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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)

INTRODUCTION

The stress-vulnerability theory of psychotic disorders posits that genetic factors interact with environmental stressors in the development of a disorder[1–3]. In this theoretical model, increased sensitivity to stress plays an important role in both onset and relapse of psychotic disorders, including schizophrenia. Extending this model, the stress sensitization hypothesis proposes that repeated exposure to environmental stressors sensitizes key neurobiological pathways to psychosis[4,5]. Early, severe or prolonged exposure to stress would lead to a dysregulated stress response and potentially explain both the role of early and current stress in the etiology of psychotic disorders.

Several environmental factors that could be conceptualized as psychosocial stressors, such as childhood trauma, stressful life events, discrimination experiences or a low level of social capital have been found to increase the risk of psychotic disorders[6–9]. Furthermore, several studies support a stress sensitization model in psychosis, showing for example that exposure to an early stressor (childhood trauma) increases later sensitivity to other stressors (e.g., social stress, population density, etc.) in patients (environment-environment ExE interaction)[10,11]. However, the fact that these studies have taken place after the onset of psychotic disorder raises causality concerns. Indeed, the assessment of recent stress could be confounded by several stressors associated with the disease itself, such as hospitalizations, stigma, substance use disorders or social drift after onset[12–14].

Psychotic symptoms may be present, to varying degrees, in non-clinical, general population samples who do not meet criteria for a clinical disorder[15–17]. The continuum theory of psychosis posits that subclinical experiences have a similar origin/etiology to full psychotic disorders[18–22]. Thus, studying risk factors associated with subclinical psychosis may provide insights into the etiology of psychosis, while reducing the potential interference of reverse causation, i.e., stress caused by the clinical disorders themselves. Furthermore, in line with the continuum theory, subclinical psychosis can be characterized by quantitative (continuous) variables, improving statistical power and the capacity to control for more potential confounders.

Several studies have previously reported associations between psychosocial stressors and subclinical psychosis. For instance, childhood trauma has been associated with increased rates of isolated psychotic symptoms in several studies[23–26]. Likewise, negative and/or stressful life events[27,28] or self-reported discrimination experiences[29] have also been associated with subclinical psychosis.

One major limitation of studies published to date is that psychosocial stressors have usually been studied in isolation, which might lead to spurious or incomplete conclusions given the likely presence of confounding/interaction with other stressors. Further work is needed to determine whether different psychosocial stressors have independent effects on subclinical psychosis and underlying dimensions (i.e., positive, negative, depressive), while controlling for other relevant stressors. Moreover, the role of population-level (e.g., social capital) factors that might interact with psychosocial stressors has rarely been explored. For example, social capital has been related to the incidence and outcome of psychotic disorders[30,31] and low levels of social capital could be a stressful condition *per se*[32] (i.e., an independent stressor), or exacerbate the effects of other psychosocial factors (discrimination, trauma, stressful life events) on subsequent psychosis risk, but evidence is lacking. Relationships between social capital and subclinical psychosis have never been investigated. Moreover, to the best of our knowledge, only two studies have analyzed the role of multiple psychosocial stressors on subclinical psychosis. The first found arguments in favor of the sensitization hypothesis[33]. The second, studying the role of childhood trauma alongside other environmental and genetic risk factors, found additive effects of these factors on subclinical psychosis scores[21].

Furthermore, recent studies have reported that exposure to psychosocial stressors was in part dependent on genetic vulnerability to psychosis[34,35], and no study has compared associations between psychosocial stressors and subclinical psychosis in both control participants and (healthy) siblings of people with a psychotic disorder. Including both groups may help tease out the genetic and environmental etiology of psychosis.

To address some of the limitations of previous work, we used a large, cross-national sample of population-based controls and siblings of subjects with a psychotic disorder, to investigate whether there was (i) an association between subclinical psychosis dimensions (positive, negative and depressive) and psychosocial stressors, and (ii) any evidence of ExE interactions between different psychosocial stressors in line with the stress sensitization hypothesis. The psychosocial stressors we explored can be conceptualized as either "early" (childhood trauma) or "prolonged" (discrimination, low level of social capital, stressful life experiences). We hypothesized that exposure to "early" stressors would enhance the effect of 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 FEP[36]. 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 population[39]. 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 dimensions[40]. 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

across the six countries[43]. Thus, CAPE results can be reliably used across the different EUGEI countries.

Psychosocial stressors measure

Childhood trauma was assessed with the Childhood Trauma Questionnaire (CTQ), a 25-item questionnaire, that measures five different domains (emotional and physical neglect; emotional, physical and sexual abuse). All items are scored on a five-point Likert-scale (1: never, to 5: very often). We used the CTQ total score as the sum of all items, thus theoretically ranging from 25-125[44].

Lifetime self-reported discrimination experiences were assessed with a modified version of the Williams' major experiences of discrimination measure (available in **Supplementary Material 1**), a 12-item scale assessing several experiences of discrimination (unfairly fired or not hired because of your ethnicity/sex/weight/etc., unfairly stopped/questioned/physically threatened or abused by the police, etc.)[45,46]. This version of the Williams' scale has already been used in a paper studying the prevalence of discrimination in South London, and its relationships with psychiatric disorders[47]. We used a total discrimination score by adding all endorsed items, ranging theoretically from 0-12.

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

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

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

Other adjustment variables

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

Ethical procedures

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

Statistical methods

First, we assessed the associations between psychosocial stressors using Spearman correlation tests. Then we analyzed the relationships between these stressors and the three CAPE dimensions scores also using Spearman correlation tests. We used Mann-Whitney U-tests to assess the differences in exposure to psychosocial stressors between controls and siblings.

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

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

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

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

Significance was based on a two-sided p-value of 0.05 throughout. R software version 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 (*rho* between 0.14 and 0.20), and negative correlations between high level of social capital and the 3 psychosocial stressors (rho 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

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

- TABLE 3 -

Multivariable modelling

After adjusting for sex, age, ethnicity, country, and control/sibling status, the different CAPE scores were independently associated with childhood trauma (β with Z-score of childhood trauma between 0.13 and 0.49) and stressful life events (β between 0.08 and 0.17). Lower social capital was associated with negative and depressive dimensions (β between 0.05 and 0.24), while self-reported discrimination experiences were only associated with the positive dimension (β=0.06). None of the interaction terms of the psychosocial stressor measures (both when introduced one by one in the multivariable analyses, and in the models with all the interactions terms) were associated with any of the 3 dimensions (see **Supplementary Table 4** for the results of the interactions). Of note, sibling status was associated with lower scores on the positive dimension (β=-0.16). The detailed results of the multivariable analyses with Z-scores of the psychosocial measures are available in the **Table 4**.

The same multivariable analyses were repeated separately for siblings and controls, and revealed globally similar results. Of note, among siblings, fewer associations reached statistical significance, and the interaction between childhood trauma and discrimination was significant (negative interaction: β=-0.15, more details of the multivariable analyses within controls and siblings in **Supplementary Table 5**).

- TABLE 4 -

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 population[56], 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 adolescents[32]), while previous studies found associations with the incidence of psychotic disorders[30]. This result is consistent with other studies regarding the influence of neighborhood characteristics such as as deprivation or social fragmentation on psychosis outcomes[6], 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

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

Analyzing the influence of environmental (including childhood trauma, cannabis use and urbanicity), sensory (hearing impairment), and familial risk factors on the occurrence of subclinical psychosis in 6,646 subjects from the general population, Pries et al. found additive effects of the risk factors: the greater the number of risk factors, the greater the odds of symptoms[21]. Consistent with this finding, in our study, the effect of recent adverse experiences (measured by the LTE) was significant for each of the 3 dimensions, independently of early adverse experience (measured by childhood trauma), and we did not find any significant interactions between the different psychosocial stressors. This may be due to a lack of statistical power to detect an ExE interaction[59], however the β values of the interactions, which are close to 0 make this unlikely.

Childhood trauma, i.e., the earliest psychosocial stressor, had the strongest associations with each of the three dimensions measured. Childhood adverse experiences have been linked with long-term changes in the hypothalamic-pituitary axis (HPA) axis[60] which may be involved in early stressor and emotional dysregulation, leading to later aberrant salience, involved in the positive dimension of psychosis[61]. Of note, childhood trauma is known to be associated with psychopathology as a whole[62,63], and consistent with prior research, childhood trauma in our study was also associated with the negative dimension[64] as well as with depressive symptoms[65] in both controls and siblings.

Self-reported discrimination experiences were associated with the positive dimension of psychosis in the global sample. Several studies, including longitudinal studies[66], have shown associations, particularly with psychotic-like experiences. They have been confirmed in recent

meta-analyses[9,29]. Consistently with the present study, some studies suggest that among the different dimensions of subclinical psychosis discrimination is specifically associated with positive psychotic symptoms[9,67]. However in contrast with the present study, discrimination experiences have also been linked to depression[68].

The associations between CAPE scores and stressful life events support the role of recent adverse experiences in the development of psychosis[8,61]. Psychosis has been theorized to combine cognitive (external attribution) bias and emotional dysregulation[69]. Stressful life events could play a trigger role for a disruption in cognitive processes in subjects at risk, leading to delusional ideas and hallucinatory experiences, the content of which may be influenced by the emotional change induced by the stressful events[70].

One point that also deserves discussion is the lower levels of the positive dimensions of subclinical psychosis among siblings in comparison to controls. This result is surprising, as siblings of people with psychotic disorder face both a greater genetic predisposition to psychotic disorders[71,72], and higher levels of psychosocial stressors, because they likely share some of the environmental characteristics of their sibling (e.g., discrimination)[73,74], and the stress associated with the psychiatric disorder of their sibling[75]. Indeed, consistent with the stress-vulnerability hypothesis, several studies found higher levels of subclinical psychosis among siblings, in comparison to controls[64,74,76]. One hypothesis that might explain the negative association in our study is that siblings might minimize their symptoms, either because they compare them to the symptoms of their sibling with a FEP, or because they fear having the same disorder, and thus deny presenting the same symptoms. Moreover, we cannot exclude a selection bias, which may have occurred if siblings with potentially higher subclinical psychosis scores refused participation. Nevertheless, in our study the stronger association between CAPE scores and self-reported discrimination in siblings is consistent with the stress-vulnerability hypothesis. Indeed, in siblings who share the genetic liability to psychosis (i.e., a vulnerability) levels of self-reported discrimination experiences are lower than in controls, but their effect is stronger. A similar result has been shown concerning urbanicity, which has been associated with a higher risk for psychotic disorders among subjects with familial liability as compared to subjects without[77].

Several limitations should be acknowledged. First, we performed cross-sectional analyses of both subclinical psychosis and psychosocial stressors with retrospective assessment for some of the variables. Due to the retrospective assessment, recall bias and reverse causality cannot be excluded entirely. Indeed, several studies showed discrepancies between prospective and retrospective measures[78]. Retrospective assessment (e.g., for childhood trauma) may be

biased by clinical outcomes (i.e., reverse causation issue)[79] for instance. Similarly, the perception of discrimination could be distorted by the presence of positive symptoms. Likewise, the perception of a low level of social capital could be influenced by depressive symptoms. With regard to the measure of stressful life events specifically, several issues have been mentioned, including intra-category variability (i.e., the fact that subjects have differing views of what comprises a "*major*" or "*serious*" event or disease), and that this variability could also be related to psychiatric symptoms[53,80]. Moreover, the mean discrimination score (median of discrimination measure: 0, IQR=1) was quite low in comparison with other studies (which unlike our study, were conducted among ethnic minorities facing higher levels of discrimination[29,81,82]). This low score has been occasionally found in previous studies[66,83], but should be interpreted taking into consideration that the version of the Williams' Major experiences of discrimination measure[46,47] has not been validated, and its cross-national invariance has not yet been studied. Thus, the findings may not be generalizable to other countries (e.g., USA). Moreover, the view of discrimination as a prolonged stressor might be misconstrued, as a major part of the experiences measured occur during adulthood. Certain experiences may however take place during childhood, adolescence or youth (unfair treatment when seeking medical care, discouragement from continuing education, etc.). Furthermore, except for ethnicity, the analyses were not adjusted for other important risk factors of psychosis, such as urbanicity and cannabis use[84,85]. However, adjustment for all the known risk factors of psychosis (economic deprivation, obstetrical complications, paternal age, etc.) was not possible, and such adjustment could cause statistical overadjustment and affect genuine relationships between subclinical psychosis and psychosocial stressors. Finally, as the sampling was not fully at random, but a mixture of random and quota sampling and thus non-probabilistic, we cannot assume that our sample was representative of the general population. However, the quota sampling method warrant same socio-demographic characteristics of the general population (age, sex, and migration) in the different countries. Moreover, we cannot exclude the possibility of selective refusal of study inclusion according to subclinical psychosis and/or psychosocial factors.

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

positive dimension, consistent with independent effects of these different psychosocial stressors.

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Conflicts of interest

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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]
Sex			
Women	791 (47.2%)	181 (31.7%)	< 0.01[1]
Men	706 (52.8%)	84 (68.3%)	
Ethnicity			
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%)	
CAPE scores			
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]
Psychosocial stressors			
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.

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.

Table 3. Spearman correlations between CAPE scores and psychosocial stressors

	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

[1]all p-values < 0.001

Table 4. Multivariable[1] 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]

[1]Adjusted 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**	☐	☐	☐☐	☐☐

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**	☐	☐	☐☐	☐☐

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**	☐	☐	☐☐	☐☐

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**	☐	☐	☐☐	☐☐

DISCRIMINATION

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

	Yes	No	N of times	Age
5. Treated by court system	☐	☐	☐☐	☐☐

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

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

	Yes	No	N of times	Age
6. Discouraged from continuing education	☐	☐	☐☐	☐☐

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

	Yes	No	N of times	Age
7. Prevented from buying, renting flat or house	☐	☐	☐☐	☐☐

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

	Yes	No	N of times	Age
8. Treated by neighbours or your family	☐	☐	☐☐	☐☐

Reason _____

DISCRIMINATION

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

	Yes	No	N of times	Age
9. Denied a loan or preferable mortgage rate	☐	☐	☐☐	☐☐

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

	Yes	No	N of times	Age
10. Received worse service than other people	☐	☐	☐☐	☐☐

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

	Yes	No	N of times	Age
11. Treated when getting medical care	☐	☐	☐☐	☐☐

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

	Yes	No	N of times	Age
12. Treated when using public transport	☐	☐	☐☐	☐☐

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)
Age	0.2%	1.9%
Sex	0.0%	0.0%
Ethnicity	0.1%	0.0%
CAPE scores		
Positive	5.3%	8.3%
Negative	4.5%	6.8%
Depressive	4.8%	6.8%
Psychosocial stressors		
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%

Supplementary Table 2. Spearman correlation matrix of the psychosocial stressors among controls and siblings

CONTROLS

	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

SIBLINGS

	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.

Supplementary Table 3. Spearman correlations between CAPE scores and psychosocial stressors among controls and siblings

CONTROLS

	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***

SIBLINGS

	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.

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
One model per interaction[1]						
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]
All interaction terms in one single model[2]						
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. Multivariable[1] analyses of the associations between the CAPE and the Z-scores of the psychosocial stressors among controls and siblings

CONTROLS

	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]**
Interactions between psychosocial stressors						
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]

SIBLINGS

	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]**
Interactions between psychosocial stressors						
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]

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