Chapter 7

Child maltreatment and clinical outcome in individuals at ultra-high risk for psychosis in the EU-GEI high risk study

Tamar C. Kraan
Eva Velthorst
Manouk Themmen
Lucia Valmaggia
Matthew J. Kempton
Phillip McGuire
Jim van Os
Bart P.F. Rutten
Filip Smit
Lieuwe de Haan
Mark van der Gaag
EU-GEI high risk study*

Schizophrenia Bulletin, in press
Abstract

Background: Child maltreatment has been associated with a wide range of mental disorders in adulthood. Whether child maltreatment is specifically associated with psychosis risk in individuals at ultra-high risk (UHR) for psychosis, or leads to a general vulnerability for overall psychopathology in the UHR stage remains unclear. The present study examines the association between child maltreatment and transition to psychosis and other mental disorders.

Methods: The sample consisted of 259 UHR individuals from the EUropean network of national schizophrenia networks studying Gene-Environment Interactions (EU-GEI) study. Participants were followed-up for two years to assess clinical outcome. Clinical outcome was assessed at 6 months, 12 months and 24 months after baseline. Child maltreatment before the age of 17 years was assessed at baseline.

Results: Our findings show that a history of emotional abuse was associated with an increased risk for transition to psychosis (OR=3.78, 95% CI=1.17 to 12.39, p=0.027). Apart from psychosis, a history of physical abuse was associated with depressive disorder (OR=4.92, 95% CI=2.12 to 11.39, p=0.001), post-traumatic stress disorder (OR=2.06, 95% CI=1.10 to 3.86, p=0.023), panic disorder (OR=2.00, 95% CI=1.00 to 3.99, p=0.048) and social phobia (OR=2.47, 95% CI=1.18 to 5.16, p=0.016) at follow-up.

Conclusion: Our findings suggest that in the UHR stage child maltreatment is a pluripotent risk factor for developing psychosis, depressive disorder, PTSD, panic disorder and social phobia in adulthood.
Introduction

A history of childhood abuse and neglect (hereafter child maltreatment) has been associated with an increased risk of developing various mental disorders in adulthood [1]. One group of severe mental illnesses that has been extensively examined in relation to child maltreatment is psychotic disorders [2]. In both clinical and population based studies, child maltreatment has been found to substantially increase psychosis risk [3, 4].

In the last two decades research has increasingly focused on early detection of psychosis. Criteria have been established to identify individuals at increased risk for a first episode of psychosis [5]. Using these Ultra High Risk (UHR) criteria [5], initial transition-to-psychosis rates ranged around an average of approximately 40% within two years [5, 6]. However, the more recent UHR studies have shown a decline in transition rate, with meta-analytic evidence suggesting a transition rate of 20% at two years, increasing to 36% after three years [7, 8]. As 70% of individuals meeting UHR criteria will not go on to develop a psychotic episode it is important to search for additional factors that may contribute to psychosis risk. One of these factors that have widely been investigated in clinical samples is child maltreatment [3]. The rate of child maltreatment in UHR populations is highly prevalent [9]. The four UHR studies that examined the effect of child maltreatment on transition to psychosis risk have yielded inconsistent findings [10-13]. While two studies found that a history of sexual abuse significantly increased the risk for transition to psychosis [12, 13], these findings could not be replicated in two other UHR cohorts [10, 11].

In addition, the few UHR studies that did consider the effect of child maltreatment in prospective designs have rarely focused on outcomes other than transition to psychosis. Two recent reports tentatively suggest that UHR individuals with a history of child maltreatment report more persistent subclinical psychotic symptoms, depression and impaired social functioning at follow-up [10, 14]. However, to the best of our knowledge there are no UHR studies that specifically examined whether child maltreatment also increases the risk of receiving a diagnosis other than psychosis (as defined by the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV)) [15]. This is important, because studying co-morbid diagnoses at follow-up may provide more insight into whether child maltreatment is associated with psychosis risk, or rather a pluripotent risk factor for developing general psychopathology in the UHR stage.
Our aims were to: (1) examine the prevalence of child maltreatment in UHR individuals compared to individuals from a control group, (2) examine the effect of child maltreatment on transition to psychosis at follow-up, and (3) examine the effect of child maltreatment on other mental Axis-I disorders other than psychosis at follow-up.

Methods

Sample
Participants were part of the prodromal work package of the European Network of Schizophrenia Networks studying Gene-Environment Interactions (EU-GEI) cohort [16]. EU-GEI is a naturalistic prospective multicenter study that aimed to identify the interactive genetic, clinical and environmental determinants of schizophrenia. A sample of UHR individuals and controls was recruited from 11 centers (Figure 1).

UHR participants, aged 15 - 35 years (18 -35 years in the centers of Cologne, Parnassia, Basel, Vienna, Paris and London), were eligible to participate if they met at least one of the UHR criteria as defined by the Comprehensive Assessment of At Risk Mental State (CAARMS) [5]: (1) Vulnerability Group: a first-degree relative with a psychotic disorder or diagnosed with schizotypal personality disorder in combination with a significant drop in functioning during at least one month in the previous year, (2) Attenuated Psychotic Symptoms (APS) Group: the presence of sub-threshold positive psychotic symptoms for at least one month during the past year, or (3) Brief Limited Intermittent Psychotic Symptoms (BLIPS) Group: an episode of frank psychotic symptoms that lasted no longer than one week, which abated spontaneously. Exclusion criteria were: (1) presence of a current or past psychotic disorder, (2) symptoms relevant for inclusion are explained by a medical disorder or drugs or alcohol dependency, (3) IQ<60.

Controls were recruited from the same geographical catchment area as the UHR group. Exclusion criteria for controls were similar to those for UHR participants. Additionally, controls were excluded when there was presence of an UHR status as defined by the CAARMS [5].

Design
Individuals with UHR symptoms were referred to the EU-GEI study by their local mental health care institution. If they agreed to participate, detailed
information on the study procedure was provided and the participant was asked to sign informed consent.

Control participants were recruited from three centers: the Institute of Psychiatry (IoP) in London, the Personal Assessment and Crisis Evaluation (PACE) clinic in Melbourne, and the Amsterdam Medical Center (AMC)/Parnassia The Hague (see Figure 1). At the IoP, controls were recruited using GP lists (including all registered patients for whom the practice is responsible for providing primary medical services) and the national postal address file as sampling frames [17]. Additionally, controls were recruited from another study at the IoP that recruited controls from the internet (using a website called Gumtree). A few other controls were PhD students from the IoP. At the AMC and Parnassia controls were recruited using a website (Proefbunny). The PACE clinic recruited controls by online advertisement.

Participants were followed up for two years and interviewed at four time points. Clinical (outcome) measures were assessed at baseline, 12 months and 24 months after baseline (or earlier if they transitioned to psychosis). In addition, six months after baseline a brief assessment was conducted. During this assessment changes in subclinical psychotic symptoms and global functioning were assessed. By the time of analyzing the data, some of the follow-up assessments were not finished yet.

If UHR participants made a transition to psychosis during the follow-up period, they were interviewed with the CAARMS. Transition to psychosis was defined as the development of full threshold psychotic disorder according to the CAARMS [5]. Where possible, subjects were assessed with the Structured Clinical Interview (SCID-I) to establish a formal diagnosis according to DSM-IV criteria [15]. When this was not possible (i.e. subjects did not want to attend follow-up assessment) clinical notes were used.
Figure 1. Flowchart of participants who reached follow-up assessment by site
Assessments

1. All participants completed a detailed sociodemographic schedule. Data on baseline demographic characteristics (e.g. age, gender, ethnicity) were assessed using the modified Medical Research Council socio-demographic schedule [16, 18].

2. The CAARMS [5] was used to assess subclinical psychotic symptoms in the year prior to assessment. The CAARMS is a semi-structured interview conducted to determine presence, severity (0-6), frequency (0-6), distress (0-100) and type of UHR symptoms. The CAARMS consists of seven subscales: 4 positive symptoms items, 2 cognitive symptom items, 3 emotional disturbance items, 3 negative symptoms items, 4 behavioral change items, 4 motor changes items and 8 general psychopathology items. Criteria for UHR are based on the 4 positive symptoms items only (unusual thought content, non-bizarre ideas, perceptual abnormalities and disorganized speech). This instrument uses the severity and frequency of UHR symptoms to discriminate between status groups (meeting UHR criteria, psychosis, or not at risk).

3. The SCID-I [19] is a standardized interview extensively used in research and clinical settings. This interview assesses current and lifetime Axis I mental disorders using criteria in accordance with the DSM-IV [15]. This questionnaire was used to assess clinical outcome.

4. Child maltreatment was retrospectively assessed with the Childhood Trauma Questionnaire (CTQ) [20]. This 25-item self-report questionnaire assesses traumatic events before the age of 17. The CTQ consists of five domains: emotional abuse, emotional neglect, sexual abuse, physical abuse and physical neglect. All items range from 1 (never) to 5 (almost always). Validated cut-off scores of the CTQ were used to evaluate whether participants with a history of maltreatment had worse clinical outcome than participants without a history of maltreatment. The CTQ subscales were dichotomized by the following cut-off scores: physical abuse >=8, sexual abuse >=6, emotional abuse >=9, physical neglect >=8 and emotional neglect >=10 [21]. The subscales were considered as present when scores were above low to moderate. Total maltreatment score was cut-off by the median.

5. A modified version of the Cannabis Experience Questionnaire [22] was administered to assess cannabis (ab)use. In the present study we controlled for current cannabis use, which was assessed with one item: ‘are you currently using cannabis [yes/no]'.

Procedure
EU-GEI was conducted in accordance with the Declaration of Helsinki. The Medical Ethics Committees of all participating sites approved the study protocol. Participants were included after written informed consent. Participants younger than 18 years of age signed for assent, while their parents signed for informed consent. Assessments were conducted by trained psychiatrists, psychologists or research assistants. A web-based training environment was developed in which research assessors had to complete a training module at the start of EU-GEI. To assess interrater reliability, research assessors had to complete online training videos every 12 months. Rating of the online training videos was mandatory; only researchers that succeeded in passing the reliability checks were permitted to assess participants included in EU-GEI.

Statistical analysis
All analyses were performed in Stata 13. Cases and controls were compared on baseline characteristics using chi-square analysis for categorical dependent variables and independent t-tests for continuous dependent variables. Fisher’s exact test was used to compare the prevalence of child maltreatment between cases and controls.

The data has a multilevel structure, because multiple observations are nested within participants (level 1) and participants are nested within sites (level 2). Therefore, multilevel models were used to control for within person level of clustering and clustering within countries. The effect of child maltreatment on transition to psychosis was estimated using multilevel logistic regression (XTMELOGIT). The dependent variable was transition to psychosis (0/1), independent variables were the dichotomized total score of child maltreatment. The dichotomized subscales of child maltreatment were examined in a separate model. Dichotomized scores of child maltreatment were used to place all risk factors (psychopathological symptoms and the various types of maltreatment) on the same (0/1) scale for better comparability and ease of interpretation.

Subsequently, we estimated the effect of child maltreatment on clinical outcome measures according to DSM-IV criteria [15]. In these models (XTMELOGIT), binary dependent variables were depressive disorder, panic disorder, social anxiety disorder, obsessive-compulsive disorder (OCD) and post-traumatic stress disorder (PTSD) (SCID-I). Independent variables were dichotomized total maltreatment score. In a separate model the dichotomized sub domains of child maltreatment were examined.
All analyses were adjusted for age, gender and current cannabis use. A significance level of $p<0.05$ was considered statistically significant.

## Results

### Sample characteristics

Demographic, clinical and functional baseline data were available for 304 UHR individuals and 50 controls. Of those who reached follow-up assessment by the time of analyzing, data on child maltreatment and clinical and functional follow-up data were available for 259 UHR individuals (53.9% male, mean age 22.7, SD 4.5) and 48 controls (55.0% male, mean age 23.98, SD 4.33). These subsamples were used in the present study (see table 1). Cases and controls did not significantly differ in terms of age ($t=1.73$, $p=0.084$), gender ($X^2=0.36$, $p=0.545$) and cannabis use ($X^2=4.68$, $p=0.096$). Of those with child maltreatment data and follow-up data available, the number of UHR individuals that transitioned to psychosis was 31 (11.9%). Eleven of those 31 made a transition to psychosis within the first 6 months, 13 at 12 months and 7 at 24 months.

### Prevalence of child maltreatment in UHR individuals and controls

We examined the difference in prevalence of child maltreatment between UHR individuals and controls. Fifty-four percent of the UHR individuals had experienced at least one form of maltreatment during child compared to 17.4% of the control sample ($p<0.001$). This difference was apparent for each form of child maltreatment: emotional abuse; cases= 62.5%, controls= 27.1% ($p<0.001$); emotional neglect; cases= 76.4%, controls= 33.3% ($p<0.001$); physical abuse; cases= 24.3%, controls= 8.3% ($p=0.014$); physical neglect; cases= 47.2%, controls= 20.8% ($p=0.001$); sexual abuse; cases= 29.9%, controls= 10.4% ($p=0.005$).

### Child maltreatment and transition to psychosis

None of the univariate odds ratios for the association between each individual subtype of maltreatment and transition to psychosis was statistically significant (see table 2). In addition, total child maltreatment did not increase the risk for transition to psychosis (OR=2.46, 95% CI=0.95 to 6.41, $p=0.065$). Examination of the adjusted odds ratios showed that, while controlling for the other subtypes, a history of emotional abuse significantly contributes to transition (OR=3.78, 95% CI=1.17 to 12.39, $p=0.027$), while the adjusted odds ratio of
Table 1. Baseline characteristics for UHR participants (N=259)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age in years (SD)</td>
<td>22.7 (4.5)</td>
</tr>
<tr>
<td>Gender male, N (%)</td>
<td>139 (53.9)</td>
</tr>
<tr>
<td>Current cannabis use, N (%)</td>
<td>62 (24.0)</td>
</tr>
<tr>
<td>UHR Intake group, N (%)</td>
<td></td>
</tr>
<tr>
<td>APS</td>
<td>203 (78.7)</td>
</tr>
<tr>
<td>Genetic Risk</td>
<td>22 (8.4)</td>
</tr>
<tr>
<td>BLIPS</td>
<td>15 (5.7)</td>
</tr>
<tr>
<td>APS and Genetic Risk</td>
<td>19 (7.2)</td>
</tr>
<tr>
<td>SCID depressive disorder, N (%)</td>
<td>72 (30.4)</td>
</tr>
<tr>
<td>SCID PTSD, N (%)</td>
<td>26 (10.1)</td>
</tr>
<tr>
<td>SCID social disorder, N (%)</td>
<td>50 (19.4)</td>
</tr>
<tr>
<td>SCID panic disorder, N (%)</td>
<td>48 (18.6)</td>
</tr>
<tr>
<td>SCID OCD, N (%)</td>
<td>22 (8.5)</td>
</tr>
<tr>
<td>Total maltreatment mean score, (SD)</td>
<td>46.8 (15.2)</td>
</tr>
<tr>
<td>Emotional abuse mean score, (SD)</td>
<td>11.6 (5.2)</td>
</tr>
<tr>
<td>Sexual abuse mean score, (SD)</td>
<td>6.9 (4.0)</td>
</tr>
<tr>
<td>Physical abuse mean score, (SD)</td>
<td>7.2 (3.5)</td>
</tr>
<tr>
<td>Physical neglect mean score, (SD)</td>
<td>8.1 (3.1)</td>
</tr>
<tr>
<td>Emotional neglect mean score, (SD)</td>
<td>13.1 (4.9)</td>
</tr>
</tbody>
</table>

Note. Demographics of subjects who reached follow-up assessment. OCD, Obsessive Compulsive Disorder; SCID, Structured Clinical Interview; PTSD, posttraumatic stress disorder; UHR, ultra-high risk; APS, attenuated psychotic symptoms; BLIPS, brief limited intermitted psychotic symptoms; SD, standard deviation.
emotional neglect protects against transition (OR=0.26, 95% CI=0.09 to 0.77, p=0.015). These findings could be caused by co-linearity, and therefore the variance inflation factor (VIF) was determined. A VIF of 1.22 was found, which is below the critical value of 10. This indicates that the findings of the adjusted odds ratios are not a statistical artefact.

**Child maltreatment and clinical outcome**

Table 3 presents findings on the association between a history of child maltreatment and DSM-IV disorders. Our results show that a history of overall child maltreatment was positively associated with depressive disorder (OR=4.92, 95% CI=2.12 to 11.39, p=0.001). Examination of the sub domains of child maltreatment revealed that a history of emotional abuse (OR=2.76, 95% CI=1.01 to 7.55, p=0.048) accounted for most of this association. Additionally, a history of physical abuse was positively associated with PTSD (OR=2.06, 95% CI=1.10 to 3.86, p=0.023), panic disorder (OR=2.00, 95% CI=1.00 to 3.99, p=0.048) and social phobia (OR=2.47, 95% CI=1.18 to 5.16, p=0.016).

<table>
<thead>
<tr>
<th></th>
<th>Adjusted Odds Ratio</th>
<th>95% CI</th>
<th>p-value</th>
<th>Unadjusted Odds Ratio</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emotional abuse</td>
<td>3.78</td>
<td><strong>1.17 - 12.39</strong></td>
<td><strong>0.027</strong></td>
<td>2.14</td>
<td>0.79 - 5.78</td>
<td>0.134</td>
</tr>
<tr>
<td>Sexual abuse</td>
<td>1.67</td>
<td>0.66 - 4.20</td>
<td>0.280</td>
<td>1.77</td>
<td>0.73 - 4.25</td>
<td>0.204</td>
</tr>
<tr>
<td>Physical abuse</td>
<td>1.08</td>
<td>0.42 - 2.82</td>
<td>0.869</td>
<td>1.39</td>
<td>0.58 - 3.33</td>
<td>0.438</td>
</tr>
<tr>
<td>Emotional neglect</td>
<td>0.26</td>
<td>0.09 - 0.77</td>
<td>0.015</td>
<td>0.48</td>
<td>0.20 - 1.16</td>
<td>0.104</td>
</tr>
<tr>
<td>Physical neglect</td>
<td>0.76</td>
<td>0.29 - 1.99</td>
<td>0.575</td>
<td>0.89</td>
<td>0.39 - 2.01</td>
<td>0.779</td>
</tr>
</tbody>
</table>

*Note.* Transition to psychosis was controlled for the effect of age, gender and cannabis use. CTQ scales were treated as dichotomized variables. In the adjusted column all subscales were entered in one model, in the unadjusted column subscales of maltreatment were entered separately.
Table 3. Associations between child maltreatment and DSM-IV disorders

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Depressive disorder</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total child maltreatment</td>
<td>4.92</td>
<td>2.12 - 11.39</td>
<td>0.001</td>
</tr>
<tr>
<td>Emotional abuse</td>
<td>2.76</td>
<td>1.01 - 7.55</td>
<td>0.048</td>
</tr>
<tr>
<td>Sexual abuse</td>
<td>0.95</td>
<td>0.42 - 2.14</td>
<td>0.895</td>
</tr>
<tr>
<td>Physical abuse</td>
<td>1.38</td>
<td>0.59 - 3.20</td>
<td>0.454</td>
</tr>
<tr>
<td>Emotional neglect</td>
<td>2.11</td>
<td>0.66 - 6.77</td>
<td>0.209</td>
</tr>
<tr>
<td>Physical neglect</td>
<td>1.97</td>
<td>0.84 - 4.62</td>
<td>0.117</td>
</tr>
<tr>
<td><strong>PTSD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total child maltreatment</td>
<td>1.60</td>
<td>0.87 - 2.95</td>
<td>0.130</td>
</tr>
<tr>
<td>Emotional abuse</td>
<td>0.73</td>
<td>0.37 - 1.42</td>
<td>0.352</td>
</tr>
<tr>
<td>Sexual abuse</td>
<td>0.91</td>
<td>0.52 - 1.62</td>
<td>0.761</td>
</tr>
<tr>
<td>Physical abuse</td>
<td>2.06</td>
<td>1.10 - 3.86</td>
<td>0.023</td>
</tr>
<tr>
<td>Emotional neglect</td>
<td>0.95</td>
<td>0.45 - 2.05</td>
<td>0.905</td>
</tr>
<tr>
<td>Physical neglect</td>
<td>1.80</td>
<td>0.99 - 3.26</td>
<td>0.054</td>
</tr>
<tr>
<td><strong>Panic disorder</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total child maltreatment</td>
<td>0.64</td>
<td>0.35 - 1.19</td>
<td>0.164</td>
</tr>
<tr>
<td>Emotional abuse</td>
<td>0.81</td>
<td>0.40 - 1.65</td>
<td>0.564</td>
</tr>
<tr>
<td>Sexual abuse</td>
<td>0.85</td>
<td>0.46 - 1.58</td>
<td>0.615</td>
</tr>
<tr>
<td>Physical abuse</td>
<td>2.00</td>
<td>1.00 - 3.99</td>
<td>0.048</td>
</tr>
<tr>
<td>Emotional neglect</td>
<td>0.67</td>
<td>0.30 - 1.49</td>
<td>0.329</td>
</tr>
<tr>
<td>Physical neglect</td>
<td>1.31</td>
<td>0.69 - 2.46</td>
<td>0.399</td>
</tr>
<tr>
<td><strong>Social phobia</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total child maltreatment</td>
<td>0.94</td>
<td>0.45 - 1.97</td>
<td>0.877</td>
</tr>
<tr>
<td>Emotional abuse</td>
<td>0.57</td>
<td>0.26 - 1.22</td>
<td>0.145</td>
</tr>
<tr>
<td>Sexual abuse</td>
<td>0.83</td>
<td>0.42 - 1.61</td>
<td>0.578</td>
</tr>
<tr>
<td>Physical abuse</td>
<td>2.47</td>
<td>1.18 - 5.16</td>
<td>0.016</td>
</tr>
<tr>
<td>Emotional neglect</td>
<td>2.02</td>
<td>0.83 - 4.92</td>
<td>0.122</td>
</tr>
<tr>
<td>Physical neglect</td>
<td>0.96</td>
<td>0.49 - 1.90</td>
<td>0.915</td>
</tr>
<tr>
<td><strong>OCD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total child maltreatment</td>
<td>1.11</td>
<td>0.64 - 1.93</td>
<td>0.714</td>
</tr>
<tr>
<td>Emotional abuse</td>
<td>0.73</td>
<td>0.40 - 1.33</td>
<td>0.299</td>
</tr>
<tr>
<td>Sexual abuse</td>
<td>1.02</td>
<td>0.61 - 1.72</td>
<td>0.932</td>
</tr>
<tr>
<td>Physical abuse</td>
<td>1.22</td>
<td>0.69 - 2.15</td>
<td>0.498</td>
</tr>
<tr>
<td>Emotional neglect</td>
<td>1.73</td>
<td>0.85 - 3.52</td>
<td>0.130</td>
</tr>
<tr>
<td>Physical neglect</td>
<td>1.02</td>
<td>0.60 - 1.73</td>
<td>0.943</td>
</tr>
</tbody>
</table>

*Note.* PTSD, posttraumatic stress disorder; OCD, obsessive compulsive disorder. CTQ scales were treated as dichotomized variables. All maltreatment subscale scores were entered in the same model. A separate model was conducted to examine the combined effect of child maltreatment on transition to psychosis using the child maltreatment sum score.
Discussion

Main findings
In congruence with earlier reports, our findings clearly indicate that child maltreatment is significantly more prevalent in young individuals who present with UHR symptoms compared to controls. Examining the different subdomains of child maltreatment separately, a history of emotional abuse held as a significant predictor of transition to a first episode of psychosis. We also examined whether a history of child maltreatment was associated with mental disorders, other than psychosis. Positive associations were found between a history of child maltreatment and depressive disorder, PTSD, panic disorder and social phobia. In sum, our findings suggest that in UHR cohorts, child maltreatment is a pluripotent risk factor for various psychopathological symptoms in adulthood.

The effect of child maltreatment in the UHR stage
In the current study we partly confirmed earlier findings pointing to a significant association between a history of child maltreatment and an increased risk for transitioning to psychosis [12, 13]. While in previous reports associations were strongest for sexual abuse, our findings showed an effect for emotional abuse. However, this effect was only apparent when controlling for the effects of other types of maltreatment. Interestingly, emotional neglect significantly protected against transition to psychosis. This is in line with a study in patients with first episode psychosis, showing that emotional abuse was significantly associated with positive symptoms, while (although not significantly) a negative effect was found for emotional neglect [23]. It might be that childhood without emotional comfort or protection teaches the child that he can stand being neglected and survive on its own. Interestingly, these findings suggest that different types of child maltreatment might have different effects on developing psychosis. However, it should also be noted that different types of child maltreatment are likely to co-occur, and further research is needed to explore the effects of child maltreatment. Although our findings on transition to psychosis are congruent with two studies from the PACE clinic [12, 13], these findings were not confirmed by two other recent UHR studies [10, 11]. An explanation for the inconsistency could be that studies reporting no association between child maltreatment and psychosis used relatively small study samples [10]. Another explanation might be that in the study of Stowkowy and colleagues [11] continuous scores of child maltreatment were examined. In the present study, UHR individuals were grouped into those who had experienced less severe child maltreatment and those who had experienced more severe child maltreatment, showing an increased risk for psychosis for those with more severe child maltreatment. Thus, more severe child maltreatment may significantly
affect psychosis risk in the UHR stage. However, significant associations were only found for emotional abuse and it might be that child maltreatment is a risk factor for UHR status but that its additional effect on transition to psychosis in the UHR stage is limited.

Our findings on the effect of child maltreatment on other outcome measures apart from psychosis are in line with previous research, showing an association between child maltreatment and depression and anxiety [24]. Overall, our results suggest that a history of child maltreatment, and in particular physical abuse, is a risk factor for various anxiety disorders in the UHR stage. Although the UHR stage was originally designed as a risk stage for psychosis, our findings tentatively suggest that the UHR stage is a transdiagnostic stage for various clinical outcomes [25]. Therefore, our findings emphasize that the focus in the UHR stage should be broader than psychosis outcome alone [26].

Our findings could be explained by the fact that adverse events during childhood, a period of significant brain maturation, probably impacted neurodevelopment. Exposure to adverse events may result in an overactive stress regulation system and permanent changes in the hypothalamic-pituitary-adrenal (HPA) axis [27-29]. An overactive HPA-axis causes increased cortisol levels in the brain, leading to increased distress in reaction to environmental stressors. Psychological processes could also explain the association between child maltreatment and psychopathology. For instance, it has been suggested that the experience of child maltreatment leads to the formation of negative self-schemas [30]. Negative self-schemas could potentially lead to the formation of depressive symptoms. Additionally, these negative self-schemas have been suggested to lead to suspiciousness and hyper vigilance to environmental stressors, which in turn could lead to psychosis [30, 31].

**Limitations and strengths**

There are several limitations to the present study that need to be acknowledged. First, the CTQ was used to assess child maltreatment. The CTQ is a retrospective self-report questionnaire and therefore the possibility of recall bias exists. However, previous research showed good reliability of recollection of adverse events in psychotic patients [32], and therefore we do not expect this affected our results to a large extent. Second, the CTQ does not examine important questions about specific details of the trauma. For instance, information on the perpetrator or distress or impact of the traumatic event is not examined with the CTQ. This additional information is needed because it might have important implications in the relation with psychosis. Third, the presence of depressive symptoms might have contributed
to an overrepresentation of child maltreatment. Fourth, the 24-month assessment was not finished by the time of analyzing the data, which may have resulted in an underrepresentation of the transition rate. Fifth, in the present study we did not control for risk factors of psychosis such as ethnicity [33] and socioeconomic status [34], which are both risk factors for psychosis. Sixth, other forms of child maltreatment (e.g. bullying or witnessing domestic violence) that have been associated with psychosis risk [35] were not analyzed in the present study. Seventh, previous research showed that recent life-events have been found to increase the risk for transition to psychosis [36] but these were not taken into account in the present study. Eighth, the control group was small in comparison to the UHR group and controls were recruited in three of the eleven EU-GEI sites, therefore the findings should be interpreted with caution. Eighth, in the current study we controlled for current cannabis use but we did not control for type or quantity of cannabis. Because more frequent cannabis use has been associated with psychosis risk [37] this is a limitation of the present study.

The major strengths of the current study were the large sample of UHR individuals and the longitudinal design.

**Conclusion**

Our findings suggest that in the UHR stage child maltreatment is a pluripotent risk factor for psychosis, depressive disorder, PTSD, panic disorder and social phobia in adulthood. Although the main focus of outcome in UHR studies has been transition to psychosis, our findings show that the focus should be broader than psychosis outcome in the UHR stage. These findings support the notion that the UHR stage is a transdiagnostic stage [25] for developing various psychiatric symptoms instead of a risk stage for psychosis outcome alone. Importantly, these findings emphasize the need for reducing the harmful effects of emotional and physical abuse during childhood. Because in particular the combination of child maltreatment and the presence of attenuated psychotic symptoms seems a precursor for severe and complex psychopathology [38], it is warranted to screen for UHR status and childhood abuse in mental health care settings.

**Acknowledgements**

This study is supported by the European Union [European Community’s Seventh Framework Program (grant agreement no. HEALTH-F2-2009-241909) (Project EU-GEI)]. Eva Velthorst is supported by grant 916-15-005 from the Netherlands Organization for Scientific Research. Matthew Kempton is supported by a Medical Research Council Fellowship (Grant MR/J008915/1).
Philip McGuire 1
Lucia R. Valmaggia 2
Matthew J. Kempton 1
Maria Calem 1
Stefania Tognin 1
Gemma Modinos 1
Lieuwe de Haan 3, 4
Mark van der Gaag 5, 6
Eva Velthorst 3, 7
Tamar C. Kraan 3
Daniella S. van Dam 3
Nadine Burger 6
Barnaby Nelson 8
Patrick McGorry 8
G Paul Amminger 8
Christos Pantelis 8
Athena Politis 8
Joanne Goodall 8
Anita Riecher-Rössler 9
Stefan Borgwardt 9
Charlotte Rapp 9
Sarah Ittig 9
Erich Studerus 9
Renata Smieskova 9
Rodrigo Bressan 10
Ary Gadelha 10
Elisa Brietzke 11
Graccielle Asevedo 10
Elsone Asevedo 10
Andre Zugman 10
Neus Barrantes-Vidal 12
Tecellli Domínguez-Martinez 13
Paula Cristóbal-Narváez 14

Thomas R. Kwapiel 15
Manel Monsonet 14
Lídia Hinojosa 14

Mathilde Kazes 16
Claire Daban 16

Julie Bourgin 16
Olivier Gay 16
Célia Mam-Lam-Fook 16
Marie-Odile Krebs 16

Dorte Nordtoft 17
Lasse Randers 17
Kristine Krakauer 17
Tanya Louise Naumann, 17
Louise Birkedal Glenthøj 17
Merete Nordentoft 17

Stephan Ruhrmann 18
Dominika Gebhard 18
Julia Arnhold 19
Joachim Klosterkötter 18

Marc De Hert 20
Ruud van Winkel 20

Gabriele Sachs 21
Iris Lasser 21
Bernadette Winklbaur 21

Bart P. Rutten 22
Jim van Os 23, 24
Affiliations

1. Department of Psychosis Studies, Institute of Psychiatry, Psychology & Neuroscience, King’s College London, De Crespigny Park, Denmark 458 Hill, London, United Kingdom SE5 8AF.

2. Department of Psychology, Institute of Psychiatry, Psychology & Neuroscience, King’s College London, De Crespigny Park, Denmark Hill, 456 London, United Kingdom SE5 8AF.

3. AMC, Academic Psychiatric Centre, Department Early Psychosis, Meibergdreef 5, 1105 AZ Amsterdam, The Netherlands.

4. Arkin Amsterdam

5. VU University, Faculty of Behavioural and Movement Sciences, Department of Clinical Psychology and EMGO+ Institute for Health and Care Research, van der Boechorststraat 1, 1081 BT Amsterdam, The Netherlands.

6. Parnassia Psychiatric Institute, Department of Psychosis Research, Zoutkeetsingel 40, 2512 HN The Hague, The Netherlands.

7. Icahn School of Medicine at Mount Sinai, department of Psychiatry, 1425 Madison Ave, New York, NY 10029.

8. Centre for Youth Mental Health, University of Melbourne, 35 Poplar Road (Locked Bag 10), Parkville, Victoria 485 3052, Australia.


10. LIIN - Lab Interdisciplinar Neurociências Clínicas, Depto Psiquiatria, Escola Paulista de Medicina, Universidade Federal de São Paulo – UNIFESP.

11. Depto Psiquiatria, Escola Paulista de Medicina, Universidade Federal de São Paulo – UNIFESP.

12. Departament de Psicologia Clínica i de la Salut (Universitat Autònoma de Barcelona), Fundació Sanitaria Sant Pere Claver (Spain), Spanish Mental Health Research Network (CIBERSAM).

13. CONACYT-Dirección de Investigaciones Epidemiológicas y Psicosociales, Instituto Nacional de Psiquiatría Ramón de la Fuente Muñiz (México).

14. Departament de Psicologia Clínica i de la Salut (Universitat Autònoma de Barcelona).

15. Department of Psychology, University of Illinois at Urbana-Champaign (USA).


17. Mental Health Center Copenhagen and Center for Clinical Intervention and Neuropsychiatric Schizophrenia Research, CINS, Mental Health Center Glostrup, Mental Health Services in the Capital Region of Copenhagen, University of Copenhagen.

18. Department of Psychiatry and Psychotherapy, University of Cologne, Cologne, Germany.

19. Psyberlin, Berlin, Germany.


21. Medical University of Vienna, Department of Psychiatry and Psychotherapy.

22. Department of Psychiatry and Neuropsychology, School for Mental Health and Neuroscience, South Limburg 463 Mental Health Research and Teaching Network, Maastricht University Medical Centre, PO. Box 616, 6200 MD 464 Maastricht, The Netherlands

23. Maastricht University Medical Center, Department of Psychiatry and Psychology, Maastricht, the Netherlands 7 460.

24. Department of Psychosis Studies, Institute of Psychiatry, Psychology & Neuroscience, King’s College London, De Crespigny Park, Denmark 458 Hill, London, United Kingdom SE5 8AF.
References


