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Evidence for interaction between genetic liability and childhood trauma in the development of psychotic symptoms

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Abstract

Purpose Whilst childhood trauma (CT) is a known risk factor across the spectrum of psychosis expression, little is known about possible interplay with genetic liability.

Methods The TwinssCan Study collected data in general population twins, focussing on expression of psychosis at the level of subthreshold psychotic experiences. A multilevel mixed-effects linear regression analysis was performed including 745 subjects to assess the interaction between genetic liability and CT. The Symptom Checklist-90 (SCL-90-R) score of the co-twin was used as an indirect measure of genetic liability to psychopathology, while the Childhood Trauma Questionnaire Short-Form (CTQ-SF) was used to assess CT in the domains of physical, emotional and sexual abuse, as well as physical and emotional neglect. The Community Assessment of Psychic Experience (CAPE) questionnaire was used to phenotypically characterize psychosis expression.

Results In the model using the CAPE total score, the interaction between CT and genetic liability was close to statistical significance ($\chi^2 = 5.6$, $df = 2$, $p = 0.06$). Analyses of CAPE subscales revealed a significant interaction between CT and genetic liability ($\chi^2 = 8.8$, $df = 2$, $p = 0.012$) for the CAPE-negative symptoms subscale, but not for the other two subscales (i.e. positive and depressive).

Conclusion The results suggest that the impact of CT on subthreshold expression of psychosis, particularly in the negative subdomain, may be larger in the co-presence of significant genetic liability for psychopathology.

Keywords Psychotic symptoms · Gene–environment interaction · Childhood trauma · General population · Genetic liability

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Introduction

Studying risk factors for schizophrenia can be important because of the high burden of this illness. However, there is interplay between genetic liability and environment, making the search for risk factors more complicated.

Psychotic syndromes present on a spectrum of severity ranging from subthreshold 'schizotypy' states, characterised by subclinical psychotic experiences in the general population at one end of the spectrum, to the diagnosis of schizophrenia indicating relatively poor outcome at the other end [1]. Studying psychosis expression in the general population, below the threshold of clinical need, may shed light on mechanisms that drive expression across the spectrum and now represents a widely used paradigm [2]. The spectrum of psychotic syndromes shows a variation in both the severity of symptoms and a variation in symptom-patterns experienced by individuals [3]. It is important to acknowledge the multidimensional expression of the psychotic syndrome, especially with respect to subclinical psychotic experiences. In the general population subclinical psychotic experiences may refer to isolated psychotic symptoms, in specific domains, that are not severe enough for a psychiatric diagnosis, but are associated with increased risk for suicidal behaviour, nonpsychotic psychiatric disorders and functional disability [4]. For this reason, dimensions of psychosis in the general population can be seen as different outcomes that need to be studied separately.

Epidemiological research has identified various environmental risk factors for psychotic disorder and expression across the spectrum of severity, opening up the possibility to examine gene–environment interplay using direct and indirect measures of genetic risk [5, 6]. Meta-analytic work suggests that childhood trauma (CT) is an important environmental risk factor for psychotic disorder [7]. A study in children aged 12 years reported that CT was associated with psychotic symptoms regardless of whether these events occurred early in life or later in childhood [8]. CT is a broad concept, which includes a number of severe and adverse experiences from either a sexual, physical or emotional origin. In the present paper, CT is defined as physical abuse, physical neglect, emotional abuse, emotional neglect and sexual abuse. Other domains of childhood adversity such as bullying, domestic violence, parental death were not included. As the genetic component of schizophrenia risk [9] as well as its overlap with genetic liability for affective and other syndromes [10–12] are well established, interplay between CT and genetic risk can be examined.

The increased vulnerability of subjects at high-risk for psychosis can be related to environmental risk factors such as CT, as demonstrated by a recent meta-analysis [13].

However, the role of genetic and epigenetic risk factors in this association remains to be further clarified [14]. Several studies have explored the interaction between specific genes and CT in the development of psychosis, but lack information on overall genetic risk [5, 15–17]. In this regard, the polygenic risk score provides a promising variable, since the entire scope of genome-wide association can be turned into a simple measure [18]. To this date, only Trotta and colleagues have explored whether a polygenic risk score modifies the association between CT and psychosis [19]. As a result of an underpowered sample, their study was not able to detect the likely genetic and environmental interactions in psychosis [19]. The present study also uses a measure of overall genetic liability as opposed to studies assessing specific genes [5, 16, 17], but does not use GWAS results. The twin design represents a useful way to study gene–environment interplay, as the level of psychopathology in one twin can be used as a marker of genetic risk for psychopathology in the other, depending on the degree of shared genes (100% for monozygotic [MZ] twins and 50% for dizygotic [DZ] twins).

The aim of the present study is to examine whether the level of psychotic experiences in twins is increased as a function of the interaction between environmental risk (CT) and genetic liability. Since the expression of the psychotic syndrome is multidimensional [20], three dimensions were analysed separately: positive symptoms, negative symptoms and depressive symptoms.

Methods

Sample and response

Participants were recruited from the East Flanders Prospective Twin Survey (EFPTS [21]), a prospective population-based, multi-birth registry situated in Flanders, Belgium. Zygosity was determined through sequential analysis based on sex, fetal membranes, umbilical cord blood groups, placental alkaline phosphatase, and DNA fingerprints. The TwinssCan project collected data on adolescents and young adults from the EFPTS [22]. The study population is aged between 15 and 35 years and includes twins, their siblings, and parents. Participants were included if they understood the study procedure, were able to provide valid, reliable, and complete data, that is from all twins in the twin pair or triplet.

988 twin pairs who were registered in the EFPTS, fulfilled the inclusion criteria and who earlier indicated that they would not mind to participate in scientific research were invited to participate in the TwinssCan project. 297 twin pairs responded (30%). In addition, an announcement was

made in the newsletter that is sent to all twins in the EFPTS to recruit more participants. This resulted in an extra 96 twin pairs. Since there were 6 triplets the total number of participants is 792.

All participants gave written informed consent; for participants below the age of 18, parents also signed an informed consent. Participants were excluded if they had a pervasive mental disorder as indicated by caregivers. The local ethics committee (Commissie Medische Ethiek van de Universitaire ziekenhuizen KU Leuven, Nr. B32220107766) approved the study. For the present analysis, siblings and parents were excluded.

Instruments

The Community Assessment of Psychic Experience (CAPE) is a self-report instrument including items on lifetime psychotic experiences (positive, negative, depressive) [23]. Mark and Toulopoulou [4] confirmed the factorial validity of CAPE's 3-dimensional structure and the subscale structures to facilitate for diverse research objectives in clinical use. For the present paper, the 42-item version was used. It has a high internal stability for detecting subthreshold experiences and adequate reliability and validity [23]. The CAPE measures both frequency and distress. For the present paper, only the frequency items were used. Those were measured on a four-point Likert scale; never (1), sometimes (2), often (3), nearly always (4). The CAPE overall sum score as well as the subscales of positive, negative, and depressive symptoms were outcomes in the present study. Measures of hypomania and disorganization are not included in the CAPE, given the complexity of capturing these by self-report in the general population.

The Childhood Trauma Questionnaire Short-Form (CTQ-SF) is a retrospective 28-item self-report questionnaire used to assess the extent to which the respondents experienced five types of negative childhood experiences: physical, sexual, and emotional abuse, and physical and emotional neglect [24]. If necessary, item scores were reversed. Three items assessed the validity of the questionnaire; these were excluded from the sum score. Each clinical subscale includes five items, and severity scores for each subscale can range between 5 and 25 [17, 24].

Due to the fact that the association between CTQ-SF and CAPE was non-linear, sum scores of the CTQ-SF were categorised. All subjects scoring above the cutoff point for moderate or severe CT as defined by Bernstein, Fink [17] (physical abuse 10, physical neglect 10, emotional abuse 13, emotional neglect 15, sexual abuse 8), were defined as CT in a dichotomous variable.

The Symptom Checklist-90-Revised (SCL-90-R) is a frequently used instrument including 90 items to screen psychopathology [25, 26] and it is available in the Dutch language [27]. Reliability and validity of the SCL-90-R have been established previously [26, 28]. SCL-90-R total sum scores at baseline and at first follow-up (after 1 year) were averaged to obtain co-twin psychopathology scores (see below).

Genetic liability was defined on the basis of (i) the level of psychopathology of the co-twin as assessed with the SCL-90-R [29] and (ii) the level of shared genes in the co-twin, consistent with previous papers [30–32]. The correlation in psychopathology score between MZ and DZ twins is the result of genetics or noise, assuming the degree of sharing an exposure to environmental risk factors is similar for MZ and DZ twins [31]. Co-twins scoring in the lowest three quartiles of the SCL-90-R total score were defined as having a low level of psychopathology and those scoring in the highest quartile as having a high level of psychopathology. Three categories of genetic liability were thus generated: (1) the co-twin has a low psychopathology score (MZ DZ low); (2) the dizygotic co-twin has a high psychopathology score (DZ high); (3) the monozygotic co-twin has a high psychopathology score (MZ high).

Statistical analyses

All analyses were performed using Stata 13 [33]. The data had a multilevel structure with individuals being clustered within twin pairs. Therefore, multilevel mixed-effects linear regression analyses were performed. The dependent variables were the CAPE total score and the positive, negative, and depressive subscales of the CAPE. The main independent variables were CT and genetic liability. In addition, the interaction CT * genetic liability was added to all models. Since linear regression was performed, interaction was analysed on an additive scale [34]. Age and gender were included as confounders. When the p value of the interaction CT * genetic liability was below 0.1, the Stata lincom routine was used to obtain regression coefficients of CT across the different categories of genetic liability.

Results

For the present analysis, data pertaining to 745 twins without missing data were used (genetic liability was missing in 37 twins). The present sample included both males and females, and both dizygotic and monozygotic twins. Sixty percent was female and the mean age was 17.2 years (Tables 1, 2). Ethnicity in the sample was rather homogeneous (96.2% speaks the Flemish language). A total of 138 subjects (18.5%) had at least one type of CT (Table 3). This was similar to or lower than other general population samples (Brazil 17% [35]; China, no total, subscales 11, 7, 2, 2, 5, respectively [36]) and far lower than various patient groups and a

Table 1 Descriptive statistics: dichotomous variables

	N (%)
Number of study subjects	745
Genetic psychopathology risk factor	
MZ DZ low[a]	562 (75.4%)
DZ high	113 (15.2%)
MZ high	70 (9.4%)
Gender	
Male	299 (40.1%)
Female	446 (59.9%)
Age categories	
14–15 year	329 (44.2%)
16–18 year	260 (34.9%)
19–34 year	156 (20.9%)
Number of twins	
MZ	269 (36.1%)
DZ	476 (63.9%)

[a]Dizygotic high risk (DZ high), monozygotic high risk (MZ high); monozygotic and dizygotic low risk (MZ DZ low)

Table 2 Descriptive statistics: continuous variables

Variables	N	Mean	SD	Range
Overall sum score CTQ-SF[a]	745	34.0	8.0	25–82
Age	745	17.2	3.3	14–34
Overall sum score CAPE	745	65.9	10.9	44–127
Subscale-positive CAPE	745	28.3	5.5	20–62
Subscale-negative CAPE	745	23.5	4.8	14–46
Subscale depression CAPE	745	14.1	2.9	8–29

[a]Childhood Trauma Questionnaire Short-Form (CTQ-SF); Community Assessment of Psychotic Experience questionnaire (CAPE)

Table 3 Distribution of types of childhood trauma (CT) determined by scores on the Childhood Trauma Questionnaire Short-Form (CTQ-SF) in our study population consisting of 745 twins from the general population

	N	%
Physical abuse	10	1.3
Physical neglect	68	9.1
Emotional abuse	69	9.3
Emotional neglect	41	5.5
Sexual abuse	22	2.9
Total	138	18.5

homeless control sample [36–38]. CT and genetic liability were associated ($\chi^2 = 8.2$, $df = 2$, $p = 0.016$). The proportion of subjects exposed to CT differed with a maximum of 10% between the strata of genetic liability (16%, 26% and 26% in MZ DZ low, DZ high and MZ high, respectively).

In the regression model of the CAPE total score, the interaction between CTQ-SF and genetic liability was close to statistical significance ($\chi^2 = 5.6$, $df = 2$, $p = 0.06$, table 4). The

CAPE subscale for negative symptoms showed a significant interaction with genetic liability ($\chi^2 = 8.8$, $df = 2$, $p = 0.012$, Table 4). Thus, the association between CT and negative symptoms was significantly higher in the MZ high group than both the low group and the DZ high group (Fig. 1). Although the interaction was not statistically significant, the Stata lincom routine showed a similar pattern in the total CAPE (Fig. 1). No significant interaction between CT and genetic liability was found for the CAPE-positive or depressive symptoms subscales (Table 4). The regression coefficients of the associations between CT and positive symptoms and between CT and depressive symptoms were 3.1 ($p < 0.001$) and 1.7 ($p < 0.001$), respectively (Table 4).

Discussion

The interaction between CT and genetic liability in the association with psychotic symptoms, measured with the CAPE, was close to statistical significance. This was driven by a significant interaction between CT and genetic liability in the model of the CAPE-negative symptoms subscale. This tentatively suggests that there is an interaction between CTQ-SF and genetic liability.

Despite the large differences when analysing the CAPE total score, regression coefficients of 5.8, 4.7 and 12.4 were not significantly different from each other. In general, a large sample size is required to show interaction [39–41]. With 745 twins, the study is not small, but power to show interaction effects nevertheless remains relatively low. The low numbers in the MZ high group ($n = 70$; 9.4%) and the low prevalence of CT ($n = 138$; 18.5%) further reduced power. Despite this, results did show statistically significant interaction in CAPE-negative symptoms. With more power, interaction in CAPE total analyses might also have been statistically significant.

There are various types of constructs to study genetic liability when aiming to study an omnibus measure, rather than molecular measures. Two studies using family history and sibling status (sibling of patient with non-affective psychotic disorder) as an omnibus measure for genetic liability showed gene–environment interaction [42, 43]. More specifically, associations between various environmental factors and the continuum of psychosis were stronger on an additive scale in subjects with a family history of psychiatric disorder [42]. Two adoptive studies assessing adoptive parents' communication deviance and biological mothers' diagnosis of schizophrenia spectrum disorder and schizophrenia, respectively, also showed gene–environment interaction [44, 45]. On the other hand, two other studies using family history to assess genetic liability did not show interaction between CT and parental psychopathology [46, 47]. A study in young adolescents defined genetic liability using information on

Table 4 Interaction between genetic liability determined by the SCL-90 score of the co-twin and childhood trauma determined by scores on the Childhood Trauma Questionnaire Short-Form (CTQ-SF) using the CAPE score as outcome

CAPE sum score →	Overall	Positive	Negative	Depressive
Chi-square of interaction term	$\chi^2 = 5.6\ df = 2$ $p = 0.06$	$\chi^2 = 1.7\ df = 2\ p = 0.43$	$\chi^2 = 8.79\ df = 2$ $p = 0.012$	$\chi^2 = 1.36\ df = 2\ p = 0.51$
Regression coefficient of CT	See Fig. 1	$B = 3.1\ p < 0.001$	See Fig. 1	$B = 1.7\ p < 0.001$
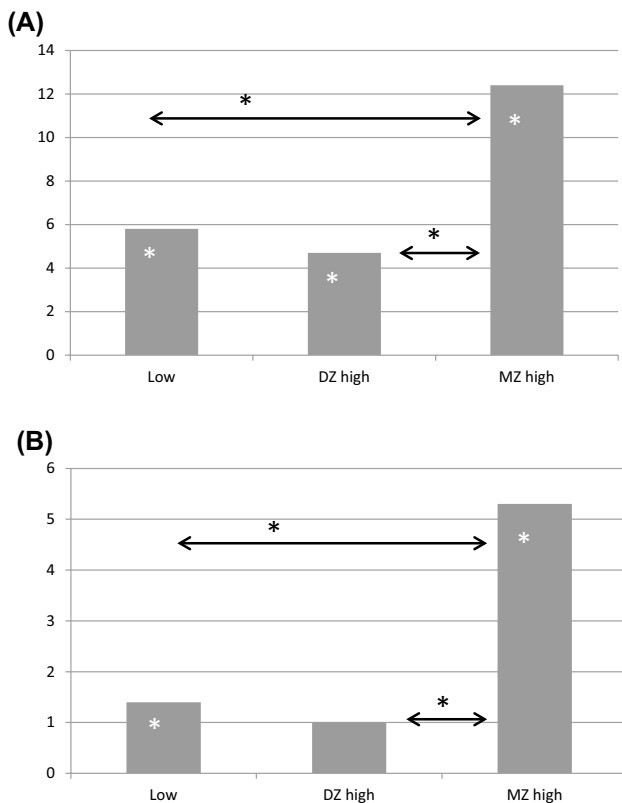
Fig. 1 Regression coefficients representing the association between childhood trauma and the Community Assessment of Psychic Experience (CAPE) scores in twins with a low genetic risk (DZ-MZ Low) or a dizygotic (DZ) or monozygotic (MZ) high risk, respectively. **a** overall sum score, **b** sub scale negative symptoms[a]. [a]Regression coefficients show the increase in CAPE score for subjects with CT compared to subjects without CT. *$p < 0.05$

psychosis from the co-twin [8]. This study did not show interaction between CT and a genetic liability variable constructed using information on psychosis from the co-twin [8]. A difference with the present study, however, is that this study used psychotic symptoms in the co-twin rather than general psychopathology in the co-twin. The difference in age range (12 years vs 14–34 years) can also be responsible for the differences in findings. Thus, while from the present results we only tentatively concluded that there is evidence for interaction, previous results from studies using omnibus measures are also not consistent and more research is needed.

The aetiology of schizophrenia heritability is polygenic [48]. More than 150 schizophrenia-associated loci have been identified using genome-wide association studies (GWAS) [9]. The polygenic risk score includes the full spectrum of genetic liability [49] and is also ideally suited to study gene–environment interaction. A pilot case–control study did not find evidence for the interaction between polygenic risk score and CT, but power was relatively low for the study of interaction. The biological significance of the polygenic risk score remains uncertain. Specific polygenic pathway scores may be more biologically informative, but a priori hypotheses justifying the use of any specific pathway are not precise and false-positive findings may ensue. Given the current weak evidence future research studying the polygenic risk score can shed more light on the gene–environment interaction [18]. Given the difficulties in using molecular measures of genetic risk, additional studies using indirect measures of genetic risk also remain useful.

GxE in CAPE-negative symptoms

The present results showed an interaction between CT and genetic liability in CAPE-negative symptoms but not in CAPE-positive or depressive symptoms. Previous research showed the main effects of CT were larger when analysing positive symptoms [14, 50]. Despite the need to analyse CAPE scales separately [4], the above-mentioned studies showing interaction did not differentiate between positive and negative symptoms [42–45]. It has been suggested that childhood neglect specifically interferes with the development of negative symptoms and that poor attachment is on the causal pathway [51]. The traumagenetic neurodevelopmental theory proposes that neurological and biochemical abnormalities found in adult schizophrenia are caused by child abuse because long-lasting biological effects accumulate over time [52]. In this theory, the two interacting patterns of response to CT are hyperarousal and the biological stress system. By reacting through hypervigilance, a phenomenon called pruning may be emphasized. This is a normal reaction which occurs in adolescence and corresponds to a decrease in the number of synapses and neuronal loss mainly in the neuropil. However, when accentuated, there is excessive neuronal loss which might be the root of progression towards negative symptoms in adulthood [53, 54]. Further research is required to examine this issue.

Intra class correlation and differences between CT subscales

It is plausible that the environment is more similar in MZ twins than in DZ twins and this would make the equal exposure assumption invalid [55]. Subsequently, this would mean that genetic liability as used in the present paper may be confounded by the environment because the exposure is, similar to genes, also shared to a greater degree in MZ twins. When examining the intra class correlation (ICC) of the CT subscales in MZ and DZ twins, physical abuse and physical neglect were more similar in MZ as compared to DZ twins, while there were no differences in the other subscales or in the total score (results available upon request). Results for the total CT and for emotional abuse were as expected; a large regression coefficient for the association between CT and CAPE score in MZ high, and not in DZ high or in MZ DZ low. On the contrary, in the subscales with differences in ICC, DZ high showed the highest degree of interaction, with directionally the lowest or even negative regression coefficients (reversed interaction). Given the differences in ICC in the subscales of physical abuse and physical neglect, we suggest that only the results for CT total score and the other subscales are valid. This also means that we implicitly assumed that all CT subscales included in the present paper show the same interaction with genetic liability. In previous studies, this assumption was also made [42, 43, 47] or only one domain was studied [46]. Because the present results only show differences between physical abuse and neglect on the one hand and emotional abuse and neglect on the other and this seems related to differences in intraclass correlation (see above), intention to harm in the abuse variables does not seem to make a difference. This contradicts previous findings [8]. Future studies in populations with higher CT prevalences can further assess interaction between genetic liability and the subscales.

Gene–environment correlation

In the present data, genetic liability and CT were associated. It has been argued that the presence of gene–environment correlation hampers the interpretation of gene–environment interaction results because in the event of correlation, CT can be on the causal pathway between genetic liability and the outcome [56–58]. Linear regression analysis, as used in the present paper, is ideally suited to disentangle association from interaction. In addition, because of the relatively low correlation, we expected, if any, partial rather than full mediation. To show that the present findings are not the result of mediation, we tested mediation in a model without interaction. The uncorrected regression coefficient between MZ high risk and CAPE total score was 2.4 ($p = 0.08$, reference MZ DZ low). After including CT, the regression

coefficient increased to 3.2 ($p = 0.017$); when assessing CAPE negative symptoms, the regression coefficient was 1.09 (n.s.) in a crude model and 1.13 (n.s.) after including the CT. Therefore, in the present study, the presence of apparent gene–environment correlation could not be interpreted as evidence of mediation. In addition, an analysis using an MZ twin approach in the TwinssCan data showed an association between CT and psychosis that cannot result from gene–environment correlation [58].

Methodological issues

CAPE is not useful as a screening tool for psychotic disorders, since the prevalence of self-reported experiences is much higher than the prevalence of the clinical disorder according to the DSM-IV [23, 59]. In this setting, however, used as a screening tool for the prevalence for psychotic experiences as a broad measure of psychometric risk for psychosis, it is suitable.

The SCL-90-R was used to define genetic liability in the co-twin, while the different CAPE dimensions were the outcome in the regression models. Cross-trait within-twin analysis is a valid method to establish genetic liability [30]. SCL-90-R was suitable to define genetic liability because it assesses general psychopathology and elsewhere, we have shown that psychotic experiences in fact reflect severity of general psychopathology [2, 60, 61] and that gene–environment interactions analyses can be productively studied using broad measures of psychopathology in defining proxy genetic risk [42, 62]. Thus, the measure of genetic liability for the different CAPE dimensions arguably should reflect the general psychopathology severity measure. The Pearson correlation between the dichotomous SCL-90-R (in the index twin) and the CAPE total score and subscales was between 0.41 and 0.54, showing sufficient differentiation between the two scales for use as, respectively, genetic exposure and outcome measures.

There is no consensus on how to categorize the CTQ-SF. Frissen and colleagues [63] and Van Nierop and colleagues [43], therefore, used a cutoff at 80% to define CT based on the CTQ-SF. Other studies, used the tertiles cutoff to define groups [64]. In a general population sample, this might be invalid as the relatively low incidence of CT will result in subjects with low trauma ending up in the highest risk category. Therefore, we used the cutoffs as defined by Bernstein, Fink [17]. A sensitivity analysis of CTQ-SF categorised in tertiles showed very similar results. However, the p value for the interaction term (CT * genetic liability) increased from 0.06 to 0.19 and from 0.012 to 0.15 in the model of total CAPE and CAPE-negative symptoms, respectively. In addition, although the CTQ-SF used in the present paper covers important constructs within the CT umbrella term, it does not cover the entire range. The CTQ-SF does

not assess domains such as bullying, domestic violence and parental death, which have also been associated with psychosis outcomes [8, 65]. Finally, although timing, severity and duration of CT are likely to impact later mental health outcomes [8, 65, 66], these were not included in the present analyses. In the present sample, prevalence of CT was rather low, resulting in analyses of the dichotomised CTQ subscales. Future research analysing samples with higher CT prevalence should consider these aspects and include the full range of experiences associated with CT.

One disadvantage of the solely retrospective use of the CTQ-SF is the fact that recall bias may occur. It is possible that a prospective tool would have shown CT in individuals currently classified as not having experienced CT. A previous validation study did show an association between CT and psychopathology regardless of whether a prospective or retrospective measurement tool was used, but retrospective self-reports often demonstrated stronger associations with psychopathology [67]. Possible explanations for this phenomenon include the underreporting of severe CT by caregivers in prospective tools and an increased 'knowledgeability' of patients about experienced CT in comparison to their parents [67]. 'Memory bias'—the improved recall of negative childhood experiences in an individual with current psychopathology—has been shown to only have a minimal influence on the correlation between self-reported CT and psychopathology [68]. Nevertheless, the current results cannot be extended to samples with prospective measures of CT.

In theory, the probability of recall bias may be highest in the oldest age group. Sensitivity analyses showed that in the youngest age groups the interaction term and regression coefficients in the genetic liability strata were similar to the main results. In the age categories with lowest recall bias, the interaction was strongest. This suggests that the stronger association in MZ high is not the result of recall bias.

Subjects included in the analyses differed from subjects with missing data (lower age and fewer with CT exposure). In addition, non-responder data were not available. Reasons for non-response were "research staff could not reach the subject", "refused", "not interested", "moved". Since only full twin pairs were included, non-response in one twin made the other twin not eligible. Previous research using the EFPTS showed that non-responders were similar in gender, mode of fertilisation, gestational age, parental age and behaviour; MZ were slightly overrepresented and birth weight was slightly higher [69]. There is no reason to expect differential non-response impacting associations and interactions assessed in the present paper (e.g. non-responders having both more genetic liability and lower CAPE scores than responders).

Furthermore, the analysis performed was restricted to data from the general population; no psychiatric patients were included. However, studying psychotic symptoms in the general population can contribute to unravelling the mechanism in full-blown clinical disorder [70]. We, therefore, believe that these results may be generalized to the clinical level, although this requires further study. Despite its exploratory nature, this study offers some insight into the interaction between genetic liability and CT. Nonetheless, more research on this topic needs to be undertaken to be able to draw definitive conclusions.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethics approval The local ethics committee (Commissie Medische Ethiek van de Universitaire ziekenhuizen KU Leuven, Nr. B32220107766) approved the study.

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