*Psychological Medicine*

**cambridge.org/psm**

## Original Article

*Members of the EU-GEI High Risk Study group author are listed at the end of the paper.

†These authors contributed equally.

**Cite this article:** See CRZ *et al* (2024). The effects of recent stressful life events on outcomes in individuals at clinical high risk for psychosis: results from the longitudinal EU-GEI high-risk study. *Psychological Medicine* **54**, 4768–4778. https://doi.org/10.1017/S0033291724003039

Received: 5 September 2024
Revised: 17 October 2024
Accepted: 28 October 2024
First published online: 8 January 2025

**Keywords:**
clinical outcomes; function; negative symptoms; positive symptoms; prodrome; recent stress; stress; stressful life events

**Corresponding author:**
Cheryl R. Z. See;
Email: cheryl.see@kcl.ac.uk

© The Author(s), 2025. Published by Cambridge University Press. This is an Open Access article, distributed under the terms of the Creative Commons Attribution licence (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted re-use, distribution and reproduction, provided the original article is properly cited.

# The effects of recent stressful life events on outcomes in individuals at clinical high risk for psychosis: results from the longitudinal EU-GEI high-risk study

Cheryl R. Z. See[1], Shuqing Si[1], Emily Hedges[1], Stefania Tognin[1], Gemma Modinos[2], Mark van der Gaag[3,4], Lieuwe de Haan[5,6], Eva Velthorst[7], Patrick McGorry[8], Barnaby Nelson[8], Anita Riecher-Rössler[9], Rodrigo Bressan[10], Neus Barrantes-Vidal[11], Marie-Odile Krebs[12], Merete Nordentoft[13], Stephan Ruhrmann[14], Gabriele Sachs[15], Bart P. Rutten[16], Jim van Os[1,16], EU-GEI High Risk Study*, Philip McGuire[17], Lucia R. Valmaggia[8,18,19,†] and Matthew J. Kempton[1,†]

[1]Department of Psychosis Studies, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK; [2]Department of Psychological Medicine, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK; [3]Faculty of Behavioural and Movement Sciences, Department of Clinical Psychology, VU University, Amsterdam, The Netherlands; [4]Department of Psychosis Research, Parnassia Psychiatric Institute, The Hague, The Netherlands; [5]Department Early Psychosis, Amsterdam UMC, Amsterdam, The Netherlands; [6]Arkin Amsterdam, Amsterdam, The Netherlands; [7]Department of Research, GGZ Noord-Holland-Noord, Heerhugowaard, The Netherlands; [8]Centre for Youth Mental Health, University of Melbourne, Parkville, VIC, Australia; [9]Medical Faculty, University of Basel, Basel, Switzerland; [10]LiNC – Lab Interdisciplinar Neurociências Clínicas, Depto Psiquiatria, Escola Paulista de Medicina, Universidade Federal de São Paulo – UNIFESP, São Paulo, Brazil; [11]Departament de Psicologia Clínica i de la Salut (Universitat Autònoma de Barcelona), Spanish Mental Health Research Network (CIBERSAM), Barcelona, Spain; [12]University Paris Descartes, Hôpital Sainte-Anne, C'JAAD, Service Hospitalo-Universitaire, Inserm U894, Institut de Psychiatrie (CNRS 3557), Paris, France; [13]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; [14]Department of Psychiatry and Psychotherapy, Faculty of Medicine and University Hospital, University of Cologne, Cologne, Germany; [15]Department of Psychiatry and Psychotherapy, Medical University of Vienna, Austria; [16]Department of Psychiatry and Neuropsychology, School for Mental Health and Neuroscience, Maastricht University Medical Centre, Maastricht, The Netherlands; [17]Department of Psychiatry, University of Oxford, Oxford, UK; [18]Department of Psychology, Institute of Psychiatry, Psychology & Neuroscience, King's College London, UK and [19]Department of Psychiatry, KU Leuven, Leuven, Belgium

## Abstract

**Background.** Recent stressful life events (SLE) are a risk factor for psychosis, but limited research has explored how SLEs affect individuals at clinical high risk (CHR) for psychosis. The current study investigated the longitudinal effects of SLEs on functioning and symptom severity in CHR individuals, where we hypothesized CHR would report more SLEs than healthy controls (HC), and SLEs would be associated with poorer outcomes.

**Methods.** The study used longitudinal data from the EU-GEI High Risk study. Data from 331 CHR participants were analyzed to examine the effects of SLEs on changes in functioning, positive and negative symptoms over a 2-year follow-up. We compared the prevalence of SLEs between CHR and HCs, and between CHR who did (CHR-T) and did not (CHR-NT) transition to psychosis.

**Results.** CHR reported 1.44 more SLEs than HC ($p < 0.001$), but there was no difference in SLEs between CHR-T and CHR-NT at baseline. Recent SLEs were associated with poorer functioning and more severe positive and negative symptoms in CHR individuals (all $p < 0.01$) but did not reveal a significant interaction with time.

**Conclusions.** CHR individuals who had experienced recent SLEs exhibited poorer functioning and more severe symptoms. However, as the interaction between SLEs and time was not significant, this suggests SLEs did not contribute to a worsening of symptoms and functioning over the study period. SLEs could be a key risk factor to becoming CHR for psychosis, however further work is required to inform when early intervention strategies mitigating against the effects of stress are most effective.

## Introduction

The presence of recent stressful life events (SLEs) has been associated with the etiology of psychosis (Brown & Birley, 1968). Meta-analytic evidence suggests that individuals with

psychosis are three times more likely to have experienced SLEs prior to onset as compared to healthy controls (HC) (Beards et al., 2013), and that SLEs are associated with psychotic relapse (Martland, Martland, Cullen, & Bhattacharyya, 2020). However, it is unclear whether SLEs contribute toward an individual becoming vulnerable to psychosis or is associated with transition to psychosis. This question could be addressed by studying recent SLEs in individuals at clinical high risk (CHR) for psychosis over time, to determine whether there are any associations between SLEs and their clinical outcomes. CHR individuals are identified as experiencing subclinical or intermittent psychotic symptoms, or as having a familial vulnerability to psychosis, defined as a recent deterioration in functioning and family history of psychosis or schizotypal personality disorder (Yung et al., 2005). To date, a small number of studies have examined recent SLEs in CHR samples and results have been inconsistent. Some studies found CHR individuals reported more recent SLEs than HC (Huang et al., 2019; Munoz-Samons et al., 2021), while other studies did not (DeVylder et al., 2013; Mason et al., 2004; Phillips, Edwards, McMurray, & Francey, 2012). Findings are also inconclusive as to whether recent SLEs exacerbate symptoms or result in poorer psychosocial function in CHR individuals. Two studies reported a higher incidence of recent SLEs was associated with higher symptom severity and lower functioning (Huang et al., 2019; Munoz-Samons et al., 2021), while one study found no association (DeVylder et al., 2013). Most of these studies were cross-sectional and could not examine the temporal relationship between SLEs and clinical outcomes (Huang et al., 2019; Munoz-Samons et al., 2021; Phillips et al., 2012; Thompson et al., 2007), and studies that analyzed longitudinal data employed smaller sample sizes which may have reduced their statistical power (DeVylder et al., 2013; Mason et al., 2004). As noted by Mayo et al. (2017), these inconsistencies in findings encourage further research efforts to understand the relationship between recent SLEs and the CHR state.

An important consideration is that CHR individuals may experience more SLEs due to their subthreshold symptoms. For example, the break-up of a relationship could be due to increasing social withdrawal. To clarify this, studies have examined independent events, which are events unlikely to be brought about by an individual's mental state (e.g. death of a loved one), and found evidence of patients reporting more independent SLEs prior to psychosis onset (Beards et al., 2020; Raune, Kuipers, & Bebbington, 2011). Previous work has also found that interpersonal events involving conflict with someone else were more prevalent in patients with psychosis as compared to controls (Mansueto & Faravelli, 2017). By considering independent and interpersonal events, we can explore whether the increased prevalence of SLEs in CHR individuals is solely attributable to their mental state.

The current study sought to address these questions by investigating the associations between recent SLEs and clinical outcomes within a CHR sample using a large longitudinal dataset from the European Network of National Schizophrenia Networks Studying Gene-Environment Interactions (EU-GEI) High-Risk study (van Os et al., 2014). Participants were recruited across Europe, Australia, and South America, ensuring geographical diversity capturing cultural and environmental contexts. We adopted two approaches: (1) group comparisons of recent SLEs at baseline between CHR and HC, and between CHR individuals who subsequently transitioned to psychosis (CHR-T) and those who did not (CHR-NT); and (2) a longitudinal analysis to investigate the impact of recent SLEs on the trajectory of changes in functioning and symptom severity within the CHR group. We hypothesized CHR individuals would report more SLEs than HC, and CHR-T would report more SLEs than CHR-NT at baseline. We also predicted that SLEs would negatively affect the trajectory of functioning, positive symptoms, and negative symptoms within the CHR group. We expected these associations would remain evident when considering independent SLEs, but not with interpersonal events, demonstrating that SLEs contribute to the CHR state independent of an individual's mental state.

Exploratory analyses considered the effects of childhood trauma and cannabis use as potential confounders. Childhood adversity is a risk factor for mental health disorders (Haidl et al., 2023), and may compound the effects of SLEs experienced in adulthood as a pathway to psychosis (Betz et al., 2020; Mansueto & Faravelli, 2017; Morgan et al., 2014). Cannabis use is associated with a higher risk of psychosis onset (Marconi, Di Forti, Lewis, Murray, & Vassos, 2016), and it has been suggested cannabis may amplify the stress response (Arranz et al., 2018). Previous work is limited in this regard, where none of the previously mentioned CHR studies adjusted for childhood trauma or cannabis use in their analyses.

## Methods

### Participants

The EU-GEI High Risk study is a multicenter, naturalistic prospective study (van Os et al., 2014). In the current study, we used a subset of participants of 331 CHR and 67 HC for which recent SLE data were available. CHR participants were recruited from early detection centers across 11 sites: London, Amsterdam, The Hague, Basel, Cologne, Melbourne, Vienna, Copenhagen, Paris, Barcelona, and São Paolo. HC participants were recruited from four sites: London, Melbourne, Amsterdam, and The Hague. The age range of participants was 14–45 years. Ethical approval was obtained locally at each site, and participants who agreed to take part in the study provided informed, written consent.

CHR participants were eligible if they met at least one of the high-risk criteria as defined by the Comprehensive Assessment of At-Risk Mental States (CAARMS) (Yung et al., 2005): Vulnerability Group, Attenuated Psychotic Symptoms, or Brief Limited Psychotic Symptoms. The exclusion criteria for all participants were: (1) current or previous diagnosis of a psychotic disorder as determined by CAARMS or the Structured Clinical Interview for DSM-IV Disorders (SCID-IV) (First & Gibbon, 2004); (2) current or previous neurological disorder; (3) symptoms explained by substance use or dependency; (4) estimated IQ < 60; or (5) unwillingness to provide blood or saliva samples. HC participants were excluded if they met any of the CHR criteria.

### Design

The EU-GEI High Risk study followed participants over a 2-year period and conducted structured in-person assessments at three timepoints: baseline, 12-months, and 24-months (Hedges et al., 2022). During the study, five sites (London, Amsterdam, The Hague, Paris, and São Paulo) were able to expand data collection to include an additional 6-month follow-up. While every effort was made to assess participants at regular time intervals, there were instances where the follow-up assessments did not align with the targeted follow-up date. In total, 98% of observations were completed within 2.5 years from baseline, but to collect as

https://doi.org/10.1017/S0033291724003039 Published online by Cambridge University Press

much data as possible, several assessments were administered beyond 2.5 years, but no more than 4 years, after baseline. The statistical model (linear mixed model [LMM]) used in the present study accounted for different follow-up times, enabling us to retain as much participant data as possible.

At each follow-up, CHR participants were re-assessed using CAARMS to determine if they had transitioned to psychosis and subsequently categorized into CHR-T or CHR-NT. When participants did not return for their follow-up assessments, clinical records were used, where available, to determine their transition status. For the present study, we focused on CHR participants prior to transition and the small number of post-transition assessments have not been included. Assessments were performed by trained raters, as previously reported in Hedges et al. (2022).

## Measures

At each visit, participants were assessed on a suite of social, clinical, neuroimaging, and blood measures (van Os et al., 2014). The instruments and measures described below are relevant to the current study, with additional information included in the online Supplementary material.

### Sociodemographic and clinical data

The Medical Research Council Sociodemographic Schedule (Mallett, 1997) was used to collect baseline demographic information. Socioeconomic status (SES) was defined by a participant's father's socioeconomic class at the time of their birth and categorized into three classes: salariat, intermediate, and working-class (Hedges et al., 2022). Current cannabis use was assessed using the modified Cannabis Experiences Questionnaire (Di Forti et al., 2019) and baseline data were dichotomized into current users and non-users. The Childhood Trauma Questionnaire (CTQ) (Bernstein et al., 2003) was used to assess childhood adversity before the age of 17, and measured using the total CTQ score. Participants' antipsychotic and antidepressant medication use, dosage and length of use were also recorded at baseline in a structured interview. Further details on the treatment of these variables are reported in the online Supplementary material.

### Recent stressful life events

Recent SLEs were counted as an event that occurred over a period of 12 months prior to the day of the assessment. The List of Threatening Experiences (LTE) questionnaire (Brugha, Bebbington, Tennant, & Hurry, 1985) was used to gather recent SLE data and was administered at baseline and at each subsequent follow-up. The 12-item questionnaire covers major categories of life events such as serious illness and injury or significant loss, and has demonstrated a high test-retest reliability (Brugha & Cragg, 1990). A total LTE score for each assessment was calculated by summing the number of events experienced within the prior 12-month period. We calculated independent and interpersonal LTE scores using a subset of items from the LTE questionnaire (denoted in online Supplementary Table S1), as seen in previous studies (Park et al., 2015; Powers, Gleason, & Oltmanns, 2013).

### Outcome measures

Global functioning was assessed using Global Assessment of Functioning (GAF) (Hall, 1995) split into disability and symptoms subscales (Hedges et al., 2022). The GAF disability subscale is similar to the established Social and Occupational Functioning Assessment Scale (Goldman, Skodol, & Lave, 1992). For the present study, GAF disability was used to measure functioning where scores ranged from 0 to 100, with higher scores indicating superior functioning.

Positive prodromal symptoms were measured using the CAARMS positive symptoms subscale by summing severity ratings for a maximum total score of 24. Negative symptoms were measured using the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1982; 1983) by summing ratings for a maximum total score of 125.

Complete observations were used in the analyses, except for childhood trauma and SANS scores, where missing items were imputed as described in the online Supplementary material.

## Statistical analysis

All analyses were performed in R version 4.3.1. The statistical significance level was set at $p < 0.05$ (two-tailed).

### Baseline analysis

The baseline characteristics of CHR and HC participants, and CHR-T and CHR-NT participants were compared using independent sample *t* tests, $\chi^2$ tests, or Fisher's exact tests as appropriate. Recent SLEs were compared across groups (CHR *v.* HC and CHR-T *v.* CHR-NT) using separate bootstrapped multiple linear regression models where LTE score was set as the dependent variable and group as the main independent variable. The comparison between CHR and HC groups was restricted to participants from sites that recruited both CHR and HC individuals. We also fit separate models including childhood trauma and cannabis use as covariates to test for any changes to the significance of our results. As the proportions across ethnicity were found to be significantly different between CHR and HC groups (Table 1), an additional sensitivity analysis was conducted to include ethnicity as a covariate of no interest. In comparing CHR-T and CHR-NT, we performed separate sensitivity analyses to control for antipsychotic and antidepressant medication use, dosage, and length of use, as psychotropic medication has been found to have some anti-stress properties (Sanson & Riva, 2020; Subramaniam, LoPilato, & Walker, 2019).

### Longitudinal analysis

The association between recent SLEs and functioning, positive symptoms, and negative symptoms were analyzed using LMMs, using the R package *lme4* (Bates, Mächler, Bolker, & Walker, 2015). LMMs include fixed and random effects, accounting for repeated measurements within each participant. LMMs do not require data to be measured at consistent time intervals, and can accommodate missing data (Detry & Ma, 2016). In the present study, we modeled a multi-level structure with participants nested in site as a random intercept. There were 11 sites, and the number of participants were dependent on the available data for each model, as observations with missing data were excluded. The longitudinal analyses were conducted only within the CHR group as the HC group was expected to exhibit little change in functioning and symptom scores over the 2-year follow-up.

Separate LMMs were fitted for each outcome measure with GAF disability, CAARMS positive symptom score, and SANS negative symptom score as the dependent variables. First, base models were fitted with LTE score and time (measured in years from baseline) as fixed effects to test for associations with the outcome measures. A second model (the 'interaction model') included the interaction term of LTE score × time to examine

https://doi.org/10.1017/S0033291724003039 Published online by Cambridge University Press

**Table 1.** Baseline characteristics for the subset of participants from sites that recruited both CHR and HC individuals, used in the CHR *v.* HC comparison

| | CHR[1] | HC | CHR *v.* HC | |
|---|---|---|---|---|
| Variable | (*n* = 210) | (*n* = 67) | *t* value /$\chi^2$ | *p* value |
| Age (years), mean (s.d.) | 22.86 (4.90) | 22.85 (4.09) | −0.02 | 0.987 |
| Sex, *n* (%) | | | | |
| Female | 107 (51.0) | 33 (49.3) | 0.06 | 0.809 |
| Ethnicity, *n* (%) | | | | |
| White | 132 (62.9) | 42 (62.7) | Fisher's exact | $3.40 \times 10^{-4}$** |
| Black | 34 (16.2) | 10 (14.9) | | |
| Mixed | 20 (9.5) | 6 (9.0) | | |
| Asian | 4 (1.9) | 9 (13.4) | | |
| Other[2] | 20 (9.5) | 0 (0.0) | | |
| Socioeconomic status[3,a], *n* (%) | | | | |
| Salariat | 61 (29.1) | 31 (46.3) | 15.67 | $3.95 \times 10^{-4}$** |
| Intermediate | 65 (31.0) | 21 (31.3) | | |
| Working class | 64 (30.5) | 5 (7.5) | | |
| Years in education[b], mean (s.d.) | 14.78 (2.95) | 16.05 (2.78) | 3.06 | 0.002** |
| Antipsychotic medication[c], *n* (%) | 12 (5.7) | 0 (0.0) | Fisher's exact | 0.074 |
| Antidepressant medication[d], *n* (%) | 55 (26.2) | 2 (3.0) | 16.53 | $4.79 \times 10^{-5}$** |
| Current cannabis use[e], *n* (%) | 59 (28.1) | 18 (26.9) | 0.47 | 0.495 |
| Childhood trauma[4,f], mean (s.d.) | 50.79 (16.23) | 34.71 (10.73) | −7.53 | $7.65 \times 10^{-13}$** |

*$p < 0.05$; **$p < 0.01$.
Participants included in the present study have LTE data recorded for at least one timepoint.
[1]Only participants from sites that recruited both CHR and HC individuals were included. These sites were London, The Hague, Amsterdam, and Melbourne; [2]other includes those of North African and other ethnic backgrounds; [3]socioeconomic status is based on the father's socioeconomic class at participant's birth; [4]Childhood Trauma Questionnaire total score.
CHR, clinical high risk; HC, healthy controls.
Data missing for: [a]20 CHR and 10 HC; [b]7CHR and 1 HC; [c]11 CHR and 8 HC; [d]55 CHR and 8 HC; [e]47 CHR and 24 HC; [f]4 CHR and 1 HC.

the effect of LTE score on the trajectory of the outcome measure over time. The analysis was repeated with independent and interpersonal LTE scores. LTE data from baseline and all follow-up assessments were used in each model. All models were fitted using restricted maximum likelihood estimation and adjusted for sex, age at baseline, and SES.

We also explored for the potential effects of childhood trauma and cannabis use on our longitudinal results by refitting the base models separately with total CTQ score and current cannabis use as additional covariates. Sensitivity analyses were conducted to include baseline antipsychotic and antidepressant medication use as dichotomous covariates of no interest, as well as antipsychotic and antidepressant medication dose equivalents and length of use (as detailed in the online Supplementary material).

To adjust for multiple comparisons, we used a 5% false discovery rate correction (Benjamini & Hochberg, 1995) inclusive of all models (59 *p* values). The *p* values reported in the results section for the baseline and longitudinal models are uncorrected, with a superscript indicating whether significant *p* values had passed correction.

There is some concern that the loss of participants over a longitudinal study can introduce a form of attrition bias as participants who continue with a study may be associated with particular characteristics (Fewtrell et al., 2008). To investigate this, we grouped CHR participants by the number of completed assessments and compared baseline characteristics across groups using one-way ANOVA, $\chi^2$, and Fisher's exact tests as appropriate. To clarify, participants who completed one assessment were compared against participants who completed two, three, or four assessments in total.

## Results

### Sample characteristics

The current study used 331 CHR and 67 HC participants who had recent SLE data recorded for at least one timepoint. Baseline characteristics for the subset of participants (from four sites that recruited both CHR and HC individuals) used in the CHR *v.* HC comparison are reported in Table 1. There were significant differences in ethnicity, with the HC group comprising of more participants from Asian and Other (inclusive of North African) ethnic backgrounds, and SES, where the HC group had a higher proportion of individuals from salariat class backgrounds and the CHR group had more individuals from working class backgrounds. In comparison to HC, CHR participants also spent fewer years in education, had experienced more childhood trauma, and a higher proportion were taking antidepressant medication at baseline. The study accepted HC participants who had non-psychotic morbidities and in the current study 11 (16.4%) participants reported having a previous or current major depressive disorder, four (6.0%) an anxiety disorder, and one (1.5%) an eating disorder at baseline, as identified using the SCID-IV (First & Gibbon, 2004).

https://doi.org/10.1017/S0033291724003039 Published online by Cambridge University Press

**Table 2.** Baseline characteristics of CHR participants, further split into CHR-T and CHR-NT

| Variable | CHR ($n = 331$) | CHR-T ($n = 61$) | CHR-NT ($n = 270$) | CHR-T *v.* CHR-NT $t$ value/$\chi^2$ | CHR-T *v.* CHR-NT $p$ value |
|---|---|---|---|---|---|
| Age (years), mean (S.D.) | 22.44 (4.98) | 22.38 (4.96) | 22.44 (4.99) | 0.09 | 0.928 |
| Sex, *n* (%) | | | | | |
| Female | 155 (46.8) | 25 (41.0) | 130 (48.2) | 1.03 | 0.311 |
| Ethnicity, *n* (%) | | | | | |
| White | 234 (70.7) | 40 (65.6) | 194 (71.9) | Fisher's exact | 0.312 |
| Black | 34 (10.3) | 11 (18.0) | 23 (8.5) | | |
| Mixed | 28 (8.5) | 4 (6.6) | 24 (8.9) | | |
| Asian | 11 (3.3) | 2 (3.3) | 9 (3.3) | | |
| Other[1] | 24 (7.3) | 4 (6.6) | 20 (7.4) | | |
| Socioeconomic status[2,a], *n* (%) | | | | | |
| Salariat | 97 (29.3) | 23 (37.7) | 74 (27.4) | 1.64 | 0.441 |
| Intermediate | 105 (31.7) | 18 (29.5) | 87 (32.2) | | |
| Working class | 90 (27.2) | 16 (26.2) | 74 (27.4) | | |
| Years in education[b], mean (S.D.) | 14.43 (3.05) | 14.19 (3.36) | 14.48 (2.99) | 0.61 | 0.543 |
| Antipsychotic medication[c], *n* (%) | 31 (9.4) | 11 (18.0) | 20 (7.4) | 7.17 | 0.007* |
| Antidepressant medication[d], *n* (%) | 91 (27.5) | 15 (24.6) | 76 (28.2) | 0.36 | 0.549 |
| Current cannabis use[e], *n* (%) | 87 (26.3) | 17 (27.9) | 70 (25.9) | $3.00 \times 10^{-3}$ | 0.953 |
| Childhood trauma[3,f], mean (S.D.) | 47.91 (15.66) | 47.88 (13.48) | 47.91 (16.13) | 0.02 | 0.987 |

*$p < 0.05$.
Participants included in the present study have LTE data recorded for at least one timepoint.
[1]Other includes those of North African and other ethnic backgrounds; [2]socioeconomic status is based on the father's socioeconomic class at participant's birth; [3]Childhood Trauma Questionnaire total score.
CHR, clinical high risk; CHR-T, CHR who transitioned to psychosis; CHR-NT, CHR who did not transition to psychosis.
Data missing for: [a]39 CHR; [b]31 CHR; [c]25 CHR; [d]34 CHR; [e]88 CHR; [f]19 CHR.

The baseline characteristics for the CHR group, further split into CHR-T and CHR-NT are reported in Table 2. There was only a significant difference in baseline antipsychotic medication where the CHR-T group reported higher use than the CHR-NT group.

At baseline, CHR individuals had mean scores of 55.39 (S.D. = 12.32) for GAF disability, 10.16 (3.97) for CAARMS positive symptoms subscale, and 20.99 (14.93) for SANS. Raw data scores for GAF disability, CAARMS, SANS, and total LTE plotted against time are presented in online Supplementary Figs S1–S4. The frequencies of the reported LTE items can be found in online Supplementary Table S1.

In total, 331 CHR individuals completed a total of 618 assessments in the study. Out of a maximum of four assessments, 152 (45.9%) participants completed one assessment, 82 (24.8%) completed two assessments, 86 (26.0%) completed three assessments, and 11 (3.3%) completed four assessments.

### *Group differences in recent SLEs at baseline*

The results from the linear regression models comparing groups at baseline are reported in Table 3 with LTE score as the dependent variable and group status as the main independent variable. CHR participants reported significantly more total recent SLEs ($M = 2.10$, S.D. = 1.74) than HC ($M = 1.15$, S.D. = 1.06), and more interpersonal events ($M = 0.63$, S.D. = 0.72) than HC ($M = 0.25$, S.D. = 0.44). There was no significant difference between the number of independent events reported by CHR ($M = 0.81$, S.D. = 0.99) and HC ($M = 0.70$, S.D. = 0.82). The significance of the results did not change when we included ethnicity as a covariate of no interest.

There were no significant differences in total SLEs between CHR-T ($M = 1.93$, S.D. = 1.47) and CHR-NT ($M = 2.14$, S.D. = 1.79), in independent events (CHR-T: $M = 0.66$, S.D. = 0.87; CHR-NT: $M = 0.84$, S.D. = 1.01), nor in interpersonal events (CHR-T: $M = 0.59$, S.D. = 0.62; CHR-NT: $M = 0.63$, S.D. = 0.74). When we included antipsychotic medication and antidepressant medication in sensitivity analyses as covariates of no interest, the significance of the results did not change.

The significance of the results from the group comparison did not change when we controlled for childhood trauma and current cannabis use. There was a significant association between CTQ score and total LTE in the model for CHR *v.* HC ($\beta = 0.018$, $p = 0.012$), and in the model for CHR-T *v.* CHR-NT ($\beta = 0.019$, $p = 0.004$), indicating participants who experienced more childhood trauma reported more recent SLEs regardless of group membership. Cannabis use was only significantly associated with total LTE score in the model comparing CHR-T *v.* CHR-NT ($\beta = 0.528$, $p = 0.023$), suggesting CHR participants who were cannabis users experienced more recent SLEs. The full results are reported in online Supplementary Tables S2 and S3.

https://doi.org/10.1017/S0033291724003039 Published online by Cambridge University Press

**Table 3.** Group differences in LTE score at baseline using multiple linear regression[1] comparing CHR and HC individuals, and CHR individuals who transitioned to psychosis to those who did not

| | | 95% CI | | |
|---|---|---|---|---|
| LTE measure | Group estimate, $\beta$ | Lower | Upper | $p$ value |
| CHR ($n = 210$) *v.* HC ($n = 67$)[2] | | | | |
| Total LTE | 1.441 | 0.952 | 1.929 | <0.001**,[a] |
| Independent LTE | 0.263 | −0.042 | 0.568 | 0.091 |
| Interpersonal LTE | 0.550 | 0.345 | 0.756 | <0.001**,[a] |
| CHR-T ($n = 61$) *v.* CHR-NT ($n = 270$) | | | | |
| Total LTE | −0.247 | −0.712 | 0.219 | 0.298 |
| Independent LTE | −0.156 | −0.435 | 0.123 | 0.273 |
| Interpersonal LTE | −0.100 | −0.302 | 0.103 | 0.332 |

**$p < 0.01$; $p$ values reported are uncorrected values. [a]findings survived false discovery rate correction for multiple comparisons.
LTE, list of threatening experiences; CHR, clinical high risk; HC, healthy controls; CHR-T, CHR who transitioned to psychosis; CHR-NT, CHR who did not transition to psychosis.
[1]All models were controlled for age at baseline, sex, socioeconomic status, and site; [2]the analysis only included a subset of participants from four sites that recruited both CHR and HC individuals. Full results in online Supplementary Tables S2 and S3.

### The longitudinal association between recent SLEs and functioning, positive symptoms, and negative symptoms

The interaction term LTE score × time was not statistically significant across all models and therefore we report only the results from the base model for interpretation in Table 4. This includes the main effects of LTE score and time (measured in years from baseline) for each of the LMMs fitted with functioning, positive symptoms, and negative symptoms, as dependent variables. All models adjusted for sex, age at baseline, and SES. The predicted marginal effects of LTE score and time on functioning and symptom severity from the base model are presented in Fig. 1. The fixed-effects estimates for all models are reported in online Supplementary Tables S4–S6.

Total LTE score had a significant negative effect on GAF disability, where a higher occurrence of recent SLEs was associated with lower functioning when controlling for time. There was a significant effect of time, where functioning was found to improve over the study period (Table 4, Fig. 1a). The interaction term LTE score × time in the interaction model was not significant suggesting that recent SLEs did not impact the rate of improvement in functioning over the follow-up period (online Supplementary Table S4).

There was a significant positive association between total LTE score and both the CAARMS positive symptoms and SANS scores, meaning a higher occurrence of recent SLEs was associated with more severe positive and negative symptoms when controlling for time. There was a significant effect of time on both CAARMS and SANS scores, indicating symptom severity decreased over the course of the study (Table 4, Fig. 1b and 1c). There was no significant effect of the interaction term LTE score × time in the interaction model, suggesting recent SLEs did not affect the rate of change in symptom severity over the 2-year follow-up (online Supplementary Table S5 and S6).

There were no significant associations between independent or interpersonal events and functioning, positive symptoms, or negative symptoms.

### Sensitivity analysis for the longitudinal data

There were no changes to the significance of the results for functioning, positive symptoms, or negative symptoms when we

**Table 4.** Estimates from the base model of the main fixed effects examining the association between recent stressful life events and functioning and symptom outcomes over the 2-year follow-up period within the CHR group[1]

| | LTE score | | | | | Time (years from baseline) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | 95% CI | | | | | 95% CI | | |
| Outcome measure/type of stressful event | Estimate | S.E. | Lower | Upper | $p$ value | Estimate | S.E. | Lower | Upper | $p$ value |
| GAF disability | | | | | | | | | | |
| Total LTE score | −1.283 | 0.340 | −1.931 | −0.574 | <0.001**,[a] | 4.618 | 0.540 | 3.510 | 5.655 | <0.001**,[a] |
| Independent LTE score | −0.739 | 0.578 | −1.828 | 0.456 | 0.202 | 5.025 | 0.533 | 3.934 | 6.053 | <0.001**,[a] |
| Interpersonal LTE score | −0.794 | 0.784 | −2.296 | 0.769 | 0.311 | 4.990 | 0.540 | 3.885 | 6.038 | <0.001**,[a] |
| CAARMS (positive symptoms) | | | | | | | | | | |
| Total LTE score | 0.292 | 0.111 | 0.076 | 0.510 | 0.009**,[a] | −2.274 | 0.180 | −2.625 | −1.915 | <0.001**,[a] |
| Independent LTE score | 0.302 | 0.188 | −0.068 | 0.675 | 0.110 | −2.346 | 0.178 | −2.693 | −1.990 | <0.001**,[a] |
| Interpersonal LTE score | 0.011 | 0.255 | −0.486 | 0.514 | 0.965 | −2.359 | 0.180 | −2.709 | −1.999 | <0.001**,[a] |
| SANS (negative symptoms) | | | | | | | | | | |
| Total LTE score | 0.966 | 0.364 | 0.239 | 1.668 | 0.008*,[a] | −3.365 | 0.546 | −4.430 | −2.281 | <0.001**,[a] |
| Independent LTE score | 0.844 | 0.627 | −0.407 | 2.055 | 0.179 | −3.621 | 0.539 | −4.669 | −2.547 | <0.001**,[a] |
| Interpersonal LTE score | 0.095 | 0.831 | −1.543 | 1.709 | 0.909 | −3.670 | 0.551 | −4.738 | −2.572 | <0.001**,[a] |

*$p < 0.05$; **$p < 0.01$; $p$ values are uncorrected values. [a]findings survived false discovery rate correction for multiple comparisons.
LTE, List of Threatening Experiences; GAF, Global Assessment of Functioning; CAARMS, Assessment of At-Risk Mental State; SANS, Scale for the Assessment of Negative Symptoms.
[1]Models included participants nested in site ($n = 11$) as random intercepts. Number of participants used in each model varied due to missing data: GAF disability, $n = 287$; CAARMS, $n = 290$; SANS, $n = 288$. All models were controlled for sex, age at baseline, and socioeconomic status; Full results in online Supplementary Tables S5 and S6.

https://doi.org/10.1017/S0033291724003039 Published online by Cambridge University Press

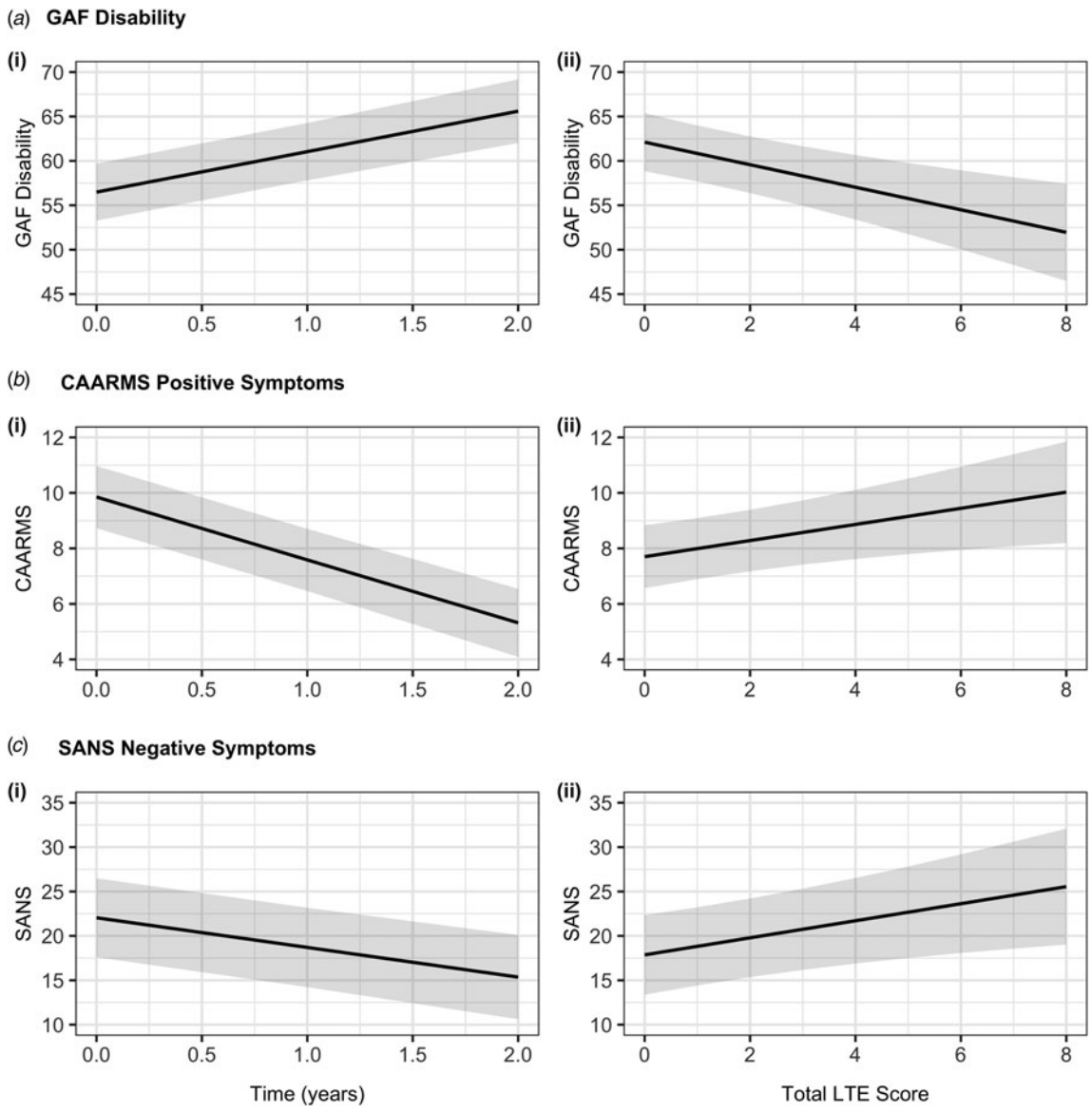



**Figure 1.** The predicted marginal effects of (i) time (measured in years from baseline) and (ii) Total List of Threatening Experiences (LTE) score on: (a) functioning as measured by the Global Assessment of Functioning (GAF) disability subscale; (b) positive symptom score measured by the Comprehensive Assessment of At-Risk Mental States (CAARMS) positive symptom severity subscale; and (c) negative symptom scores measured by the Scale for the Assessment of Negative Symptoms (SANS), using the linear mixed model estimates from the base model. The graphs show overall poorer functioning and more severe symptoms associated with a higher LTE score controlling for time, and an improvement in functioning and symptom scores over the course of the study. The grey band represents the 95% confidence interval. All models control for sex, age at baseline, and socioeconomic status, with participants nested in site modeled as random intercepts.

adjusted for baseline antipsychotic and antidepressant medication use, dosage and length of use, nor when we included childhood trauma as a covariate in each model. There were no significant associations between childhood trauma and functioning, positive symptoms, or negative symptoms (online Supplementary Tables S4b, S5b, and S6b).

When the base model was adjusted for current cannabis use, the significance of the results did not change for GAF disability (online Supplementary Table S4b), nor was there a significant main effect of cannabis use on functioning. However, the main effects of LTE score on positive symptoms and negative symptoms were no longer significant when controlling for cannabis use, and there was no significant main effect of cannabis use on either positive or negative symptoms (online Supplementary Tables S5b and S6b).

Participants were grouped by the number of completed assessments and baseline characteristics were compared to test for attrition bias, in line with recommended reporting requirements (Fewtrell et al., 2008). There were significant differences across groups in the years spent in education ($F_{(3,296)} = 8.30$, $p < 0.001$), CAARMS positive symptom scores ($F_{(3,324)} = 6.78$, $p < 0.001$), ethnicity (Fisher's exact $p = 0.020$), and in baseline antipsychotic medication use (Fisher's exact $p = 0.011$) (online Supplementary Table S7).

## Discussion

This is the largest longitudinal study to date investigating the effects of recent SLEs on functioning and symptom severity in individuals at CHR for psychosis. As hypothesized, we found

https://doi.org/10.1017/S0033291724003039 Published online by Cambridge University Press

CHR individuals reported more total recent SLEs and interpersonal SLEs than HCs at baseline. Contrary to our prediction, there was no significant difference in the number of SLEs reported by CHR-T individuals as compared to CHR-NT individuals, nor were there any differences in the number of independent and interpersonal SLEs between CHR-T and CHR-NT at baseline. Our final hypothesis was partially confirmed in our longitudinal analyses: recent SLEs were associated with lower functioning, and more severe positive and negative symptoms when controlling for time. However, while we observed an improvement in functioning and symptoms over the course of the study, recent SLEs did not affect the longitudinal trajectories of either of these outcome measures. The significance of our results did not change when we adjusted for childhood trauma, although when adjusting for cannabis use, we found SLEs were no longer significantly associated with positive or negative symptoms.

Our finding that CHR individuals reported more recent SLEs than HCs is consistent in previous studies that measured recent SLEs across 12 months (Huang et al., 2019; Munoz-Samons et al., 2021), as has been done in the current study. Where our findings conflict with previous work, recent SLEs were measured over a shorter period of 1 (Phillips et al., 2012) and 3 months (DeVylder et al., 2013). We found that CHR individuals did not report significantly more independent events than HC, suggesting that the higher prevalence of SLEs reported by CHR individuals could be a consequence of their subclinical symptoms. This is further supported by our findings that CHR individuals reported more interpersonal events than HCs, possibly driven by a heightened sensitivity to interpersonal issues (Georgiades et al., 2023). It is also possible that interpersonal events themselves contribute to the CHR state as proposed in cognitive models, where the appraisal of interpersonal events results in negative schemas, leading to the development of psychosis (Lovatt, Mason, Brett, & Peters, 2010).

Contrary to our hypothesis but similar to previous work (DeVylder et al., 2013; Mason et al., 2004), the number of SLEs did not differ between CHR-T and CHR-NT groups. However, given that CHR-T individuals transitioned at varying timepoints during study, there may not have been any discernible differences at baseline due to variation in the staging of psychosis progression within the CHR-T group. There were insufficient data in the current study to examine recent SLEs in the CHR-T group precipitating their transition date, which would be an important consideration in future studies. The CHR group is also highly variable and heterogeneous in terms of clinical presentation and is highly comorbid with other mental disorders (Solmi et al., 2023). It is estimated only approximately 20% of CHR individuals transition to psychosis after 2 years (Salazar de Pablo et al., 2021a, 2021b). It is possible that recent SLEs are not directly associated with transition to psychosis, and instead may have a broader effect on the general psychopathology of CHR individuals. A network analysis by Betz et al. (2020) found that recent SLEs were not directly linked to psychotic symptoms but were mediated by other symptoms such as depression and anxiety.

Poorer functioning and more severe positive and negative symptoms were associated with a higher incidence of recent SLEs overall, which supports findings by Munoz-Samons et al. (2021), but differs from other CHR studies (DeVylder et al., 2013; Thompson et al., 2007). This could be due to methodological differences in study design and analyses. For instance, Thompson et al. (2007) was a cross-sectional study using correlational analysis, while the current study analyzed a larger, longitudinal dataset which would have increased statistical power.

The significance of results from the baseline comparison between CHR and HC individuals and the longitudinal findings did not change when we adjusted for childhood adversity, which suggests recent SLEs may have their own distinct contribution to the psychopathology of psychosis. We found that individuals who had experienced more childhood adversity reported more recent SLEs at baseline, irrespective of their group membership (CHR *v.* HC or CHR-T *v.* CHR-NT). As has been suggested by Morgan et al. (2014), early adversity is more likely to lead to adult disadvantage, resulting in a higher incidence of SLEs. Our results further suggest SLEs may impact symptom outcomes via cannabis use, which has been previously proposed (Arranz et al., 2018). There is evidence of a bi-directional effect between cannabis and stress, where stress is associated with higher cannabis use, and long-term cannabis use is associated with a blunted stress response, therefore affecting stress-related outcomes (al'Absi & Allen, 2021; Glodosky, Cuttler, & McLaughlin, 2021). However, 88 participants were missing data on cannabis use and so the results should be interpreted with caution.

The CHR group exhibited an overall improvement in functioning and symptoms over time although their outcomes were still poorer than the HC group. This has previously been observed in studies examining outcomes in help-seeking CHR samples (Addington et al., 2011; Brandizzi et al., 2015). However, contrary to our hypothesis, the trajectory of outcomes appeared to be unaffected by the occurrence of recent SLEs. We may posit that recent SLEs is a risk factor for an individual becoming CHR for psychosis, rather than having a significant influence over the progression of their clinical outcomes while in the CHR state. Previous work has found that individuals who were referred to early intervention psychosis services but did not meet the CHR criteria exhibited many overlapping risk factors (2024). In addition, given that our sample comprised of individuals who contacted clinical services, treatment received during the study could have countered any deleterious effects of SLEs, although we found there were no changes to the significance of our results when controlling for antipsychotic and antidepressant medication.

It is possible that results were obscured by the heterogeneity of the CHR group, where previous studies have not only identified distinct subgroups of CHR individuals with differing trajectories of clinical outcomes (Allswede et al., 2020; Healey et al., 2018), but also found different risk factors associated with the clinical staging of CHR individuals (Wigman, van der Tuin, van den Berg, Muller, & Booij, 2023). Recent SLEs may therefore have a significant effect on the trajectory of clinical outcomes for a particular CHR subgroup but not another, and further work is required to clarify this.

We must also consider that stress is subjective to an individual, and that it may be the perceived experience that affects the trajectory of outcomes within the CHR state rather than the prevalence of events (Haidl et al., 2018). CHR individuals have been found to exhibit an impaired tolerance to stress associated with poorer outcomes (DeVylder et al., 2013; Munoz-Samons et al., 2021), and they have reported higher levels of distress despite reporting fewer recent SLEs compared to HC (Kraan, Velthorst, Smit, de Haan, & van der Gaag, 2015). Future studies should consider incorporating subjective stress measures.

### Limitations and strengths

As is commonly faced in retrospective studies, recent SLE and childhood adversity data are subject to recall bias, although

https://doi.org/10.1017/S0033291724003039 Published online by Cambridge University Press

previous work has demonstrated that memory biases appear to have minimal effect on the relationship between self-reported adversity and psychopathology, with retrospective data potentially being a more useful risk indicator (Fergusson, Horwood, & Boden, 2011; Newbury et al., 2018). The items in the LTE questionnaire may not have been appropriate for the age range of our study, where younger participants may not have had the same exposure to the type of life events included in the questionnaire such as the loss of a job, while experiences such as difficulties at school were not captured. The current study also did not record psychological treatment which could have meant changes in behavior or adaptive coping to improve resilience could have obscured results. This could be of interest in future work, given the associations with functioning and symptom severity, and potential protective factors (Mian, Lattanzi, & Tognin, 2018; Stainton et al., 2019). Longitudinal data pertaining to antipsychotic and antidepressant medication use were unfortunately unavailable, which is a significant limitation of the study. We found there were some differences between participants based on how many assessments they had completed indicating potential attrition bias, which is a broader challenge in longitudinal studies (Fewtrell et al., 2008; Homman, Smart, O'Neill, & MacCabe, 2021). This may also affect our statistical analysis as LMMs assume data are missing at random.

The main strength of our study is in the use of a large dataset to examine the effect of recent SLEs on the trajectory of outcomes in CHR individuals over time. Using LMMs meant greater statistical power as the models took into account the variation between participants and site, used all observed datapoints, and adjusted for covariates of no interest. The EU-GEI High Risk study collected a wide range of social and environmental variables, which subsequently meant we could adjust for childhood trauma and cannabis use, which had not been done in previous CHR studies of recent SLEs. Further work is still required to understand recent SLEs as a risk factor for psychosis to determine when early intervention strategies seeking to mitigate against the effects of stress can be most effective.

**Supplementary material.** The supplementary material for this article can be found at https://doi.org/10.1017/S0033291724003039

**Funding statement.** The European Network of National Schizophrenia Networks Studying Gene-Environment Interactions (EU-GEI) Project is funded by grant agreement HEALTH-F2-2010-241909 (Project EU-GEI) from the European Community's Seventh Framework Programme. C. See is supported by the UK Medical Research Council (MR/N013700/1) and King's College London member of the MRC Doctoral Training Partnership in Biomedical Sciences. Additional support was provided by a Medical Research Council Fellowship to M. Kempton (grant MR/J008915/1), and by the Ministerio de Ciencia, Innovación e Universidades (PSI2017-87512-C2-1-R) and the Generalitat de Catalunya (2017SGR1612) to N. Barrantes-Vidal. M. Kempton receives funding support from the National Institute for Health and Care Research (NIHR) Maudsley Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. E. Velthorst receives funding support from the National Institute for Mental Health (1R01MH128971-01A1). The views expressed are those of the authors and not necessarily those of the NIHR, or the Department of Health and Social Care. For the purposes of open access, the author has applied a Creative Commons Attribution (CC BY) license to any Accepted Author Manuscript version arising from this submission.

**Competing interests.** None.

**EU-GEI High Risk Study group authors**

Philip McGuire[1,2], Sara Pisani[1], Mathilde Antoniades[3], Maria Calem[1], Stefania Tognin[1], Gemma Modinos[4], Lieuwe de Haan[5,6], Mark van der Gaag[7,8], Eva Velthorst[9], Tamar C. Kraan[5], Daniella S. van Dam[5], Nadine Burger[8], Barnaby Nelson[10], Patrick McGorry[10], G. Paul Amminger[10], Christos Pantelis[11], Athena Politis[10], Joanne Goodall[10], Anita Riecher-Rössler[12], Stefan Borgwardt[12], Erich Studerus[12], Rodrigo Bressan[13], Ary Gadelha[13], Elisa Brietzke[14], Graccielle Asevedo[13], Elson Asevedo[13], Andre Zugman[13], Neus Barrantes-Vidal[15], Tecelli Domínguez-Martínez[16], Anna Racioppi[17], Thomas R. Kwapil[18], Manel Monsonet[17], Lídia Hinojosa[17], Mathilde Kazes[19], Claire Daban[19], Julie Bourgin[19], Olivier Gay[19], Célia Mam-Lam-Fook[19], Marie-Odile Krebs[19], Dorte Nordholm[20], Lasse Randers[20], Kristine Krakauer[20], Louise Glenthøj[20], Birte Glenthøj[21], Merete Nordentoft[20], Stephan Ruhrmann[22], Dominika Gebhard[22], Julia Arnhold[23], Joachim Klosterkötter[22], Gabriele Sachs[24], Iris Lasser[24], Bernadette Winklbaur[24], Philippe A. Delespaul[25,26], Bart P. Rutten[25], Jim van Os[1,25]

**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 Psychiatry, University of Oxford, Oxford, United Kingdom
3. Department of Psychiatry, Icahn School of Medicine at Mount Sinai, 1425 Madison Ave, New York, NY 10029, United States
4. Department of Psychological Medicine, Institute of Psychiatry, Psychology & Neuroscience, King's College London, De Crespigny Park, Denmark 458 Hill, London, United Kingdom SE5 8AF
5. AMC, Academic Psychiatric Centre, Department Early Psychosis, Meibergdreef 5, 1105 AZ Amsterdam, The Netherlands
6. Arkin Amsterdam, The Netherlands
7. VU University, Faculty of Behavioural and Movement Sciences, Department of Clinical Psychology, van der Boechorststraat 7, 1081 BT Amsterdam, The Netherlands
8. Parnassia Psychiatric Institute, Department of Psychosis Research, Zoutkeetsingel 40, 2512 HN The Hague, The Netherlands
9. Department of Research, GGZ Noord-Holland-Noord, Heerhugowaard, The Netherlands
10. Centre for Youth Mental Health, University of Melbourne, 35 Poplar Road (Locked Bag 10), Parkville, Victoria 485 3052, Australia
11. Melbourne Neuropsychiatry Centre, University of Melbourne & Melbourne Health, Carlton South, VIC, Australia
12. University of Basel, Switzerland
13. LiNC – Lab Interdisciplinar Neurociências Clínicas, Depto Psiquiatria, Escola Paulista de Medicina, Universidade Federal de São Paulo – UNIFESP, Brazil
14. Depto Psiquiatria, Escola Paulista de Medicina, Universidade Federal de São Paulo – UNIFESP, Brazil
15. Departament de Psicologia Clínica i de la Salut (Universitat Autònoma de Barcelona), Spanish Mental Health Research Network (CIBERSAM), Spain
16. CONACYT-Dirección de Investigaciones Epidemiológicas y Psicosociales, Instituto Nacional de Psiquiatría Ramón de la Fuente Muñiz, México.
17. Departament de Psicologia Clínica i de la Salut (Universitat Autònoma de Barcelona), Spain
18. Department of Psychology, University of Illinois at Urbana-Champaign, USA
19. University Paris Descartes, Hôpital Sainte-Anne, C'JAAD, Service Hospitalo-Universitaire, Inserm U894, Institut de Psychiatrie (CNRS 3557) Paris, France
20. 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, Denmark
21. Centre for Neuropsychiatric Schizophrenia Research (CNSR) & Centre for Clinical Intervention and Neuropsychiatric Schizophrenia Research (CINS), Mental Health Centre Glostrup, University of Copenhagen, Glostrup, Denmark
22. Department of Psychiatry and Psychotherapy, Faculty of Medicine and University Hospital, University of Cologne, Cologne, Germany
23. Psyberlin, Berlin, Germany

https://doi.org/10.1017/S0033291724003039 Published online by Cambridge University Press

24. Medical University of Vienna, Department of Psychiatry and Psychotherapy, Austria
25. Department of Psychiatry and Neuropsychology, School for Mental Health and Neuroscience, Maastricht University Medical Centre, P.O. Box 616, 6200 MD 464 Maastricht, The Netherlands
26. Mondriaan Mental health Trust, P.O. Box 4436 CX Heerlen, The Netherlands

## References

Addington, J., Cornblatt, B. A., Cadenhead, K. S., Cannon, T. D., McGlashan, T. H., Perkins, D. O., … Heinssen, R. (2011). At clinical high risk for psychosis: Outcome for nonconverters. *American Journal of Psychiatry*, *168*(8), 800–805. https://doi.org/10.1176/appi.ajp.2011.10081191

al'Absi, M., & Allen, A. M. (2021). Impact of acute and chronic cannabis use on stress response regulation: Challenging the belief that Cannabis is an effective method for coping. *Frontiers in Psychology*, *12*, 687106. https://doi.org/10.3389/fpsyg.2021.687106

Allswede, D. M., Addington, J., Bearden, C. E., Cadenhead, K. S., Cornblatt, B. A., Mathalon, D. H., … Cannon, T. D. (2020). Characterizing covariant trajectories of individuals at clinical high risk for psychosis across symptomatic and functional domains. *American Journal of Psychiatry*, *177*(2), 164–171. https://doi.org/10.1176/appi.ajp.2019.18111290

Andreasen, N. C. (1982). Negative symptoms in schizophrenia. Definition and reliability. *Archives of General Psychiatry*, *39*(7), 784–788. https://doi.org/10.1001/archpsyc.1982.04290070020005

Andreasen, N. C. (1983). *The scale for the assessment of negative symptoms* (*SANS*). Iowa City, Iowa: The University of Iowa.

Arranz, S., Monferrer, N., Jose Algora, M., Cabezas, A., Sole, M., Vilella, E., … Sanchez-Gistau, V. (2018). The relationship between the level of exposure to stress factors and cannabis in recent onset psychosis. *Schizophrenia Research*, *201*, 352–359. https://doi.org/10.1016/j.schres.2018.04.040

Bates, D., Mächler, M., Bolker, B., & Walker, S. (2015). Fitting linear mixed-effects models using lme4. *Journal of Statistical Software*, *67*(1), 1–48. https://doi.org/10.18637/jss.v067.i01

Beards, S., Gayer-Anderson, C., Borges, S., Dewey, M. E., Fisher, H. L., & Morgan, C. (2013). Life events and psychosis: A review and meta-analysis. *Schizophrenia Bulletin*, *39*(4), 740–747. https://doi.org/10.1093/schbul/sbt065

Beards, S., Fisher, H. L., Gayer-Anderson, C., Hubbard, K., Reininghaus, U., Craig, T. J., … Morgan, C. (2020). Threatening life events and difficulties and psychotic disorder. *Schizophrenia Bulletin*, *46*(4), 814–822. https://doi.org/10.1093/schbul/sbaa005

Benjamini, Y., & Hochberg, Y. (1995). Controlling the false discovery rate: A practical and powerful approach to multiple testing. *Journal of the Royal Statistical Society: Series B* (*Methodological*), *57*(1), 289–300. https://doi.org/10.1111/j.2517-6161.1995.tb02031.x

Bernstein, D. P., Stein, J. A., Newcomb, M. D., Walker, E., Pogge, D., Ahluvalia, T., … Zule, W. (2003). Development and validation of a brief screening version of the Childhood Trauma Questionnaire. *Child Abuse & Neglect*, *27*(2), 169–190. https://doi.org/10.1016/s0145-2134(02)00541-0

Brandizzi, M., Valmaggia, L., Byrne, M., Jones, C., Iwegbu, N., Badger, S., … Fusar-Poli, P. (2015). Predictors of functional outcome in individuals at high clinical risk for psychosis at six years follow-up. *Journal of Psychiatric Research*, *65*, 115–123. https://doi.org/10.1016/j.jpsychires.2015.03.005

Brown, G. W., & Birley, J. L. T. (1968). Crises and life changes and the onset of schizophrenia. *Journal of Health and Social Behavior*, *9*(3), 203–214. https://doi.org/10.2307/2948405

Brugha, T. S., & Cragg, D. (1990). The list of threatening experiences: The reliability and validity of a brief life events questionnaire. *Acta Psychiatrica Scandinavica*, *82*(1), 77–81. https://doi.org/10.1111/j.1600-0447.1990.tb01360.x

Brugha, T., Bebbington, P., Tennant, C., & Hurry, J. (1985). The list of threatening experiences: A subset of 12 life event categories with considerable long-term contextual threat. *Psychological Medicine*, *15*(1), 189–194. https://doi.org/10.1017/s003329170002105x

Betz, L. T., Penzel, N., Kambeitz-Ilankovic, L., Rosen, M., Chisholm, K., Stainton, A., … Consortium P. (2020). General psychopathology links burden of recent life events and psychotic symptoms in a network approach. *NPJ Schizophrenia*, *6*(1), 40. https://doi.org/10.1038/s41537-020-00129-w

Detry, M. A., & Ma, Y. (2016). Analyzing repeated measurements using mixed models. *JAMA*, *315*(4), 407–408. https://doi.org/10.1001/jama.2015.19394

DeVylder, J. E., Ben-David, S., Schobel, S. A., Kimhy, D., Malaspina, D., & Corcoran, C. M. (2013). Temporal association of stress sensitivity and symptoms in individuals at clinical high risk for psychosis. *Psychological Medicine*, *43*(2), 259–268. https://doi.org/10.1017/S0033291712001262

Di Forti, M., Quattrone, D., Freeman, T. P., Tripoli, G., Gayer-Anderson, C., Quigley, H., … van der Ven, E. (2019). The contribution of cannabis use to variation in the incidence of psychotic disorder across Europe (EU-GEI): A multicentre case-control study. *The Lancet Psychiatry*, *6*(5), 427–436. https://doi.org/10.1016/s2215-0366(19)30048-3

Haidl, T., Rosen, M., Schultze-Lutter, F., Nieman, D., Eggers, S., & Heinimaa, M. … European Prediction of Psychosis Study G (2018). Expressed emotion as a predictor of the first psychotic episode – results of the European prediction of psychosis study. *Schizophrenia Research*, *199*, 346–352. https://doi.org/10.1016/j.schres.2018.03.019

Fergusson, D. M., Horwood, L. J., & Boden, J. M. (2011). Structural equation modeling of repeated retrospective reports of childhood maltreatment. *International Journal of Methods in Psychiatric Research*, *20*(2), 93–104. https://doi.org/10.1002/mpr.337

Fewtrell, M. S., Kennedy, K., Singhal, A., Martin, R. M., Ness, A., Hadders-Algra, M., … Lucas, A. (2008). How much loss to follow-up is acceptable in long-term randomised trials and prospective studies? *Archives of Disease in Childhood*, *93*(6), 458–461. https://doi.org/10.1136/adc.2007.127316

First, M. B., & Gibbon, M. (2004). The structured clinical interview for DSM-IV axis I disorders (SCID-I) and the structured clinical interview for DSM-IV axis II disorders (SCID-II). In M. J. Hilsesnroth & D. L. Segal (Eds.), *Comprehensive handbook of psychological assessment* (pp. 134–143). Hoboken, New Jersey: John Wiley & Sons, Inc.

Georgiades, A., Almuqrin, A., Rubinic, P., Mouhitzadeh, K., Tognin, S., & Mechelli, A. (2023). Psychosocial stress, interpersonal sensitivity, and social withdrawal in clinical high risk for psychosis: A systematic review. *Schizophrenia*, *9*, 38. https://doi.org/10.1038/s41537-023-00362-z

Glodosky, N. C., Cuttler, C., & McLaughlin, R. J. (2021). A review of the effects of acute and chronic cannabinoid exposure on the stress response. *Frontiers in Neuroendocrinology*, *63*, 100945. https://doi.org/10.1016/j.yfrne.2021.100945

Goldman, H. H., Skodol, A. E., & Lave, T. R. (1992). Revising axis V for DSM-IV: A review of measures of social functioning. *American Journal of Psychiatry*, *149*(9), 1148–1156.

Haidl, T. K., Hedderich, D. M., Rosen, M., Kaiser, N., Seves, M., Lichtenstein, T., … Koutsouleris, N. (2023). The non-specific nature of mental health and structural brain outcomes following childhood trauma. *Psychological Medicine*, *53*(3), 1005–1014. https://doi.org/10.1017/S0033291721002439

Hall, R. C. (1995). Global assessment of functioning. A modified scale. *Psychosomatics*, *36*(3), 267–275. https://doi.org/10.1016/S0033-3182(95)71666-8

Healey, K. M., Penn, D. L., Perkins, D., Woods, S. W., Keefe, R. S. E., & Addington, J. (2018). Latent profile analysis and conversion to psychosis: Characterizing subgroups to enhance risk prediction. *Schizophrenia Bulletin*, *44*(2), 286–296. https://doi.org/10.1093/schbul/sbx080

Hedges, E. P., Dickson, H., Tognin, S., Modinos, G., Antoniades, M., van der Gaag, M., … Kempton, M. J. (2022). Verbal memory performance predicts remission and functional outcome in people at clinical high-risk for psychosis. *Schizophrenia Research. Cognition*, *28*, 100222. https://doi.org/10.1016/j.scog.2021.100222

Homman, L. E., Smart, S. E., O'Neill, F., & MacCabe, J. H. (2021). Attrition in longitudinal studies among patients with schizophrenia and other psychoses; findings from the STRATA collaboration. *Psychiatry Research*, *305*, 114211. https://doi.org/10.1016/j.psychres.2021.114211

Huang, Z. H., Hou, C. L., Huang, Y. H., He, X. Y., Wang, Q. W., Chen, X., … Jia, F. J. (2019). Individuals at high risk for psychosis experience more childhood trauma, life events and social support deficit in comparison to healthy controls. *Psychiatry Research*, *273*, 296–302. https://doi.org/10.1016/j.psychres.2019.01.060

https://doi.org/10.1017/S0033291724003039 Published online by Cambridge University Press

Kraan, T., Velthorst, E., Smit, F., de Haan, L., & van der Gaag, M. (2015). Trauma and recent life events in individuals at ultra high risk for psychosis: Review and meta-analysis. *Schizophrenia Research*, *161*(2-3), 143–149. https://doi.org/10.1016/j.schres.2014.11.026

Lovatt, A., Mason, O., Brett, C., & Peters, E. (2010). Psychotic-like experiences, appraisals, and trauma. *Journal of Nervous and Mental Disease*, *198*(11), 813–819. https://doi.org/10.1097/NMD.0b013e3181f97c3d

Mallett, R. (1997). *Sociodemographic schedule*. London, UK: Institute of Psychiatry.

Mansueto, G., & Faravelli, C. (2017). Recent life events and psychosis: The role of childhood adversities. *Psychiatry Research*, *256*, 111–117. https://doi.org/10.1016/j.psychres.2017.06.042

Marconi, A., Di Forti, M., Lewis, C. M., Murray, R. M., & Vassos, E. (2016). Meta-analysis of the association between the level of cannabis use and risk of psychosis. *Schizophrenia Bulletin*, *42*(5), 1262–1269. https://doi.org/10.1093/schbul/sbw003

Martland, N., Martland, R., Cullen, A. E., & Bhattacharyya, S. (2020). Are adult stressful life events associated with psychotic relapse? A systematic review of 23 studies. *Psychological Medicine*, *50*(14), 2302–2316. https://doi.org/10.1017/S0033291720003554

Mason, O., Startup, M., Halpin, S., Schall, U., Conrad, A., & Carr, V. (2004). Risk factors for transition to first episode psychosis among individuals with 'at-risk mental states'. *Schizophrenia Research*, *71*(2–3), 227–237. https://doi.org/10.1016/j.schres.2004.04.006

Mayo, D., Corey, S., Kelly, L. H., Yohannes, S., Youngquist, A. L., Stuart, B. K., … Loewy, R. L. (2017). The role of trauma and stressful life events among individuals at clinical high risk for psychosis: A review. *Frontiers in Psychiatry*, *8*, 55. https://doi.org/10.3389/fpsyt.2017.00055

Mian, L., Lattanzi, G. M., & Tognin, S. (2018). Coping strategies in individuals at ultra-high risk of psychosis: A systematic review. *Early intervention in Psychiatry*, *12*(4), 525–534. https://doi.org/10.1111/eip.12492

Morgan, C., Reininghaus, U., Fearon, P., Hutchinson, G., Morgan, K., Dazzan, P., … Craig, T. (2014). Modelling the interplay between childhood and adult adversity in pathways to psychosis: Initial evidence from the AESOP study. *Psychological Medicine*, *44*(2), 407–419. https://doi.org/10.1017/S0033291713000767

Munoz-Samons, D., Tor, J., Rodriguez-Pascual, M., Alvarez-Subiela, X., Sugranyes, G., de la Serna, E., … Baeza, I. (2021). Recent stressful life events and stress sensitivity in children and adolescents at clinical risk for psychosis. *Psychiatry Research*, *303*, 114017. https://doi.org/10.1016/j.psychres.2021.114017

Naughton, S., Brady, A., Geary, E., Counihan, E., & Clarke, M. (2024). An exploratory study of psychosis risk factors in individuals who are referred but do not meet criteria for an early intervention in psychosis service. *BJPsych Open*, *10*(1), e21. https://doi.org/10.1192/bjo.2023.640

Newbury, J. B., Arseneault, L., Moffitt, T. E., Caspi, A., Danese, A., Baldwin, J. R., … Fisher, H. L. (2018). Measuring childhood maltreatment to predict early-adult psychopathology: Comparison of prospective informant-reports and retrospective self-reports. *Journal of Psychiatric Research*, *96*, 57–64. https://doi.org/10.1016/j.jpsychires.2017.09.020

Park, S., Hatim, A., Si, T. M., Jeon, H. J., Srisurapanont, M., Bautista, D., … Hong, J. P. (2015). Stressful life events preceding the onset of depression in Asian patients with major depressive disorder. *The International Journal of Social Psychiatry*, *61*(8), 735–742. https://doi.org/10.1177/0020764015577842

Phillips, L. J., Edwards, J., McMurray, N., & Francey, S. (2012). Comparison of experiences of stress and coping between young people at risk of psychosis and a non-clinical cohort. *Behavioural and Cognitive Psychotherapy*, *40*(1), 69–88. https://doi.org/10.1017/S1352465811000397

Powers, A. D., Gleason, M. E., & Oltmanns, T. F. (2013). Symptoms of borderline personality disorder predict interpersonal (but not independent) stressful life events in a community sample of older adults. *Journal of Abnormal Psychology*, *122*(2), 469–474. https://doi.org/10.1037/a0032363

Raune, D., Kuipers, E., & Bebbington, P. (2011). Stressful and intrusive life events preceding first episode psychosis. *Epidemiologia e Psichiatria Sociale*, *18*(3), 221–228. https://doi.org/10.1017/s1121189x00000506

Salazar de Pablo, G., Davies, C., de Diego, H., Solmi, M., Shin, J. I., Carvalho, A. F., … Fusar-Poli, P. (2021a). Transition to psychosis in randomized clinical trials of individuals at clinical high risk of psychosis compared to observational cohorts: A systematic review and meta-analysis. *European Psychiatry*, *64*(1), e51. https://doi.org/10.1192/j.eurpsy.2021.2222

Salazar de Pablo, G., Radua, J., Pereira, J., Bonoldi, I., Arienti, V., Besana, F., … Fusar-Poli, P. (2021b). Probability of transition to psychosis in individuals at clinical high risk: An updated meta-analysis. *JAMA Psychiatry*, *78*(9), 970–978. https://doi.org/10.1001/jamapsychiatry.2021.0830

Sanson, A., & Riva, M. A. (2020). Anti-stress properties of atypical antipsychotics. *Pharmaceuticals*, *13*(10), 322. https://doi.org/10.3390/ph13100322

Solmi, M., Soardo, L., Kaur, S., Azis, M., Cabras, A., Censori, M., … Fusar-Poli, P. (2023). Meta-analytic prevalence of comorbid mental disorders in individuals at clinical high risk of psychosis: The case for transdiagnostic assessment. *Molecular Psychiatry*, *28*(6), 2291–2300. https://doi.org/10.1038/s41380-023-02029-8

Stainton, A., Chisholm, K., Kaiser, N., Rosen, M., Upthegrove, R., Ruhrmann, S., … Wood, S. J. (2019). Resilience as a multimodal dynamic process. *Early intervention in Psychiatry*, *13*(4), 725–732. https://doi.org/10.1111/eip.12726

Subramaniam, A., LoPilato, A., & Walker, E. F. (2019). Psychotropic medication effects on cortisol: Implications for research and mechanisms of drug action. *Schizophrenia Research*, *213*, 6–14. https://doi.org/10.1016/j.schres.2019.06.023

Thompson, K. N., Phillips, L. J., Komesaroff, P., Yuen, H. P., Wood, S. J., Pantelis, C., … McGorry, P. D. (2007). Stress and HPA-axis functioning in young people at ultra high risk for psychosis. *Journal of Psychiatric Research*, *41*(7), 561–569. https://doi.org/10.1016/j.jpsychires.2006.05.010

van Os, J., Rutten, B. P., Myin-Germeys, I., Delespaul, P., Viechtbauer, W., van Zelst, C., … Mirjanic, T. (2014). Identifying gene-environment interactions in schizophrenia: Contemporary challenges for integrated, large-scale investigations. *Schizophrenia Bulletin*, *40*(4), 729–736. https://doi.org/10.1093/schbul/sbu069

Wigman, J. T. W., van der Tuin, S., van den Berg, D., Muller, M. K., & Booij, S. H. (2023). Mental health, risk and protective factors at micro- and macro-levels across early at-risk stages for psychosis: The Mirorr study. *Early intervention in Psychiatry*, *17*(5), 478–494. https://doi.org/10.1111/eip.13343

Yung, A. R., Yuen, H. P., McGorry, P. D., Phillips, L. J., Kelly, D., Dell'Olio, M., … Buckby, J. (2005). Mapping the onset of psychosis: The comprehensive assessment of at-risk mental states. *Australian and New Zealand Journal of Psychiatry*, *39*(11-12), 964–971. https://doi.org/10.1080/j.1440-1614.2005.01714.x

https://doi.org/10.1017/S0033291724003039 Published online by Cambridge University Press