

## VU Research Portal

### **Child Maltreatment and Clinical Outcome in Individuals at Ultra-High Risk for Psychosis in the EU-GEI High Risk Study**

Kraan, Tamar C.; Velthorst, Eva; Themmen, Manouk; Valmaggia, Lucia; Kempton, Matthew J.; McGuire, Phillip; Van Os, Jim; Rutten, Bart P.F.; Smit, Filip; De Haan, Lieuwe; Van Der Gaag, Mark; McGuire, Philip; Valmaggia, Lucia R.; Calem, Maria; Tognin, Stefania; Modinos, Gemma; Burger, Nadine; Van Dam, Daniella S.; Barrantes-Vidal, Neus; Domínguez-Martínez, Tecelli

**published in**

Schizophrenia Bulletin

2018

**DOI (link to publisher)**

[10.1093/schbul/sbw162](https://doi.org/10.1093/schbul/sbw162)

**document version**

Publisher's PDF, also known as Version of record

**document license**

Article 25fa Dutch Copyright Act

[Link to publication in VU Research Portal](#)

**citation for published version (APA)**

Kraan, T. C., Velthorst, E., Themmen, M., Valmaggia, L., Kempton, M. J., McGuire, P., Van Os, J., Rutten, B. P. F., Smit, F., De Haan, L., Van Der Gaag, M., McGuire, P., Valmaggia, L. R., Calem, M., Tognin, S., Modinos, G., Burger, N., Van Dam, D. S., Barrantes-Vidal, N., ... EU-GEI High Risk Study (2018). Child Maltreatment and Clinical Outcome in Individuals at Ultra-High Risk for Psychosis in the EU-GEI High Risk Study. *Schizophrenia Bulletin*, 44(3), 584-592. <https://doi.org/10.1093/schbul/sbw162>

**General rights**

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal

**Take down policy**

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

**E-mail address:**

[vuresearchportal.ub@vu.nl](mailto:vuresearchportal.ub@vu.nl)

## Child Maltreatment and Clinical Outcome in Individuals at Ultra-High Risk for Psychosis in the EU-GEI High Risk Study

Tamar C. Kraan<sup>1,2</sup>, Eva Velthorst<sup>1,3</sup>, Manouk Themmen<sup>2</sup>, Lucia Valmaggia<sup>4</sup>, Matthew J. Kempton<sup>5</sup>, Phillip McGuire<sup>5</sup>, Jim van Os<sup>6,7</sup>, Bart P. F. Rutten<sup>8</sup>, Filip Smit<sup>9–11</sup>, Lieuwe de Haan<sup>1</sup>, Mark van der Gaag<sup>\*,2,12</sup>, and EU-GEI High Risk Study<sup>13</sup>

<sup>1</sup>Department of Psychiatry, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands; <sup>2</sup>Department of Psychosis Research, Parnassia Psychiatric Institute, The Hague, The Netherlands; <sup>3</sup>Departments of Psychiatry and Preventive Medicine, Icahn School of Medicine, Mount Sinai, NY; <sup>4</sup>Department of Psychology, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK; <sup>5</sup>Department of Psychosis Studies, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK; <sup>6</sup>Department of Psychiatry and Psychology, Maastricht University Medical Center, Maastricht, The Netherlands; <sup>7</sup>King's College London, King's Health Partners, Department of Psychosis Studies, Institute of Psychiatry, London, UK; <sup>8</sup>Department of Psychiatry and Neuropsychology, School for Mental Health and Neuroscience, Maastricht University, Maastricht, The Netherlands; <sup>9</sup>Department of Clinical Psychology, VU University and EMGO Institute for Health and Care Research, Amsterdam, The Netherlands; <sup>10</sup>Department of Public Mental Health, Trimbos Institute (Netherlands Institute of Mental Health and Addiction), Utrecht, The Netherlands; <sup>11</sup>Department of Epidemiology and Biostatistics, VU University Medical Center, Amsterdam, The Netherlands; <sup>12</sup>Department of Clinical Psychology, VU University and Amsterdam Public Health research institute, Amsterdam, The Netherlands

<sup>13</sup>A full list of authors and affiliations appears in the Appendix.

\*To whom correspondence should be addressed; Department of Clinical Psychology, VU University Amsterdam, Van der Boechorststraat 1, 1081 BT Amsterdam, The Netherlands; tel: +31-6-45780463, fax: +31-20-5988758, e-mail: [m.vander.gaag@vu.nl](mailto:m.vander.gaag@vu.nl)

**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 2 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,  $P = .027$ ). Apart from psychosis, a history of physical abuse was associated with depressive disorder (OR = 4.92, 95% CI = 2.12 to 11.39,  $P = .001$ ), post-traumatic stress disorder (OR = 2.06, 95% CI = 1.10 to 3.86,  $P = .023$ ), panic disorder (OR = 2.00, 95% CI = 1.00 to 3.99,  $P = .048$ ) and social phobia (OR = 2.47, 95% CI = 1.18 to 5.16,  $P = .016$ ) at follow-up. **Conclusion:** Our findings suggest that in the UHR stage child maltreatment is a pluripotent risk factor

for developing psychosis, depressive disorder, post-traumatic stress disorder (PTSD), panic disorder, and social phobia in adulthood.

**Key words:** child maltreatment/ultra high risk/psychosis/clinical outcome

### 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.<sup>1</sup> One group of severe mental illnesses that has been extensively examined in relation to child maltreatment is psychotic disorders.<sup>2</sup> In both clinical and population based studies, child maltreatment has been found to substantially increase psychosis risk.<sup>3,4</sup>

In the last 2 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.<sup>5</sup> Using these ultra-high risk (UHR) criteria,<sup>5</sup> initial transition-to-psychosis rates ranged around an average of approximately 40% within 2 years.<sup>5,6</sup> However, the more recent UHR studies have shown a decline in transition rate, with meta-analytic evidence suggesting a transition rate of 20% at 2 years, increasing to 36% after

3 years.<sup>7,8</sup> 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.<sup>3</sup> The rate of child maltreatment in UHR populations is highly prevalent.<sup>9</sup> The 4 UHR studies that examined the effect of child maltreatment on transition to psychosis risk have yielded inconsistent findings.<sup>10-13</sup> While 2 studies found that a history of sexual abuse significantly increased the risk for transition to psychosis,<sup>12,13</sup> these findings could not be replicated in 2 other UHR cohorts.<sup>10,11</sup>

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.<sup>10,14</sup> 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]).<sup>15</sup> This is important, because studying comorbid 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 Axis-I mental disorders other than psychosis at follow-up.

## Methods

### Sample

Participants were part of the prodromal work package of the European network of national schizophrenia networks studying Gene-Environment Interactions (EU-GEI) cohort.<sup>16</sup> 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

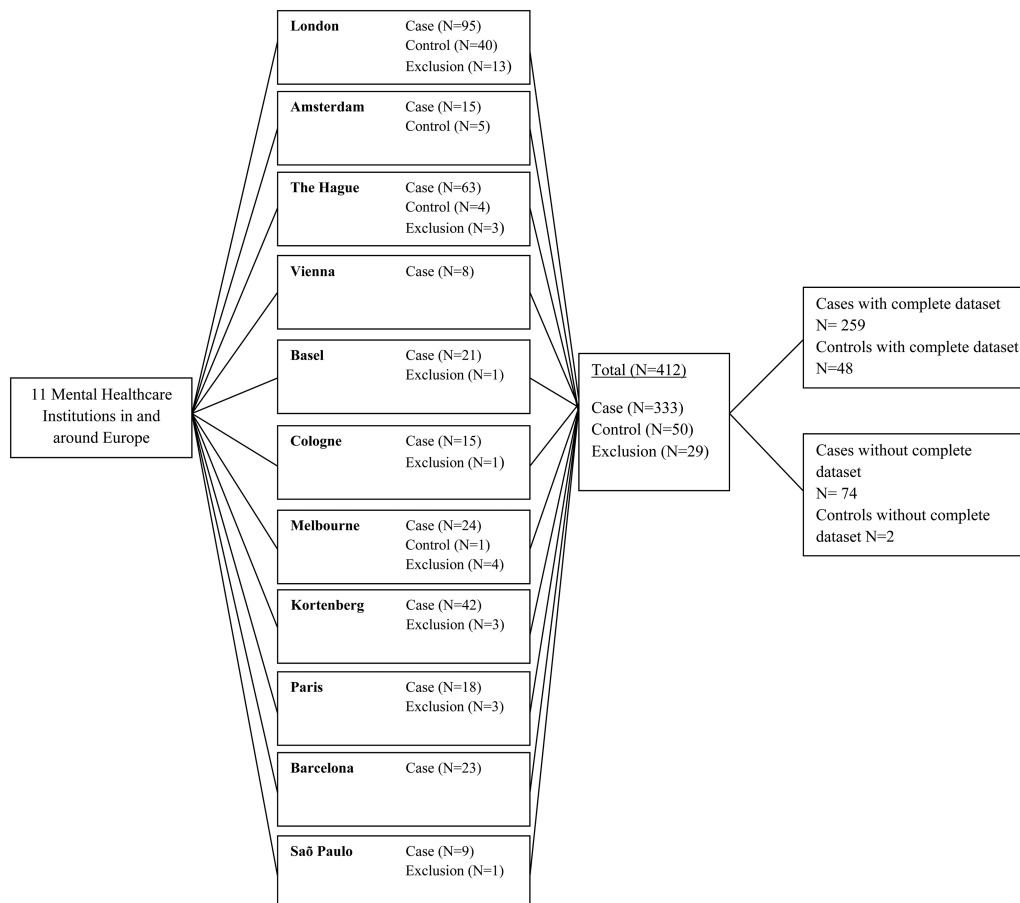


Fig. 1. Flowchart of participants who reached follow-up assessment by site.

Assessment of At Risk Mental State (CAARMS)<sup>5</sup>: (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 1 month in the previous year, (2) Attenuated Psychotic Symptoms (APS) Group: the presence of sub-threshold positive psychotic symptoms for at least 1 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 1 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.<sup>5</sup>

### 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 3 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 (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.<sup>17</sup> 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 2 years and interviewed at 4 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, 6 months after baseline a brief assessment was conducted. During this assessment changes in sub-clinical 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.<sup>5</sup> Where possible, subjects were

assessed with the Structured Clinical Interview (SCID-I) to establish a formal diagnosis according to DSM-IV criteria.<sup>15</sup> When this was not possible (ie, subjects did not want to attend follow-up assessment) clinical notes were used.

### Assessments

1. All participants completed a detailed sociodemographic schedule. Data on baseline demographic characteristics (eg, age, gender, ethnicity) were assessed using the modified Medical Research Council socio-demographic schedule.<sup>16,18</sup>
2. The CAARMS<sup>5</sup> 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 7 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<sup>19</sup> 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.<sup>15</sup> This questionnaire was used to assess clinical outcome.
4. Child maltreatment was retrospectively assessed with the Child Trauma Questionnaire (CTQ).<sup>20</sup> This 25-item self-report questionnaire assesses traumatic events before the age of 17. The CTQ consists of 5 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  $\geq 8$ , sexual abuse  $\geq 6$ , emotional abuse  $\geq 9$ , physical neglect  $\geq 8$  and emotional neglect  $\geq 10$ .<sup>21</sup> 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<sup>22</sup> 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.<sup>15</sup> 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  $P < .05$  was considered statistically significant.

### Results

#### Sample Characteristics

Demographic, clinical and functional baseline data were available for 304 UHR individuals and 50 controls. Of subjects 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 (table 1). Cases and controls did not significantly differ in terms of age ( $t = 1.73$ ,  $P = .084$ ), gender ( $X^2 = 0.36$ ,  $P = .545$ ) and cannabis use ( $X^2 = 4.68$ ,  $P = .096$ ). Of subjects 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 childhood compared to 17.4% of the control sample ( $P < .001$ ). This difference was apparent for each form of child maltreatment: emotional abuse; cases = 62.5%, controls = 27.1% ( $P < .001$ ); emotional neglect; cases = 76.4%, controls = 33.3% ( $P < .001$ ); physical abuse; cases = 24.3%, controls = 8.3% ( $P = .014$ );

**Table 1.** Baseline Characteristics for UHR Participants ( $N = 259$ )

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

*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.

physical neglect; cases = 47.2%, controls = 20.8% ( $P = .001$ ); sexual abuse; cases = 29.9%, controls = 10.4% ( $P = .005$ ).

*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 (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,  $P = .065$ ).

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,  $P = .027$ ), while the adjusted odds ratio of emotional neglect protects against transition (OR = 0.26, 95% CI = 0.09 to 0.77,  $P = .015$ ). 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 ORs are not a statistical artifact.

*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,  $P = .001$ ). 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,  $P = .048$ ) 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,  $P = .023$ ), panic disorder (OR = 2.00, 95% CI = 1.00 to 3.99,  $P = .048$ ) and social phobia (OR = 2.47, 95% CI = 1.18 to 5.16,  $P = .016$ ).

**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 sub domains 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.<sup>12,13</sup> 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.<sup>23</sup> 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 2 studies from the PACE clinic,<sup>12,13</sup> these findings were not confirmed by 2 other recent UHR studies.<sup>10,11</sup> An explanation for the inconsistency could be that studies reporting no association between child maltreatment and psychosis used relatively

**Table 2.** The Effect of Child Maltreatment on Transition to Psychosis

	Adjusted Odds Ratio	95% CI	P-value	Unadjusted Odds Ratio	95% CI	P-value
Emotional abuse	<b>3.78</b>	<b>1.17–12.39</b>	<b>.027</b>	2.14	0.79–5.78	.134
Sexual abuse	1.67	0.66–4.20	.280	1.77	0.73–4.25	.204
Physical abuse	1.08	0.42–2.82	.869	1.39	0.58–3.33	.458
Emotional neglect	0.26	0.09–0.77	.015	0.48	0.20–1.16	.104
Physical neglect	0.76	0.29–1.99	.575	0.89	0.39–2.01	.779

*Note:* Transition to psychosis was controlled for the effect of age, gender and cannabis use. Child Trauma Questionnaire (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. The bold values indicate significance level  $P < .05$ .

**Table 3.** Associations Between Child Maltreatment and DSM-IV Disorders

		Odds Ratio	95% CI	<i>P</i> -value
Depressive disorder	Total child maltreatment	<b>4.92</b>	<b>2.12–11.39</b>	<b>.001</b>
	Emotional abuse	<b>2.76</b>	<b>1.01–7.55</b>	<b>.048</b>
	Sexual abuse	0.95	0.42–2.14	.895
	Physical abuse	1.38	0.59–3.20	.454
	Emotional neglect	2.11	0.66–6.77	.209
	Physical neglect	1.97	0.84–4.62	.117
PTSD	Total child maltreatment	1.60	0.87–2.95	.130
	Emotional abuse	0.73	0.37–1.42	.352
	Sexual abuse	0.91	0.52–1.62	.761
	Physical abuse	<b>2.06</b>	<b>1.10–3.86</b>	<b>.023</b>
	Emotional neglect	0.95	0.45–2.05	.905
	Physical neglect	1.80	0.99–3.26	.054
Panic disorder	Total child maltreatment	0.64	0.35–1.19	.164
	Emotional abuse	0.81	0.40–1.65	.564
	Sexual abuse	0.85	0.46–1.58	.615
	Physical abuse	<b>2.00</b>	<b>1.00–3.99</b>	<b>.048</b>
	Emotional neglect	0.67	0.30–1.49	.329
	Physical neglect	1.31	0.69–2.46	.399
Social phobia	Total child maltreatment	0.94	0.45–1.97	.877
	Emotional abuse	0.57	0.26–1.22	.145
	Sexual abuse	0.83	0.42–1.61	.578
	Physical abuse	<b>2.47</b>	<b>1.18–5.16</b>	<b>.016</b>
	Emotional neglect	2.02	0.83–4.92	.122
	Physical neglect	0.96	0.49–1.90	.915
OCD	Total child maltreatment	1.11	0.64–1.93	.714
	Emotional abuse	0.73	0.40–1.33	.299
	Sexual abuse	1.02	0.61–1.72	.932
	Physical abuse	1.22	0.69–2.15	.498
	Emotional neglect	1.73	0.85–3.52	.130
	Physical neglect	1.02	0.60–1.73	.943

*Note:* PTSD, post-traumatic stress disorder; OCD, obsessive compulsive disorder. Child Trauma Questionnaire (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. The bold values indicate significance level  $P < .05$ .

small study samples.<sup>10</sup> Another explanation might be that in the study of Stowkowy and colleagues<sup>11</sup> 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.<sup>24</sup> 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.<sup>25</sup> Therefore, our findings emphasize that the focus in the UHR stage should be broader than psychosis outcome alone.<sup>26</sup>

Our findings could be explained by the fact that adverse events during child, 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.<sup>27–29</sup> 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.<sup>30</sup> 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.<sup>30,31</sup>

### 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,<sup>32</sup> 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. Fourth, in the present study we did not control for risk factors of psychosis such as ethnicity<sup>33</sup> and socioeconomic status,<sup>34</sup> which are both risk factors for psychosis. Fifth, other forms of child maltreatment (eg, bullying or witnessing domestic violence) that have been associated with psychosis risk<sup>35</sup> were not analyzed in the present study. Sixth, previous research showed that recent life-events have been found to increase the risk for transition to psychosis<sup>36</sup> but these were not taken into account in the present study. Seventh, the control group was small in comparison to the UHR group and controls were recruited in 3 of the 11 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<sup>37</sup> 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<sup>25</sup> 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,<sup>38</sup> it is warranted to screen for UHR status and childhood abuse in mental health care settings.

### Funding

This study is supported by the European Union (European Community's Seventh Framework Program [grant agreement no. HEALTH-F2-2009–241909; Project EU-GEI]). E.V. is supported by grant 916-15-005 from the Netherlands Organization for Scientific Research. M.J.K. is supported by a Medical Research Council Fellowship (grant MR/J008915/1).

### Acknowledgment

The authors have declared that there are no conflicts of interest in relation to the subject of this study.

### EU-GEI High Risk Study—Group Author List

#### Authors

Philip McGuire<sup>1</sup>, Lucia R. Valmaggia<sup>2</sup>, Matthew J. Kempton<sup>1</sup>, Maria Calem<sup>1</sup>, Stefania Tognin<sup>1</sup>, Gemma Modinos<sup>1</sup>, Lieuwe de Haan<sup>3</sup>, Mark van der Gaag<sup>4,5</sup>, Eva Velthorst<sup>3,6</sup>, Tamar C. Kraan<sup>3</sup>, Nadine Burger<sup>5</sup>, Daniella S. van Dam<sup>3</sup>, Neus Barrantes-Vidal<sup>7,8,9,10</sup>, Tecelli Domínguez-Martínez<sup>7</sup>, Paula Cristóbal-Narváez<sup>7</sup>, Thomas R. Kwapil<sup>8</sup>, Manel Monsonet-Bardají<sup>7</sup>, Lúcia Hinojosa<sup>7</sup>, Anita Riecher-Rössler<sup>11</sup>, Stefan Borgwardt<sup>11</sup>, Charlotte Rapp<sup>11</sup>, Sarah Ittig<sup>11</sup>, Erich Studerus<sup>11</sup>, Renata Smieskova<sup>11</sup>, Rodrigo Bressan<sup>12</sup>, Ary Gadelha<sup>12</sup>, Elisa Brietzke<sup>13</sup>, Graciele Asevedo<sup>12</sup>, Elson Asevedo<sup>12</sup>, Andre Zugman<sup>12</sup>, Stephan Ruhrmann<sup>14</sup>, Dominika Gebhard<sup>14</sup>, Julia Arnhold<sup>15</sup>, Joachim Klosterkötter<sup>14</sup>, Dorte Nordholm<sup>16</sup>, Lasse Randers<sup>16</sup>, Kristine Krakauer<sup>16</sup>, Tanya Louise Naumann<sup>16</sup>, Louise Birkedal Glenthøj<sup>16</sup>, Merete Nordentoft<sup>16</sup>, Marc De Hert<sup>17</sup>, Ruud van Winkel<sup>17</sup>, Barnaby Nelson<sup>18</sup>, Patrick McGorry<sup>18</sup>, Paul Amminger<sup>18</sup>, Christos Pantelis<sup>18</sup>, Athena Politis<sup>18</sup>, Joanne Goodall<sup>18</sup>, Gabriele Sachs<sup>19</sup>, Iris Lasser<sup>19</sup>, Bernadette Winklbaur<sup>19</sup>, Mathilde Kazes<sup>20</sup>, Claire Daban<sup>20</sup>, Julie Bourgin<sup>20</sup>, Olivier Gay<sup>20</sup>, Célia Mam-Lam-Fook<sup>20</sup>, Marie-Odile Krebs<sup>20</sup>, Bart P. Rutten<sup>21</sup>, Jim van Os<sup>1,22</sup>

#### Affiliations

<sup>1</sup>Department of Psychosis Studies, Institute of Psychiatry, King's College London, London, United Kingdom; <sup>2</sup>Department of Psychology, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, United Kingdom; <sup>3</sup>Department of Psychiatry, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands; <sup>4</sup>Department of Clinical Psychology, VU University and Amsterdam



Public Mental Health research institute, Amsterdam, The Netherlands; <sup>5</sup>Department of Psychosis Research, Parnassia Psychiatric Institute, The Hague, The Netherlands; <sup>6</sup>Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, United States of America; <sup>7</sup>Departament de Psicologia, Clínica i de la Salut, Universitat Autònoma de Barcelona, Barcelona, Spain; <sup>8</sup>Departament de Salut Mental, Sant Pere Claver-Fundació Sanitària, Barcelona, Spain; <sup>9</sup>Spanish Mental Health Research Network, CIBERSAM, Spain; <sup>10</sup>Department of Psychology, University of North Carolina at Greensboro, Greensboro, United States of America; <sup>11</sup>Center for Gender Research and Early Detection, Psychiatric University Clinics Basel, Basel, Switzerland; <sup>12</sup>LiNC - Lab Interdisciplinar Neurociências Clínicas, Depto Psiquiatria, Escola Paulista de Medicina, Universidade Federal de São Paulo – UNIFESP, São Paulo, Brazil; <sup>13</sup>Pogram for cognition and Intervention in Individuals in At-Risk Mental States (PRISMA), Department of Psychiatry, Universidade Federal de São Paulo, São Paulo, Brazil; <sup>14</sup>Department of Psychiatry and Psychotherapy, University of Cologne, Cologne, Germany; <sup>15</sup>Psyberlin, Berlin, Germany; <sup>16</sup>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, Copenhagen, Denmark; <sup>17</sup>Department of Neuroscience, University Psychiatric Centre, Catholic University Leuven, Leuven, Belgium; <sup>18</sup>Centre for Youth Mental Health, University of Melbourne, Melbourne, Australia; <sup>19</sup>Department of Psychiatry and Psychotherapy, Medical University of Vienna, Vienna, Austria; <sup>20</sup>University Paris Descartes, Hôpital Sainte-Anne, C'JAAD, Service Hospitalo-Universitaire, Inserm U894, Institut de Psychiatrie, Paris, France; <sup>21</sup>Department of Psychiatry and Neuropsychology, School for Mental Health and Neuroscience, Maastricht University Medical Centre, Maastricht, The Netherlands; <sup>22</sup>Department of Psychiatry and Psychology, Maastricht University Medical Center, Maastricht, The Netherlands.

## References

- Teicher MH, Samson JA. Childhood maltreatment and psychopathology: a case for ecophenotypic variants as clinically and neurobiologically distinct subtypes. *Am J Psychiatry*. 2013;170:1114–1133.
- Bendall S, Jackson HJ, Hulbert CA, McGorry PD. Childhood trauma and psychotic disorders: a systematic, critical review of the evidence. *Schizophr Bull*. 2008;34:568–579.
- Varese F, Smeets F, Drukker M, et al. Childhood adversities increase the risk of psychosis: a meta-analysis of patient-control, prospective- and cross-sectional cohort studies. *Schizophr Bull*. 2012;38:661–671.
- Kelleher I, Harley M, Lynch F, Arseneault L, Fitzpatrick C, Cannon M. Associations between childhood trauma, bullying and psychotic symptoms among a school-based adolescent sample. *Br J Psychiatry*. 2008;193:378–382.
- Yung AR, Yuen HP, McGorry PD, et al. Mapping the onset of psychosis: the Comprehensive Assessment of At-Risk Mental States. *Aust N Z J Psychiatry*. 2005;39:964–971.
- McGlashan TH, Zipursky RB, Perkins D, et al. Randomized, double-blind trial of olanzapine versus placebo in patients prodromally symptomatic for psychosis. *Am J Psychiatry*. 2006;163:790–799.
- Fusar-Poli P, Bonoldi I, Yung AR, et al. Predicting psychosis: meta-analysis of transition outcomes in individuals at high clinical risk. *Arch Gen Psychiatry*. 2012;69:220–229.
- Simon AE, Velthorst E, Nieman DH, Linszen D, Umbricht D, de Haan L. Ultra high-risk state for psychosis and non-transition: a systematic review. *Schizophr Res*. 2011;132:8–17.
- Kraan T, Velthorst E, Smit F, de Haan L, van der Gaag M. Trauma and recent life events in individuals at ultra high risk for psychosis: review and meta-analysis. *Schizophr Res*. 2015;161:143–149.
- Kraan T, van Dam DS, Velthorst E, et al. Childhood trauma and clinical outcome in patients at ultra-high risk of transition to psychosis. *Schizophr Res*. 2015;169:193–198.
- Stowkowy J, Liu L, Cadenhead KS, et al. Early traumatic experiences, perceived discrimination and conversion to psychosis in those at clinical high risk for psychosis. *Soc Psychiatry Psychiatr Epidemiol*. 2016;51:497–503.
- Bechdolf A, Thompson A, Nelson B, et al. Experience of trauma and conversion to psychosis in an ultra-high-risk (prodromal) group. *Acta Psychiatr Scand*. 2010;121:377–384.
- Thompson AD, Nelson B, Yuen HP, et al. Sexual trauma increases the risk of developing psychosis in an ultra high-risk “prodromal” population. *Schizophr Bull*. 2014;40:697–706.
- Yung A, Cotter J, Wood S, McGorry P, Thompson A, Nelson B, Lin A. Childhood maltreatment and transition to psychotic disorder independently predict long-term functioning in young people at ultra-high risk for psychosis. *Psychol Med*. 2015;45:3453–3465.
- APA. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV)*. Washington, DC: American Psychiatric Press Inc; 1994.
- European Network of National Networks studying Gene-Environment Interactions in Schizophrenia. Identifying gene-environment interactions in schizophrenia: contemporary challenges for integrated, large-scale investigations. *Schizophr Bull*. 2014;40:729–736.
- Reininghaus U, Kempton MJ, Valmaggia L, et al. Stress sensitivity, aberrant salience, and threat anticipation in early psychosis: an experience sampling study. *Schizophr Bull*. 2016;42:712–722.
- Mallett R. *Sociodemographic schedule*. London, UK: Section of Social Psychiatry, Institute of Psychiatry; 1997.
- First M, Spitzer R, Gibbon M, Williams JB. *Structured Clinical Interview for DSM-IV Axis I Disorders (SCID)*. New York, NY: New York State Psychiatric Institute Biometrics Research; 1995.
- Bernstein DP, Stein JA, Newcomb MD, et al. Development and validation of a brief screening version of the Childhood Trauma Questionnaire. *Child Abuse Negl*. 2003;27:169–190.
- Bernstein DP, Fink L. *Childhood Trauma Questionnaire: A Retrospective Self-Report: Manual*. San Antonio, TX: Harcourt Brace & Company; 1998.

22. Barkus EJ, Stirling J, Hopkins RS, Lewis S. Cannabis-induced psychosis-like experiences are associated with high schizotypy. *Psychopathology*. 2006;39:175–178.
23. Ramsay CE, Flanagan P, Gantt S, Broussard B, Compton MT. Clinical correlates of maltreatment and traumatic experiences in childhood and adolescence among predominantly African American, socially disadvantaged, hospitalized, first-episode psychosis patients. *Psychiatry Res*. 2011;188:343–349.
24. Li M, D'Arcy C, Meng X. Maltreatment in childhood substantially increases the risk of adult depression and anxiety in prospective cohort studies: systematic review, meta-analysis, and proportional attributable fractions. *Psychol Med*. 2016;46:717–730.
25. McGorry P, Nelson B. Why we need a transdiagnostic staging approach to emerging psychopathology, early diagnosis, and treatment. *JAMA Psychiatry*. 2016;73:191–192.
26. Lin A, Wood SJ, Nelson B, Beavan A, McGorry P, Yung AR. Outcomes of nontransitioned cases in a sample at ultra-high risk for psychosis. *Am J Psychiatry*. 2015;172:249–258.
27. Walker EF, Diforio D. Schizophrenia: a neural diathesis-stress model. *Psychol Rev*. 1997;104:667–685.
28. Danese A, McEwen BS. Adverse childhood experiences, allostasis, allostatic load, and age-related disease. *Physiol Behav*. 2012;106:29–39.
29. Day FL, Valmaggia LR, Mondelli V, et al. Blunted cortisol awakening response in people at ultra high risk of developing psychosis. *Schizophr Res*. 2014;158:25–31.
30. Garety PA, Kuipers E, Fowler D, Freeman D, Bebbington PE. A cognitive model of the positive symptoms of psychosis. *Psychol Med*. 2001;31:189–195.
31. Kilcommons AM, Morrison AP. Relationships between trauma and psychosis: an exploration of cognitive and dissociative factors. *Acta Psychiatr Scand*. 2005;112:351–359.
32. Fisher HL, Craig TK, Fearon P, et al. Reliability and comparability of psychosis patients' retrospective reports of childhood abuse. *Schizophr Bull*. 2011;37:546–553.
33. Selten J-P, Veen N, Feller W, et al. Incidence of psychotic disorders in immigrant groups to The Netherlands. *Br J Psych*. 2001;178:367–372.
34. Byrne M, Agerbo E, Eaton WW, Mortensen PB. Parental socio-economic status and risk of first admission with schizophrenia. *Soc Psychiatry Psychiatr Epidemiol*. 2004;39:87–96.
35. van Dam DS, van der Ven E, Velthorst E, Selten JP, Morgan C, de Haan L. Childhood bullying and the association with psychosis in non-clinical and clinical samples: a review and meta-analysis. *Psychol Med*. 2012;42:2463–2474.
36. Beards S, Gayer-Anderson C, Borges S, Dewey ME, Fisher HL, Morgan C. Life events and psychosis: a review and meta-analysis. *Schizophr Bull*. 2013;39:740–747.
37. Di Forti M, Marconi A, Carra E, et al. Proportion of patients in south London with first-episode psychosis attributable to use of high potency cannabis: a case-control study. *Lancet Psychiatry*. 2015;2:233–238.
38. Okkels N, Trabjerg B, Arendt M, Pedersen CB. Traumatic stress disorders and risk of subsequent schizophrenia spectrum disorder or bipolar disorder: a Nationwide Cohort Study. *Schizophr Bull*. 2017;43:180–186. doi:10.1093/schbul/sbw1082