events, for example by screening for trauma, and offering trauma treatment to reduce the high levels of emotional arousal and distress which results from the experience of early trauma and recent life events.

**Role of the funding source**
There was no direct funding source for this study.

**Contributors**
None.

**Conflict of interest**
None.

**Acknowledgments**
We are supported by the European Union [European Community’s Seventh Framework Program (grant agreement no. HEALTH-F2-2009-241909) (Project EU-GEI)].
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