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► **To cite this version:**

Baptiste Pignon, Mohamed Lajnef, James B Kirkbride, Hugo Peyre, Aziz Ferchiou, et al.. The Independent Effects of Psychosocial Stressors on Subclinical Psychosis: Findings From the Multinational EU-GEI Study. *Schizophrenia Bulletin*, 2021, 10.1093/schbul/sbab060 . hal-03337986

HAL Id: hal-03337986

<https://hal.science/hal-03337986v1>

Submitted on 14 Sep 2021

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Draft Manuscript for Review. Please review online at <http://mc.manuscriptcentral.com/oup/szbltn>

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Journal:	<i>Schizophrenia Bulletin</i>
Manuscript ID	SZBLTN-ART-20-0835.R2
Manuscript Type:	Regular Article
Date Submitted by the Author:	n/a
Complete List of Authors:	<p>Pignon, Baptiste; Albert Chenevier Hospital, ; Lajnef, Mohamed Kirkbride, James; University College London, Division of Psychiatry; Peyre, Hugo Ferchiou, Aziz Richard, Jean-Romain; Univ Paris Est Créteil, INSERM, IMRB, Translational Neuropsychiatry Baudin, Grégoire Tosato, Sarah; University of Verona, Department of Neurosciences, Biomedicine and Movement Sciences, Section of Psychiatry and Clinical Psychology Jongsma, Hannah de Haan, Lieuwe; Amsterdam UMC -AMC Campus, Psychiatry Tarricone, Ilaria; University of Bologna, Department of Medical and Surgical Science, Psychiatry Unit, Alma Mater Studiorum Bernardo, Miquel; Hospital Clinic of Barcelona, Psychiatry Velthorst, Eva; Icahn School of Medicine at Mount Sinai, Department of Psychiatry, Early Psychosis; Icahn School of Medicine at Mount Sinai, departments of psychiatry and preventive medicine Braca, Mauro Arango, Celso; Child and Adolescent Psychiatry Department, Instituto de Investigación Sanitaria Gregorio Marañón, IiSGM. Hospital General Universitario Gregorio Marañón, CIBERSAM Arrojo, Manuel; Instituto de Investigación Sanitaria de Santiago de Compostela (IDIS) Servizo Galego de Saúde (SERGAS), Hospital Clínico Universitario; Complejo Hospitalario Universitario de Santiago de Compostela, Servizo de Psiquiatría Bobes, Julio; Universidad de Oviedo, Facultad de Medicina Del-Ben, Cristina; Universidade de Sao Paulo Campus de Ribeirao Preto, Neuroscience and Behavior, Division of Psychiatry Di Forti, Marta; Institute of Psychiatry, Psychosis Studies Gayer-Anderson, Charlotte; King's College London, Health Services and Population Research Jones, Peter; University of Cambridge, Psychiatry La Cascia, caterina; Palermo University, Dept of Experimental Biomedicine and Clinical Neuroscience -section of Psychiatry Lasalvia, Antonio; University of Verona, Public Health and Community</p>

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Keywords:	<p>Subclinical psychosis, Schizotypy, Psychotic symptoms, Psychosocial stress, Childhood trauma, Stressful life events, Social capital, Discrimination, Environment*environment interaction</p>

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The independent effects of psychosocial stressors on subclinical psychosis: findings from the multinational EU-GEI study

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ABSTRACT

The influence of psychosocial stressors on psychosis risk has usually been studied in isolation and after the onset of the disorder, potentially ignoring important confounding relationships or the fact that some stressors that may be the consequence of the disorder rather than preexisting. The study of subclinical psychosis could help to address some of these issues. In this study, we investigated whether there was (i) an association between dimensions of subclinical psychosis and several psychosocial stressors including: childhood trauma, self-reported discrimination experiences, low social capital, and stressful life experiences, and (ii) any evidence of environment-environment (ExE) interactions between these factors.

Data were drawn from the EUGEI study, in which healthy controls (N=1497) and siblings of subjects with a psychotic disorder (N=265) were included in six countries. The association between psychosocial stressors and subclinical psychosis dimensions (positive, negative and depressive dimension as measured by the Community Assessment of Psychic Experiences (CAPE) scale) and possible ExE interactions were assessed using linear regression models.

After adjusting for sex, age, ethnicity, country, and control/sibling status, childhood trauma (β for positive dimension: 0.13, negative: 0.49, depressive: 0.26) and stressful life events (positive: 0.08, negative: 0.16, depressive: 0.17) were associated with the three dimensions. Lower social capital was associated with the negative and depression dimensions (negative: 0.26, depressive: 0.13), and self-reported discrimination experiences with the positive dimension (0.06).

Our findings are in favor of independent, cumulative and non-specific influences of social adversities in subclinical psychosis in non-clinical populations, without arguments for ExE interactions.

Keywords

Subclinical psychosis, Schizotypy, Psychotic symptoms, Positive subclinical symptoms, Negative subclinical symptoms, Depressive subclinical symptoms, Psychosocial stress, Childhood trauma, Stressful life events, Social capital, Discrimination, Community Assessment of Psychic Experiences (CAPE)

104 INTRODUCTION

105 The stress-vulnerability theory of psychotic disorders posits that genetic factors interact
106 with environmental stressors in the development of a disorder¹⁻³. In this theoretical model,
107 increased sensitivity to stress plays an important role in both onset and relapse of psychotic
108 disorders, including schizophrenia. Extending this model, the stress sensitization hypothesis
109 proposes that repeated exposure to environmental stressors sensitizes key neurobiological
110 pathways to psychosis^{4,5}. Early, severe or prolonged exposure to stress would lead to a
111 dysregulated stress response and potentially explain both the role of early and current stress in
112 the etiology of psychotic disorders.

113 Several environmental factors that could be conceptualized as psychosocial stressors,
114 such as childhood trauma, stressful life events, discrimination experiences or a low level of
115 social capital have been found to increase the risk of psychotic disorders⁶⁻⁹. Furthermore,
116 several studies support a stress sensitization model in psychosis, showing for example that
117 exposure to an early stressor (childhood trauma) increases later sensitivity to other stressors
118 (e.g., social stress, population density, etc.) in patients (environment-environment ExE
119 interaction)^{10,11}. However, the fact that these studies have taken place after the onset of
120 psychotic disorder raises causality concerns. Indeed, the assessment of recent stress could be
121 confounded by several stressors associated with the disease itself, such as hospitalizations,
122 stigma, substance use disorders or social drift after onset¹²⁻¹⁴.

123 Psychotic symptoms may be present, to varying degrees, in non-clinical, general
124 population samples who do not meet criteria for a clinical disorder¹⁵⁻¹⁷. The continuum theory
125 of psychosis posits that subclinical experiences have a similar origin/etiology to full psychotic
126 disorders¹⁸⁻²². Thus, studying risk factors associated with subclinical psychosis may provide
127 insights into the etiology of psychosis, while reducing the potential interference of reverse
128 causation, i.e., stress caused by the clinical disorders themselves. Furthermore, in line with the
129 continuum theory, subclinical psychosis can be characterized by quantitative (continuous)
130 variables, improving statistical power and the capacity to control for more potential
131 confounders.

132 Several studies have previously reported associations between psychosocial stressors
133 and subclinical psychosis. For instance, childhood trauma has been associated with increased
134 rates of isolated psychotic symptoms in several studies²³⁻²⁶. Likewise, negative and/or stressful
135 life events^{27,28} or self-reported discrimination experiences²⁹ have also been associated with
136 subclinical psychosis.

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2
3 137 One major limitation of studies published to date is that psychosocial stressors have
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5 138 usually been studied in isolation, which might lead to spurious or incomplete conclusions given
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7 139 the likely presence of confounding/interaction with other stressors. Further work is needed to
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9 140 determine whether different psychosocial stressors have independent effects on subclinical
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11 141 psychosis and underlying dimensions (i.e., positive, negative, depressive), while controlling for
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13 142 other relevant stressors. Moreover, the role of population-level (e.g., social capital) factors that
14
15 143 might interact with psychosocial stressors has rarely been explored. For example, social capital
16
17 144 has been related to the incidence and outcome of psychotic disorders^{30,31} and low levels of
18
19 145 social capital could be a stressful condition *per se*³² (i.e., an independent stressor), or exacerbate
20
21 146 the effects of other psychosocial factors (discrimination, trauma, stressful life events) on
22
23 147 subsequent psychosis risk, but evidence is lacking. Relationships between social capital and
24
25 148 subclinical psychosis have never been investigated. Moreover, to the best of our knowledge,
26
27 149 only two studies have analyzed the role of multiple psychosocial stressors on subclinical
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29 150 psychosis. The first found arguments in favor of the sensitization hypothesis³³. The second,
30
31 151 studying the role of childhood trauma alongside other environmental and genetic risk factors,
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33 152 found additive effects of these factors on subclinical psychosis scores²¹.

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35 153 Furthermore, recent studies have reported that exposure to psychosocial stressors was
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37 154 in part dependent on genetic vulnerability to psychosis^{34,35}, and no study has compared
38
39 155 associations between psychosocial stressors and subclinical psychosis in both control
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41 156 participants and (healthy) siblings of people with a psychotic disorder. Including both groups
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43 157 may help tease out the genetic and environmental etiology of psychosis.

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45 158 To address some of the limitations of previous work, we used a large, cross-national
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47 159 sample of population-based controls and siblings of subjects with a psychotic disorder, to
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49 160 investigate whether there was (i) an association between subclinical psychosis dimensions
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51 161 (positive, negative and depressive) and psychosocial stressors, and (ii) any evidence of ExE
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53 162 interactions between different psychosocial stressors in line with the stress sensitization
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55 163 hypothesis. The psychosocial stressors we explored can be conceptualized as either “early”
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57 164 (childhood trauma) or “prolonged” (discrimination, low level of social capital, stressful life
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59 165 experiences). We hypothesized that exposure to “early” stressors would enhance the effect of
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166 adversity later in life.

METHODS

EU-GEI study

Data were collected in the “*European network of national schizophrenia networks studying gene-environment interactions*” (EU-GEI) study, a multicentre case-sibling-control study of genetic and environmental determinants of the occurrence, severity and outcome of psychotic disorders. For the second work-package of the study (WP2: Functional Enviromics), three categories of participants were recruited between 2010 and 2015: (i) subjects presenting with a first-episode of psychotic disorder (FEP), (ii) population-based healthy controls, and; (iii) siblings of participants with FEP³⁶. Participants were recruited across 6 countries: Brazil, France, Italy, the Netherlands, Spain, and the United Kingdom^{37,38}. In the present analyses, only controls and siblings were included.

Subjects

Population-based controls and siblings had no personal history of psychosis, and controls were recruited from the same catchment areas as the cases. In each centre, controls were recruited using a mixture of random and quota sampling to ensure control participants were broadly representative of the population at-risk from which cases could present in each catchment area on predefined variables (age, sex, and migration)³⁶.

Subclinical psychosis measure

The Community Assessment of Psychic Experiences (CAPE) is a 42-item, self-report questionnaire that has been developed to measure lifetime subclinical psychotic dimensions in the general population³⁹. For each item, 4 answers were possible according to the frequency of their occurrences (from never to nearly always). A meta-analysis found that the CAPE displays a three-dimensional symptom structure: positive, negative and depressive dimensions⁴⁰. We therefore used the sum of endorsed items to quantify each of the three psychotic dimensions consistent with previous studies^{22,41,42}. To construct these dimension scores, we dichotomized answers on each CAPE item (never vs. sometimes or more) and summed the positive answers. This led to theoretical positive dimension scores between 0-20, negative dimension scores between 0-14, and depressive dimension scores between 0-8.

We have previously demonstrated the cross-national invariance of the CAPE assessment in the EUGEI WP2 samples: equivalent factorial structures, factor loadings and thresholds

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3 200 across the six countries⁴³. Thus, CAPE results can be reliably used across the different EUGEI
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5 201 countries.

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8 203 ***Psychosocial stressors measure***

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10 204 Childhood trauma was assessed with the Childhood Trauma Questionnaire (CTQ), a 25-
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12 205 item questionnaire, that measures five different domains (emotional and physical neglect;
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14 206 emotional, physical and sexual abuse). All items are scored on a five-point Likert-scale (1:
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16 207 never, to 5: very often). We used the CTQ total score as the sum of all items, thus theoretically
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18 208 ranging from 25-125⁴⁴.

19 209 Lifetime self-reported discrimination experiences were assessed with a modified
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21 210 version of the Williams' major experiences of discrimination measure (available in
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23 211 **Supplementary Material 1**), a 12-item scale assessing several experiences of discrimination
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25 212 (unfairly fired or not hired because of your ethnicity/sex/weight/etc., unfairly
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27 213 stopped/questioned/physically threatened or abused by the police, etc.)^{45,46}. This version of the
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29 214 Williams' scale has already been used in a paper studying the prevalence of discrimination in
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31 215 South London, and its relationships with psychiatric disorders⁴⁷. We used a total discrimination
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33 216 score by adding all endorsed items, ranging theoretically from 0-12.

34 217 Perceived social capital in each participant's immediate neighborhood was assessed
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36 218 using the Social Environment Assessment Tool (SEAT), a 23-item questionnaire. This tool was
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38 219 designed to capture four dimensions of social capital: civic disorder (CD), impact of civic
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40 220 disorder (ICD), informal social control (ISC), and social cohesion and trust (SCT)⁴⁸⁻⁵¹.
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42 221 Respondents answer according to a five-point Likert-scale (1: unusual, to 5: very common).
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44 222 Sum scores for 4 subscales were derived then standardized to Z-scores (i.e., to a mean equal to
45
46 223 0, and a standard-deviation equal to 1). The total social capital score was obtained by adding
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48 224 the weighted scale scores ($SEAT\ score = zCD + 0.51 * zICD + 1.6 * zISC + zSCT$) based on the
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50 225 factorial structure of the instrument. This scale has shown excellent goodness-of-fit statistics
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52 226 (data available on request forthcoming). Our analyses were restricted to the total social capital
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54 227 score, which we inverted for analyses so that higher scores were associated with *lower* social
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56 228 capital.

57 229 Finally, stressful life events were assessed using the List of Threatening Experiences
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59 230 (LTE) which comprises 20 binary items^{52,53}. This scale assesses 20 events usually associated
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231 with major stress over the course of the previous 6 months including: serious injury or illness
232 in oneself or a close relative, death of parent/child/partner, death of a family member, death of

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3 233 a friend, separation from a partner, loss of job or financial difficulties. The total score ranges
4 234 theoretically from 0-20.

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8 236 ***Other adjustment variables***

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10 237 We also collected information on age, sex, country, and ethnicity as possible
11 238 confounding factors. Age was measured at the time of the interview. Ethnicity was self-defined
12 239 according to one of 6 categories: Asian, Black, North African, White, Mixed, Other.

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17 241 ***Ethical procedures***

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19 242 Ethical approval was obtained from local research ethics committees in each country.
20 243 The EU-GEI Project was funded by the European Community's Seventh Framework Program
21 244 under grant agreement no. HEALTH-F2-2010-241909.

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25
26 246 ***Statistical methods***

27
28 247 First, we assessed the associations between psychosocial stressors using Spearman
29 248 correlation tests. Then we analyzed the relationships between these stressors and the three
30 249 CAPE dimensions scores also using Spearman correlation tests. We used Mann-Whitney U-
31 250 tests to assess the differences in exposure to psychosocial stressors between controls and
32 251 siblings.

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36 252 Second, we fitted linear regression models to analyze independent and specific effects
37 253 of each psychosocial stressor on each of our three subclinical psychosis outcomes (i.e., each of
38 254 the three CAPE dimensions). We fitted multivariable models, controlling for other relevant
39 255 psychosocial stressors as well as age, sex, ethnicity, country, and control-sibling status (i.e., *a*
40 256 *priori* confounders)^{18,54,55}. As CAPE scores did not follow a normal distribution (as shown by
41 257 Shapiro tests with a p-value < 0.05, and graphical methods), a Box-Cox transformation of all
42 258 continuous variables (CAPE scores) was performed to fulfil the normality assumption required
43 259 by the parametric procedure. Complete case analysis was used.

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49 260 Third, we tested for evidence of ExE interactions between our four psychosocial
50 261 stressors on each outcome in our multivariable models. Each interaction (i.e., CTQxLTE,
51 262 CTQxSEAT, LTExSEAT, etc.) was tested separately, by introducing interaction terms in the 4
52 263 multivariable models. In a final model, all the interaction terms were pooled into a single model
53 264 for each of the outcomes.

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3 265 To facilitate comparisons of effect sizes of the different psychosocial stressor measures,
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5 266 Z-scores of these variables were calculated and used in the multivariable models.

6 267 The analyses were repeated among sibling and control subsamples, as siblings may
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8 268 experience different exposure and different response to the same exposure.

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10 269 Significance was based on a two-sided p-value of 0.05 throughout. R software version
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12 270 3.6.0, with “stats”, “car” and “lattice” packages, was used.

RESULTS

Sample characteristics

The sample was composed of 1,762 subjects, including 1,497 controls (85.0%) and 265 siblings (15.0%), of those 972 were men (55.2%) and 790 were women (44.8%). The median age for the controls was 33 years (IQR [26-47]), and 30 years (IQR [23-38]) for the siblings. The proportion of women was higher among controls, and controls were older. The proportion of people from non-white ethnic backgrounds differed between controls (21.3%) and siblings (24.1%), with a higher proportion of subjects of Black ethnicity (8.1% vs. 4.9%) and a lower proportion of subjects of Mixed ethnicity in controls (7.7% vs. 15.5%). Regarding CAPE scores, positive dimensions were higher among controls in comparison with siblings. Scores on the CTQ were higher among siblings while siblings reported fewer discrimination experiences. More details are available in the **Table 1**.

- TABLE 1 -

Correlations between psychosocial stressors

The correlation matrix (**Table 2**) revealed small but statistically robust ($p < 0.001$) correlations between all stressors. We observed positive correlations between childhood trauma, self-reported discrimination experiences, and stressful life events (ρ between 0.14 and 0.20), and negative correlations between high level of social capital and the 3 psychosocial stressors (ρ between -0.15 and -0.08). Correlations between psychosocial stressors showed similar patterns of magnitude and direction within both the control and sibling groups (except for social capital and stressful life events and social capital among siblings which were not associated, see **Supplementary Table 2** for analyses within controls and siblings).

- TABLE 2 -

Correlations between subclinical psychosis scores and psychosocial stressors

All psychosocial stressors were positively correlated with the different CAPE dimensions (**Table 3**). Higher perceived social capital scores were associated, as expected, with

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3 303 lower positive, negative and depressive dimension scores. Correlations ranged from -0.13
4 304 (higher social capital associated with lower depressive score) to 0.29 (childhood trauma and
5 305 negative dimension). Correlations showed similar patterns of direction within both the control
6 306 and sibling groups, with higher levels of correlation between CAPE scores and self-reported
7 307 discrimination experiences among siblings vs. controls (see **Supplementary Table 3** for
8 308 analyses within controls and siblings).

13 309

15 310 **- TABLE 3 -**

17 311

19 312 ***Multivariable modelling***

21 313 After adjusting for sex, age, ethnicity, country, and control/sibling status, the different
22 314 CAPE scores were independently associated with childhood trauma (β with Z-score of
23 315 childhood trauma between 0.13 and 0.49) and stressful life events (β between 0.08 and 0.17).
24 316 Lower social capital was associated with negative and depressive dimensions (β between 0.05
25 317 and 0.24), while self-reported discrimination experiences were only associated with the positive
26 318 dimension ($\beta=0.06$). None of the interaction terms of the psychosocial stressor measures (both
27 319 when introduced one by one in the multivariable analyses, and in the models with all the
28 320 interactions terms) were associated with any of the 3 dimensions (see **Supplementary Table 4**
29 321 for the results of the interactions). Of note, sibling status was associated with lower scores on
30 322 the positive dimension ($\beta=-0.16$). The detailed results of the multivariable analyses with Z-
31 323 scores of the psychosocial measures are available in the **Table 4**.

32 324 The same multivariable analyses were repeated separately for siblings and controls, and
33 325 revealed globally similar results. Of note, among siblings, fewer associations reached statistical
34 326 significance, and the interaction between childhood trauma and discrimination was significant
35 327 (negative interaction: $\beta=-0.15$, more details of the multivariable analyses within controls and
36 328 siblings in **Supplementary Table 5**).

39 329

51 330 **- TABLE 4 -**

53 331

DISCUSSION

In the cross-national and non-clinical EUGEI sample we assessed the effects of several psychosocial stressors (childhood trauma, stressful life-events, self-reported discrimination experiences and low social capital) on different subclinical psychosis dimensions for the first time. Subclinical psychosis was assessed with the CAPE and all analyses were adjusted for relevant sociodemographic factors (age, sex, country and ethnicity). This revealed that childhood trauma and stressful life events were associated with higher scores on the positive, negative and depressive dimensions. Lower social capital was associated with higher scores on negative and depressive dimensions, while self-reported discrimination experiences were associated with the positive dimension.

Overall, as all evaluated psychosocial stressors were associated with subclinical psychosis, and as no interaction between these stressors was significant, these findings are consistent with an independent effect of the different psychosocial stressors. Moreover, as the different psychosocial stressors were (with the exception of discrimination) similarly associated with the different dimensions, our findings are consistent with a common etiology for the 3 dimensions.

This study contributes to our understanding of the relationships between psychosis and early, recent, and prolonged psychosocial stressors. The major strength of this study is the concomitant analysis of several psychosocial stressors. In concordance with a recent study in the American general population⁵⁶, we confirm the existence of significant correlations between different stressors and we show that these stressors have independent effects on the 3 dimensions of subclinical psychosis. In addition, we found that a low level of social capital is associated with higher levels of negative and depressive dimensions. This ecological neighborhood-level factor had never been studied in relation with subclinical psychosis outcomes in adults before (of note, Solmi et al. found an association between maternal neighborhood stress and the rate of psychotic symptoms among 13 year old adolescents³²), while previous studies found associations with the incidence of psychotic disorders³⁰. This result is consistent with other studies regarding the influence of neighborhood characteristics such as as deprivation or social fragmentation on psychosis outcomes⁶, including subclinical psychosis^{57,58}.

Surprisingly, the absence of any strong evidence of interactions between the psychosocial stressors and especially between early and recent stress was not consistent with our hypothesis and the sensitization hypothesis. This result also differs from the results of

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3 365 Lataster et al.³³. In this 10-year follow-up of adolescents and young adults from the general
4 population in Germany (N=1,722), authors found non-additive interactions between early and
5 366 recent psychosocial risk factors on the risk for positive psychotic symptoms (i.e., delusional
6 367 symptoms and/or hallucinations): unadjusted analyses showed associations between early and
7 368 recent adversity and further psychotic symptoms, but these associations disappeared after
8 369 statistical adjustment. Additive interactions between early and recent adversity were significant
9 370 only for the fourth and highest level of recent adversity (adjusted risk ratio for the combined
10 371 early and higher level of recent adversity = 4.08, 95% CI [2.02-8.24], p-value=0.032).
11 372 Differences in results of this and our study might be explained by important methodological
12 373 differences. For example, Lataster et al. study was longitudinal (three follow-up surveys
13 374 covering a mean period of 8.4 years) and analyzed only two psychosocial stressors categorical
14 375 variables (childhood trauma, dichotomized; and recent trauma and negative life events, four
15 376 levels).

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17 378 Analyzing the influence of environmental (including childhood trauma, cannabis use
18 379 and urbanicity), sensory (hearing impairment), and familial risk factors on the occurrence of
19 380 subclinical psychosis in 6,646 subjects from the general population, Pries et al. found additive
20 381 effects of the risk factors: the greater the number of risk factors, the greater the odds of
21 382 symptoms²¹. Consistent with this finding, in our study, the effect of recent adverse experiences
22 383 (measured by the LTE) was significant for each of the 3 dimensions, independently of early
23 384 adverse experience (measured by childhood trauma), and we did not find any significant
24 385 interactions between the different psychosocial stressors. This may be due to a lack of statistical
25 386 power to detect an ExE interaction⁵⁹, however the β values of the interactions, which are close
26 387 to 0 make this unlikely.

27 388 Childhood trauma, i.e., the earliest psychosocial stressor, had the strongest associations
28 389 with each of the three dimensions measured. Childhood adverse experiences have been linked
29 390 with long-term changes in the hypothalamic-pituitary axis (HPA) axis⁶⁰ which may be involved
30 391 in early stressor and emotional dysregulation, leading to later aberrant salience, involved in the
31 392 positive dimension of psychosis⁶¹. Of note, childhood trauma is known to be associated with
32 393 psychopathology as a whole^{62,63}, and consistent with prior research, childhood trauma in our
33 394 study was also associated with the negative dimension⁶⁴ as well as with depressive symptoms⁶⁵
34 395 in both controls and siblings.

35 396 Self-reported discrimination experiences were associated with the positive dimension
36 397 of psychosis in the global sample. Several studies, including longitudinal studies⁶⁶, have shown
37 398 associations, particularly with psychotic-like experiences. They have been confirmed in recent

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3 399 meta-analyses^{9,29}. Consistently with the present study, some studies suggest that among the
4 400 different dimensions of subclinical psychosis discrimination is specifically associated with
5 401 positive psychotic symptoms^{9,67}. However in contrast with the present study, discrimination
6 402 experiences have also been linked to depression⁶⁸.

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10 403 The associations between CAPE scores and stressful life events support the role of
11 404 recent adverse experiences in the development of psychosis^{8,61}. Psychosis has been theorized
12 405 to combine cognitive (external attribution) bias and emotional dysregulation⁶⁹. Stressful life
13 406 events could play a trigger role for a disruption in cognitive processes in subjects at risk, leading
14 407 to delusional ideas and hallucinatory experiences, the content of which may be influenced by
15 408 the emotional change induced by the stressful events⁷⁰.

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20 409 One point that also deserves discussion is the lower levels of the positive dimensions of
21 410 subclinical psychosis among siblings in comparison to controls. This result is surprising, as
22 411 siblings of people with psychotic disorder face both a greater genetic predisposition to psychotic
23 412 disorders^{71,72}, and higher levels of psychosocial stressors, because they likely share some of the
24 413 environmental characteristics of their sibling (e.g., discrimination)^{73,74}, and the stress associated
25 414 with the psychiatric disorder of their sibling⁷⁵. Indeed, consistent with the stress-vulnerability
26 415 hypothesis, several studies found higher levels of subclinical psychosis among siblings, in
27 416 comparison to controls^{64,74,76}. One hypothesis that might explain the negative association in our
28 417 study is that siblings might minimize their symptoms, either because they compare them to the
29 418 symptoms of their sibling with a FEP, or because they fear having the same disorder, and thus
30 419 deny presenting the same symptoms. Moreover, we cannot exclude a selection bias, which may
31 420 have occurred if siblings with potentially higher subclinical psychosis scores refused
32 421 participation. Nevertheless, in our study the stronger association between CAPE scores and
33 422 self-reported discrimination in siblings is consistent with the stress-vulnerability hypothesis.
34 423 Indeed, in siblings who share the genetic liability to psychosis (i.e., a vulnerability) levels of
35 424 self-reported discrimination experiences are lower than in controls, but their effect is stronger.
36 425 A similar result has been shown concerning urbanicity, which has been associated with a higher
37 426 risk for psychotic disorders among subjects with familial liability as compared to subjects
38 427 without⁷⁷.

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43 428 Several limitations should be acknowledged. First, we performed cross-sectional
44 429 analyses of both subclinical psychosis and psychosocial stressors with retrospective assessment
45 430 for some of the variables. Due to the retrospective assessment, recall bias and reverse causality
46 431 cannot be excluded entirely. Indeed, several studies showed discrepancies between prospective
47 432 and retrospective measures⁷⁸. Retrospective assessment (e.g., for childhood trauma) may be

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3 433 biased by clinical outcomes (i.e., reverse causation issue)⁷⁹ for instance. Similarly, the
4 434 perception of discrimination could be distorted by the presence of positive symptoms. Likewise,
5 435 the perception of a low level of social capital could be influenced by depressive symptoms.
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7 436 With regard to the measure of stressful life events specifically, several issues have been
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9 437 mentioned, including intra-category variability (i.e., the fact that subjects have differing views
10 438 of what comprises a “*major*” or “*serious*” event or disease), and that this variability could also
11 439 be related to psychiatric symptoms^{53,80}. Moreover, the mean discrimination score (median of
12 440 discrimination measure: 0, IQR=1) was quite low in comparison with other studies (which
13 441 unlike our study, were conducted among ethnic minorities facing higher levels of
14 442 discrimination^{29,81,82}). This low score has been occasionally found in previous studies^{66,83}, but
15 443 should be interpreted taking into consideration that the version of the Williams’ Major
16 444 experiences of discrimination measure^{46,47} has not been validated, and its cross-national
17 445 invariance has not yet been studied. Thus, the findings may not be generalizable to other
18 446 countries (e.g., USA). Moreover, the view of discrimination as a prolonged stressor might be
19 447 misconstrued, as a major part of the experiences measured occur during adulthood. Certain
20 448 experiences may however take place during childhood, adolescence or youth (unfair treatment
21 449 when seeking medical care, discouragement from continuing education, etc.). Furthermore,
22 450 except for ethnicity, the analyses were not adjusted for other important risk factors of psychosis,
23 451 such as urbanicity and cannabis use^{84,85}. However, adjustment for all the known risk factors of
24 452 psychosis (economic deprivation, obstetrical complications, paternal age, etc.) was not
25 453 possible, and such adjustment could cause statistical overadjustment and affect genuine
26 454 relationships between subclinical psychosis and psychosocial stressors. Finally, as the sampling
27 455 was not fully at random, but a mixture of random and quota sampling and thus non-
28 456 probabilistic, we cannot assume that our sample was representative of the general population.
29 457 However, the quota sampling method warrant same socio-demographic characteristics of the
30 458 general population (age, sex, and migration) in the different countries. Moreover, we cannot
31 459 exclude the possibility of selective refusal of study inclusion according to subclinical psychosis
32 460 and/or psychosocial factors.

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51 461 Overall, this international and multicentre study assessed positive, negative and
52 462 depressive dimensions of subclinical psychosis among controls and siblings from the general
53 463 population and simultaneously analyzed the role of different psychosocial stressors. Childhood
54 464 trauma, and stressful life events were significantly associated with the three subclinical
55 465 psychosis dimensions, while lower social capital was associated with the negative and
56 466 depressive dimensions, and self-reported discrimination experiences associated with the

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467 positive dimension, consistent with independent effects of these different psychosocial
468 stressors.
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3 470 ***Acknowledgments***

471 EU-GEI WP2 Group: Kathryn Hubbard, Stephanie Beards, Simona A. Stilo, Mara Parellada,
472 Pedro Cuadrado, José Juan Rodríguez Solano, Angel Carracedo, David Fraguas, Álvaro
473 Andreu-Bernabeu, Gonzalo López, Bibiana Cabrera, Esther Lorente-Rovira, Paz Garcia-
474 Portilla, Javier Costas, Estela Jiménez-López, Mario Matteis, Marta Rapado-Castro, Emiliano
475 González, Covadonga M. Díaz-Caneja, Emilio Sánchez, Manuel Durán-Cutilla, Nathalie
476 Franke, Fabian Termorshuizen, Daniella van Dam, Elsje van der Ven, Elles Messchaart,
477 Stéphane Jamain, Thomas Charpeaud, Anne-Marie Tronche, Flora Frijda, Giovanna Marrazzo,
478 Lucia Sideli, Crocettarachele Sartorio, Fabio Seminerio, Camila Marcelino Loureiro, Rosana
479 Shuhama, Mirella Ruggeri, Chiara Bonetto, Doriana Cristofalo, Domnico Berardi, Marco Seri,
480 Elena Bonora, Giuseppe D'Andrea, Laura Ferraro, Giada Tripoli, Silvia Amoretti, Gisela
481 Mezquida

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483 ***Conflicts of interest***

484 The funder had no involvement in study design, data collection, analysis, interpretation
485 of findings, manuscript preparation or the decision to submit the paper for publication.

486 Dr. Kirkbride is supported by the National Institute for Health Research (NIHR)
487 University College London Hospital (UCLH) Biomedical Research Centre (BRC).

488 Dr. Bernardo has been a consultant for, received grant/research support and honoraria
489 from, and been on the speakers/advisory board of ABBiotics, Adamed, Angelini, Casen
490 Recordati, Janssen-Cilag, Menarini, Rovi and Takeda.

491 Dr. Arango has received support by the Spanish Ministry of Science and Innovation.
492 Instituto de Salud Carlos III (SAM16PE07CP1, PI16/02012, PI19/024), co-financed by ERDF
493 Funds from the European Commission, "A way of making Europe", CIBERSAM. Madrid
494 Regional Government (B2017/BMD-3740 AGES-CM-2), European Union Structural Funds.
495 European Union Seventh Framework Program under grant agreements FP7-4-HEALTH-2009-
496 2.2.1-2-241909 (Project EU-GEI) and FP7-HEALTH-2013-2.2.1-2-603196 (Project
497 PSYSCAN); and European Union H2020 Program under the Innovative Medicines Initiative 2
498 Joint Undertaking (grant agreement No 115916, Project PRISM, and grant agreement No
499 777394, Project AIMS-2-TRIALS), Fundación Familia Alonso and Fundación Alicia
500 Koplowitz.

501 Dr. Di Forti reports personal fees from Janssen outside the submitted work, without
502 conflict of interest with the present study.

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Table 1. Description and comparisons of the CAPE and of the psychosocial stress measures according to control/sibling status			
	Controls (N = 1497)	Siblings (N = 265)	Comparisons
	Median (IQR), mean (SD) or N (%)	Median (IQR), mean (SD) or N (%)	
Age	33 (21), 36.1 (12.9)	30 (15), 31.3 (9.4), 1.9%	< 0.01 ²
<i>Sex</i>			
Women	791 (47.2%)	181 (31.7%)	< 0.01 ¹
Men	706 (52.8%)	84 (68.3%)	
<i>Ethnicity</i>			
Asian	33 (2.2%)	3 (1.1%)	< 0.01 ¹
Black	121 (8.1%)	13 (4.9%)	
North African	24 (1.6%)	6 (2.3%)	
White	1178 (78.7%)	201 (75.9%)	
Mixed	116 (7.7%)	41 (15.5%)	
Other	24 (1.7%)	1 (3.8%)	
<i>CAPE scores</i>			
Positive	4 (4), 4.9 (2.9)	4 (4), 4.5 (3.0)	0.02 ²
Negative	6 (6), 6.2 (3.6)	6 (6), 5.8 (3.7)	0.18 ²
Depressive	4 (3), 4.4 (2.0)	4 (3), 4.2 (2.1)	0.13 ²
<i>Psychosocial stressors</i>			
Childhood trauma	31 (11), 34.6 (10.9)	33 (12), 37.3 (6.9)	< 0.01 ²
Self-reported discrimination experiences	0.0 (1.0), 0.6 (1.0)	0.0 (1.0), 0.4 (0.9)	0.02 ²
Stressful life events	1 (2), 1.5 (1.4)	1 (1), 1.5 (1.5)	0.29 ²
Social capital	0.0 (3.4), 0 (2.5)	0.1 (3.4), 0 (2.5)	0.56 ²
Abbreviations: IQR = interquartile range, NA: unavailable data, SD = standard-deviation. Legend: ¹ p-value of chi-square tests; ² p-value of Mann-Whitney.			

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Table 2. Spearman correlation matrix of the psychosocial stressors

	Childhood trauma	Self-reported discrimination experiences	Stressful life events	Social capital
Childhood trauma	1.00			
Self-reported discrimination experiences	0.17***	1.00		
Stressful life events	0.14***	0.20***	1.00	
Social capital	-0.15***	-0.08***	-0.11***	1.00

Legend: p-values: *: < 0.05, **: < 0.01, ***: < 0.001.

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	Positive dimension ¹	Negative dimension ¹	Depressive dimension ¹
Childhood trauma	0.26	0.29	0.27
Self-reported discrimination experiences	0.15	0.13	0.12
Stressful life events	0.18	0.13	0.20
Social capital	-0.13	-0.13	-0.14

¹all p-values < 0.001

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Table 4. Multivariable¹ analyses of the relationships between the Z-scores of the different psychosocial stressors and the 3-dimension scores

	Positive dimension		Negative dimension		Depressive dimension	
	β	95 % CI	β	95 % CI	β	95 % CI
Childhood trauma	0.13	[0.10; 0.17]***	0.49	[0.37; 0.61]***	0.26	[0.19; 0.33]***
Self-reported discrimination experiences	0.06	[0.02; 0.10]**	0.05	[-0.09; 0.19]	0.05	[-0.03; 0.13]
Stressful life events	0.08	[0.04; 0.12]***	0.16	[0.04; 0.28]*	0.17	[0.11; 0.24]***
Lower social capital	0.03	[0.00; 0.07]	0.26	[0.14; 0.38]***	0.13	[0.06; 0.20]***
Siblings (vs. controls)	-0.16	[-0.26; -0.05]**	-0.28	[-0.62; -0.06]	-0.19	[-0.19; 0.01]

¹Adjusted for age, sex, country, and ethnicity.
Legend: *: < 0.05, **: < 0.01, ***: < 0.001.

DISCRIMINATION

Supplementary material 1: Discrimination measure in the EUGEI study

In the following questions we are interested in the way other people have treated you or your beliefs about how other people have treated you. Can you tell me if any of the following has ever happened to you? Please indicate number of times, age at first occurrence and note the main reason for this. **Then:**

For any reason, have you ever been unfairly...

		Yes	No	N of times	Age (first occurred)
1.	Fired	<input type="text"/>	<input type="text"/>	<input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/>

Reason O1 Gender O2 Race, ethnicity O3 Religion O4 Mental Illness O5 Sexuality O6 Age O7 Other (specify):

		Yes	No	N of times	Age (first occurred)
2.	Not hired for a job	<input type="text"/>	<input type="text"/>	<input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/>

Reason O1 Gender O2 Race, ethnicity O3 Religion O4 Mental Illness O5 Sexuality O6 Age O7 Other (specify):

		Yes	No	N of times	Age
3.	Denied promotion	<input type="text"/>	<input type="text"/>	<input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/>

Reason O1 Gender O2 Race, ethnicity O3 Religion O4 Mental Illness O5 Sexuality O6 Age O7 Other (specify):

		Yes	No	N of times	Age
4.	Stopped, questioned threatened by police	<input type="text"/>	<input type="text"/>	<input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/>

DISCRIMINATION

Reason O1 O2 Race, O3 O4 Mental O5 O6 O7 Other
 Gender ethnicity Religion Illness Sexuality Age (specify):

5. Treated by court system

	Yes	No	N of times	Age

Reason O1 O2 Race, O3 O4 Mental O5 O6 O7 Other
 Gender ethnicity Religion Illness Sexuality Age (specify):

For any reason, have you ever been unfairly...

6. Discouraged from continuing education

	Yes	No	N of times	Age

Reason O1 O2 Race, O3 O4 Mental O5 O6 O7 Other
 Gender ethnicity Religion Illness Sexuality Age (specify):

7. Prevented from buying, renting flat or house

	Yes	No	N of times	Age

Reason O1 O2 Race, O3 O4 Mental O5 O6 O7 Other
 Gender ethnicity Religion Illness Sexuality Age (specify):

8. Treated by neighbours or your family

	Yes	No	N of times	Age

Reason

DISCRIMINATION

O1 Gender O2 Race, ethnicity O3 Religion O4 Mental Illness O5 Sexuality O6 Age O7 Other (specify):

9. Denied a loan or preferable mortgage rate

	Yes	No	N of times	Age
	<input type="text"/>	<input type="text"/>	<input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/>

Reason O1 Gender O2 Race, ethnicity O3 Religion O4 Mental Illness O5 Sexuality O6 Age O7 Other (specify):

10. Received worse service than other people

	Yes	No	N of times	Age
	<input type="text"/>	<input type="text"/>	<input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/>

Reason O1 Gender O2 Race, ethnicity O3 Religion O4 Mental Illness O5 Sexuality O6 Age O7 Other (specify):

11. Treated when getting medical care

	Yes	No	N of times	Age
	<input type="text"/>	<input type="text"/>	<input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/>

Reason O1 Gender O2 Race, ethnicity O3 Religion O4 Mental Illness O5 Sexuality O6 Age O7 Other (specify):

12. Treated when using public transport

	Yes	No	N of times	Age
	<input type="text"/>	<input type="text"/>	<input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/>

Reason O1 Gender O2 Race, ethnicity O3 Religion O4 Mental Illness O5 Sexuality O6 Age O7 Other (specify):

Supplementary Table 1. Proportions of unavailable data (%)		
	Controls (N = 1497)	Siblings (N = 265)
<i>Age</i>	0.2%	1.9%
<i>Sex</i>	0.0%	0.0%
<i>Ethnicity</i>	0.1%	0.0%
<i>CAPE scores</i>		
Positive	5.3%	8.3%
Negative	4.5%	6.8%
Depressive	4.8%	6.8%
<i>Psychosocial stressors</i>		
Childhood trauma	0.8%	3.8%
Self-reported discrimination experiences	4.4%	4.5%
Stressful life events	16.5%	17.4%
Social capital	10.4%	7.5%

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Supplementary Table 2. Spearman correlation matrix of the psychosocial stressors among controls and siblings				
<i>CONTROLS</i>				
	Childhood trauma	Self-reported discrimination experiences	Stressful life events	Social capital
Childhood trauma	1.00			
Self-reported discrimination experiences	0.17***	1.00		
Stressful life events	0.13***	0.20***	1.00	
Social capital	-0.14***	-0.09***	-0.13***	1.00
<i>SIBLINGS</i>				
	Childhood trauma	Self-reported discrimination experiences	Stressful life events	Social capital
Childhood trauma	1.00			
Self-reported discrimination experiences	0.24***	1.00		
Stressful life events	0.21**	0.26***	1.00	
Social capital	-0.19***	-0.08	0.03	1.00

Legend: p-values: *: < 0.05, **: < 0.01, ***: < 0.001.

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Supplementary Table 3. Spearman correlations between CAPE scores and psychosocial stressors among controls and siblings			
<i>CONTROLS</i>			
	Positive dimension	Negative dimension	Depressive dimension
Childhood trauma	0.26***	0.30***	0.26***
Self-reported discrimination experiences	0.14***	0.12***	0.10***
Stressful life events	0.19***	0.13***	0.19***
Social capital	-0.13***	-0.12***	-0.13***
<i>SIBLINGS</i>			
	Positive dimension	Negative dimension	Depressive dimension
Childhood trauma	0.26***	0.27***	0.35***
Self-reported discrimination experiences	0.24***	0.21***	0.19**
Stressful life events	0.19**	0.18*	0.27***
Social capital	-0.12	-0.20**	-0.22***
Legend: p-values: *: < 0.05, **: < 0.01, ***: < 0.001.			

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Supplementary Table 4. Multivariable analyses of the relationships between the Z-scores of the different psychosocial stressors and the CAPE scores among pooled siblings and controls						
	Positive dimension		Negative dimension		Depressive dimension	
	β	95 % CI	β	95 % CI	β	95 % CI
<i>One model per interaction¹</i>						
Childhood trauma x self-reported discrimination experiences	-0.03	[-0.06; 0.01]	0.00	[-0.09; 0.10]	0.00	[-0.01; 0.00]
Self-reported discrimination experiences x stressful life events	-0.01	[-0.03; 0.01]	-0.01	[-0.08; 0.06]	-0.03	[-0.06; 0.06]
Self-reported discrimination experiences x low social capital	0.00	[-0.03; 0.03]	-0.06	[-0.17; 0.05]	-0.03	[-0.07; 0.01]
Childhood trauma x stressful life events	-0.01	[-0.03; 0.02]	-0.02	[-0.09; 0.05]	-0.04	[-0.02; 0.06]
Childhood trauma x low social capital	-0.03	[-0.06; 0.00]	-0.04	[-0.15; 0.07]	0.02	[-0.10; 0.02]
Low social capital x stressful life events	0.02	[-0.01; 0.04]	0.04	[-0.04; 0.12]	0.01	[-0.03; 0.06]
<i>All interaction terms in one single model²</i>						
Childhood trauma x self-reported discrimination experiences	-0.10	[-0.23; 0.02]	-0.10	[-0.61; 0.20]	-0.01	[-0.26; 0.24]
Self-reported discrimination experiences x stressful life events	-0.13	[-0.32; 0.05]	-0.13	[-0.59; 0.57]	0.01	[-0.34; 0.37]
Self-reported discrimination experiences x low social capital	-0.08	[-0.31; 0.15]	0.02	[-0.76; 0.73]	-0.14	[-0.58; 0.30]
Childhood trauma x stressful life events	0.00	[-0.07; 0.08]	0.00	[-0.26; 0.24]	0.05	[-0.09; 0.20]
Childhood trauma x low social capital	-0.04	[-0.14; 0.06]	-0.04	[-0.14; 0.10]	-0.12	[-0.31; 0.07]
Low social capital x stressful life events	0.02	[-0.07; 0.10]	0.02	[-0.04; 0.08]	0.09	[-0.07; 0.26]
¹ The interaction terms were introduced one by one in the multivariable analyses with the following factors: psychosocial stressors (childhood trauma, self-reported discrimination experiences, stressful life events, low social capital) and the adjustment factors (age, sex, ethnicity, country and sibling/control status); ² All interaction terms in the same model, with the same adjustment factors. Legend: *: < 0.05, **: < 0.01, ***: < 0.001.						

Supplementary Table 5. Multivariable¹ analyses of the associations between the CAPE and the Z-scores of the psychosocial stressors among controls and siblings						
<i>CONTROLS</i>						
	Positive dimension		Negative dimension		Depressive dimension	
	β	95 % CI	β	95 % CI	β	95 % CI
Childhood trauma	0.14	[0.10; 0.18]***	0.44	[0.33; 0.60]***	0.24	[0.17; 0.32]***
Self-reported discrimination experiences	0.05	[0.01; 0.10]*	0.05	[-0.09; 0.20]	0.05	[-0.03; 0.13]
Stressful life events	0.08	[0.04; 0.12]***	0.16	[0.03; 0.29]*	0.18	[0.11; 0.25]***
Lower social capital	0.03	[-0.01; 0.07]	0.22	[0.09; 0.35]**	0.10	[0.03; 0.18]**
<i>Interactions between psychosocial stressors</i>						
Childhood trauma x self-reported discrimination experiences	-0.03	[-0.06; 0.01]	0.03	[-0.08; 0.13]	0.00	[-0.06; 0.06]
Self-reported discrimination experiences x stressful life events	-0.01	[-0.03; 0.01]	0.00	[-0.07; 0.07]	-0.03	[-0.07; 0.01]
Self-reported discrimination experiences x lower social capital	0.01	[-0.03; 0.04]	-0.04	[-0.15; 0.07]	-0.02	[-0.09; 0.04]
Childhood trauma x stressful life events	-0.01	[-0.03; 0.02]	-0.02	[-0.10; 0.06]	0.02	[-0.03; 0.06]
Childhood trauma x lower social capital	-0.03	[-0.07; 0.01]	-0.03	[-0.15; 0.10]	-0.04	[-0.11; 0.03]
Lower social capital x stressful life events	0.02	[-0.01; 0.05]	0.03	[-0.05; 0.12]	0.01	[-0.04; 0.06]
<i>SIBLINGS</i>						
	Positive dimension		Negative dimension		Depressive dimension	
	β	95 % CI	β	95 % CI	β	95 % CI
Childhood trauma	0.09	[-0.01; 0.20]	0.58	[0.26; 0.90]***	0.32	[0.12; 0.52]**
Self-reported discrimination experiences	0.21	[0.03; 0.39]*	0.27	[-0.29; 0.82]	0.17	[-0.18; 0.51]
Stressful life events	0.12	[0.00; 0.24]	0.18	[-0.19; 0.55]	0.11	[-0.11; 0.34]
Lower social capital	0.08	[-0.03; 0.19]	0.50	[0.16; 0.85]**	0.30	[0.09; 0.51]**
<i>Interactions between psychosocial stressors</i>						
Childhood trauma x self-reported discrimination experiences	-0.15	[-0.27; -0.03]*	-0.25	[-0.61; 0.12]	-0.04	[-0.26; 0.19]
Self-reported discrimination experiences x stressful life events	-0.15	[-0.31; 0.01]	-0.11	[-0.60; 0.38]	0.05	[-0.25; 0.35]
Self-reported discrimination experiences x lower social capital	-0.09	[-0.29; 0.10]	-0.17	[-0.79; 0.44]	-0.21	[-0.58; 0.15]
Childhood trauma x stressful life events	-0.01	[-0.08; 0.06]	-0.03	[-0.25; 0.19]	0.06	[-0.07; 0.20]
Childhood trauma x lower social capital	-0.01	[-0.04; 0.06]	-0.18	[-0.44; 0.09]	-0.10	[-0.27; 0.06]
Lower social capital x stressful life events	0.01	[-0.06; 0.09]	0.08	[-0.15; 0.32]	0.06	[-0.09; 0.20]

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¹Adjusted for age, sex, ethnicity, and country.
Legend: *: < 0.05, **: < 0.01, ***: < 0.001.