

Title: Childhood adversity and psychosis: examining whether the association is due to genetic confounding using a monozygotic twin differences approach

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Abstract

Purpose: To test whether the association between childhood adversity and positive and negative psychotic experiences is due to genetic confounding.

Method: Childhood adversity and psychotic experiences were assessed in a sample of 226 twins from the general population. A monozygotic (MZ) twin differences approach was used to assess possible genetic confounding.

Results: In the whole sample, childhood adversity was significantly associated with positive ($\beta = .45$; $SE = .16$; $p = .008$) and negative psychotic experiences ($\beta = .77$; $SE = .18$; $p < .01$). Within-pair MZ twin differences in exposure to childhood adversity were significantly associated with differences in positive ($\beta = .71$; $SE = .29$; $p = .016$) and negative psychotic experiences ($\beta = .98$; $SE = .38$; $p = .014$) in a subsample of 86 MZ twin pairs.

Conclusions: Individuals exposed to childhood adversity are more likely to report psychotic experiences. Furthermore, our findings indicate that unique environmental effects of childhood adversity contribute to the development of psychotic experiences.

Keywords: psychosis, childhood adversity, twins, environment, genetics, general population.

1. Introduction

A growing body of research indicates that attenuated psychotic experiences are present in a substantial proportion of healthy individuals (1-3). This evidence supports the conceptualization of psychosis as a continuous trait, the distribution of which extends into the general population (4-5). In the absence of illness and need of treatment, these milder forms of psychotic symptoms are referred to as psychotic experiences (4). The study of the risk factors underlying the expression of psychotic experiences can greatly contribute to the understanding of the psychotic disorders because it has been shown that i) psychotic experiences precede the onset of psychosis, thus psychotic experiences can help to identify subjects at risk (1, 6) and ii) clinical and subclinical psychotic symptoms are likely to involve common risk factors in their etiology (1-2, 4). In this context, childhood adversity constitutes an environmental risk factor which has been frequently related to the expression of both clinical (7-8) and subclinical psychotic symptoms or psychotic experiences (9-10).

Interestingly, despite the efforts made in the genetics of psychotic disorders in the last decades, a growing body of research points toward a contribution of environmental factors, including childhood adversity, to their etiology (11-13). Furthermore, Van Os and colleagues (11) have recently pointed out that genetic factors involved in these disorders are likely to operate via environmental factors by making individuals more sensitive (gene-environment interaction) or prone (gene-environment correlation) to certain environments (14). These mechanisms of gene-environment interplay may underlie previously reported associations between environmental risk factors such as childhood adversity and psychotic outcomes. Indeed, two recent studies provide evidence for gene-environment interaction effects in the association between psychosocial stress factors and psychotic experiences in samples drawn from the general population (15-16). However, it would be also important to clarify whether environmental factors *per se* have an impact on the expression of psychosis. So far associations between environmental risk factors and psychotic outcomes have been explored without controlling for genetic confounding (11), that is, individuals at increased genetic risk for psychosis may be more vulnerable to be victimised because of traits associated with psychosis, such as cognitive

impairments, impaired social functioning, oddness or others. To the best of our knowledge, only one study provided evidence for an association between childhood trauma and risk to develop psychotic symptoms after controlling for genetic liability for psychosis (17). Therefore, although childhood adversity as an environmental risk factor for psychosis has been extensively studied and the neurobiological impact of early adverse events in the brain it is well-established (18-20), whether the association between childhood adversity and psychosis is likely causal or merely reflects gene-environment correlation remains to be examined.

In this context, twin designs offer a unique opportunity to disentangle genetic and environmental effects on complex phenotypes such as psychotic experiences (21). Specifically, the monozygotic (MZ) twin differences approach has been referred to as a strong test of the unique environmental experiences that make family members different from each other (also called non-shared environment) independently of genetics (22-24). Since MZ twins are, nearly always, identical at the DNA sequence level (21); phenotypic differences observed between MZ twins must be explained by differential exposure to environmental factors. In other words, if differences in the expression of subclinical psychotic experiences in MZ twins are associated with exposure to childhood adversity, this would provide strong evidence that the observed association between childhood adversity and psychosis is not due to genetic confounding.

Therefore, the present study aimed to examine i) whether childhood adversity was associated with positive and negative psychotic experiences in a twin sample from the general population, ii) to what extent MZ twins were similar for their exposure to childhood adversity and presence of psychotic experiences and iii) whether differences in exposure to childhood adversity were associated with differences in the expression of psychotic experiences in a subsample of MZ twins.

2. Subjects and Methods

2.1 Participants

The sample consisted in 230 Spanish adult twins (115 twin pairs) from the general population including 86 MZ twin pairs. The mean age was 34 years (SD=13.28) and 34.2% of the subjects were males. Recruiting was conducted from the University of Barcelona Twin Register and media advertisements. Identified twin pairs were first contacted by telephone and invited to participate. Exclusion criteria applied were age under 17 and over 65 years, a medical history of neurological disturbance, presence of sensory or motor alterations and current substance misuse or dependence. All subjects were from Caucasian origin. Written informed consent was obtained from all participants after a detailed description of the study aims and design, approved by the local Ethics Committee.

2.2 Measures

To assess childhood adversity, we used an adapted version of the Adverse Childhood Experiences Questionnaire (ACE.Q; (25)). This questionnaire assesses the exposure to events of childhood abuse, childhood neglect and household dysfunction. Three items regarding bullying and parental loss were added to the original version. Our adapted version consists on 19 items. Each item assesses the exposure to a particular adverse event. Participants are requested to answer “yes” or “no” to each item which indicates whether they were exposed or not to each adverse event. Items are detailed in the Appendix. All the positive answers are added up to obtain a total childhood adversity score which ranges from 0 to 19.

The Community Assessment of Psychic Experiences (CAPE; (26)) was used to assess positive and negative psychotic experiences. This validated self-report questionnaire measures the lifetime prevalence of psychotic experiences in a frequency scale ranging from ‘never’ to ‘nearly always’. The positive dimension of the CAPE includes items mainly referring to hallucinations and delusions such as ‘do you ever feel as if things in magazines or TV were written especially for you?’. The negative dimension mainly assesses alogia, avolition, anhedonia and lack of interest in social relationships. An example of item is ‘do you ever feel that you experience few or no emotions at important events?’. The CAPE provides a total

continuous score per dimension ranging from 20 to 80 in the positive dimension and from 14 to 56 in the negative dimension.

Zygoty was established genotyping 16 loci: 15 short tandem repeat (STR) loci and amelogenin, the gender determining marker. Genomic DNA was extracted from peripheral blood cells using the Real Extraction DNA Kit (Durviz S.L.U., Valencia, Spain). The PowerPlex® 16 System (Promega Corporation) allowed the co-amplification and three-color detection of 16 loci. Twins with only one divergent allele were genotyped a second time to limit the scope for genotyping error. Identity on all the markers can be used to assign monozygoty with greater than 99% accuracy (27).

As data derived from this twin sample has not been published yet, further characteristics of the sample are reported for descriptive purposes. Apart from age and sex, sociodemographic characteristics include estimated Intelligence Quotient (IQ) assessed by four subtests (Block design, matrix reasoning, information and vocabulary) from the Wechsler Adult Intelligence Scale (WAIS-III; (28-29)); level of education (elementary school, high school and university), birth of place ('urban' when the twins were born in the city of Barcelona and 'non-urban' when they were born at other Spanish towns with lower number of habitants compared to Barcelona city) and socioeconomic status (SES). A continuous score representing SES was obtained using four-factor index of social status developed by Hollingshead (30-31). SES scores ranging from 8 to 30 were defined as "Low SES" and scores between 31 and 66 were classified as "Average SES" (32). Of note, some of these measures were not available for all subjects.

2.3 Statistical Analysis

Data was analysed in three phases. First, multiple regression models were conducted to map the association between childhood adversity and positive and negative psychotic experiences. In these models, childhood adversity was the variable of interest, sex and age were included as covariates and positive and negative psychotic experiences were used as the outcome measures. Separate models were conducted for each outcome measure. The non-independence of clustered twin data was corrected for by using tests based on the sandwich or Huber/White variance estimator (33). In these analyses, the individual was the unit of analysis.

Second, MZ intrapair correlations were calculated for childhood adversity and positive and negative psychotic experiences. These analyses let us confirm that MZ twins differed in their exposure to childhood adversity and their scores for positive and negative psychotic experiences. The proportion of the variance of the phenotype which can be directly attributable to unique environment (which includes measurement error) can be obtained by this formula: $1 - r_{MZ}$ where r represents the within-pair correlation (34).

Third, associations between intrapair differences in childhood adversity, positive and negative psychotic experiences were analysed by linear regression analysis. Intrapair scores were calculated for childhood adversity, positive and negative psychotic experiences by subtracting the score of the Twin 2 from the score of Twin 1 (Twin 1 – Twin 2). Twins were randomly assigned to be 1 or 2. Associations between intrapair differences in CA and intrapair differences in positive and negative PLEs scores were conducted in a subsample of 85 MZ twin pairs. Because intrapair analyses in MZ twins fully control for genetic influences, any association between the abovementioned variables would be attributable to environmental factors (23, 35) and thus, reject the hypothesis that the association is due to genetic confounding. In the last two analyses each MZ twin pair was the unit of analysis.

Statistical analyses were carried out in STATA 10.0 (36) following the procedures described in Carlin and colleagues (37).

3. Results

Most of the sample was composed of females (66.1%), the average age was 33.8 years (SD=13.3) and more than half of the sample had completed university educational level (59.3%). Average IQ scores were within the normal range for non-clinical samples (103.3; SD=11.5). Around half of the sample was born in non-urban areas (58.7%). Most of the twins were of average SES level (65.8%). The MZ twin subsample showed very similar sociodemographic characteristics compared to the whole twin sample (Table 1).

Positive CAPE score ranged from 13 to 39 (mean=25.3; SD=4.0) and negative CAPE score ranged from 12 to 49 (Mean=22.1; SD=4.8). Scores for the positive (Mean=25.7; SD=4.24) and

negative dimension (mean=22.5; SD=5.05) of CAPE were very similar in the MZ twin subsample. In order to obtain the prevalence of psychotic experiences in the current sample, CAPE scores were recoded to 0 (never, sometimes) and 1 (often, almost always). Specifically, 37.1% - 38.8% of the sample often, or almost always, experienced at least one positive or negative psychotic experience. Similarly, in the MZ twin subsample, 41% of the sample often, or almost always, experienced at least one positive or negative psychotic experience.

With regard to childhood adversity (CA) score, the mean was 2.0 (SD=2.2) and it ranged from 0 to 14. In the MZ twin subsample, CA score also ranged from 0 to 14 and the mean was 2.0 (SD=2.4). In the whole sample, 26.3% of the individuals did not experience any adverse childhood event and 26.3% reported one adverse childhood event; the rest of the sample reported two or more adverse childhood events. Similarly, in the MZ twin subsample, 27.3% of the individuals did not report any adverse childhood event, 26% reported one adverse childhood event and the rest reported two or more adverse childhood events.

First, regarding the association between CA and psychotic experiences, analyses based on the whole sample showed that CA was significantly associated with both positive ($\beta=.45$; SE=.16; $p=.008$) and negative psychotic experiences ($\beta=.77$; SE=.18; $p<.01$) (Table 1).

Second, we conducted within-pair correlations to index the similarity for the outcome measures and the variable of interest between twin 1 and twin 2 in the subsample of MZ twin pairs. The within-pair correlations for positive and negative psychotic experiences were $r=0.48$ ($p<.01$) and $r=0.44$ ($p<.01$) respectively. Therefore, around 58-62% of the variance of CAPE could be attributed to unique environmental factors not shared by twins. In regard to CA score, the within-pair correlation was $r=0.79$ ($p<.01$). Thus, although most of the childhood adverse events experienced by the twins are common, some of them are specific (21% of the variance of childhood adversity).

Finally, regression analyses using within-pair MZ differences showed that MZ differential exposure to childhood adversity was significantly related to phenotypic differences in both positive ($\beta=.66$; SE=.28; $p=.026$) and negative dimensions of psychotic experiences ($\beta=.93$; SE=.37; $p=.014$) (Table 2).

4. Discussion

To our knowledge, this is the first study adding evidence to the growing literature on the relationship between childhood adversity and psychotic experiences using a MZ-twin differences approach. The MZ-twin differences design ensures that pure unique or nonshared environmental effects, rather than gene-environment interaction or evocative gene-environment correlation, are quantified (24).

Firstly, the present twin sample from the general population showed similar means and prevalences of psychotic experiences to those reported previously in singleton samples also using the CAPE questionnaire (3, 15). In respect to childhood adversity, in a large community-based study using the original version of the ACE questionnaire 36.1% of the sample reported 0 adverse childhood experiences, 26.0% reported one adverse childhood experience and the rest reported two or more adverse childhood experiences (38). These prevalences are very similar to those reported in the current sample.

Secondly, in agreement with previous studies (9-10, 39-40), our findings provide support for the association between childhood adversity and psychotic experiences in the general population.

Thirdly, the fact that within-pair MZ correlations were not equal to 1 for any of the measured phenotypes indicated that we could test for unique environmental effects of childhood adversity on psychotic experiences.

Fourthly, regarding the primary goal of the current study, within-pair MZ differences in exposure to childhood adversity were significantly related to phenotypic differences for both positive and negative dimensions of psychotic experiences. Because the members of the MZ twin pair are genetically identical to each other, any environmental effects operate upon genotype effects that do not differ between the members of the MZ twin pair (24). These findings indicate that the association between childhood adversity and psychosis cannot be solely attributed to genetic confounding and thus, that childhood adversity may represent a true risk factor for the development of psychotic experiences.

These results are in agreement with those reported by Arseneault and colleagues (17) who reported that childhood adversity may constitute a risk factor for the development of psychotic symptoms independently of the genetic background of the individual.

Proposed neurobiological and psychological mechanisms of risk underlying this association also add plausibility to these findings. Converging evidence from neurobiology and epidemiology suggests that early adverse events cause enduring brain dysfunction (18, 41-42). Persistent exposure or impact of stressors in the developing brain has been proposed to lead to chronically heightened stress-induced glucocorticoid release which, in turn, may impact on the hypothalamic-pituitary-adrenal (HPA) axis. Dysregulation of the HPA axis has been suggested to contribute to the dopaminergic abnormalities that are generally thought to be involved in the expression of psychotic phenotype (20, 43). At the psychological level, exposure to early adversity may create, also, a cognitive vulnerability, characterized by a tendency to perceive the self as powerless and others as malevolent, which in combination with an externalizing attribution style may ultimately lead to paranoid interpretation of anomalous experiences (44-45). These risk mechanisms could be moderated by genetic variants, making some individuals more sensitive to psychosocial stress factors than others (15-16).

The results of the present study should be interpreted in the context of its limitations. First, due to the limited sample size our findings require replication and have to be interpreted with caution. However, the sample showed to be representative of the general population regarding the sociodemographic characteristics and the prevalences of the variables studied. Second, the cross-sectional nature of our design did not allow inference of causal associations. Third, the retrospective measure of CA may be influenced by recall bias. Nevertheless it is worth it to mention that retrospective self-reports of childhood trauma are more likely to be an underestimation of the true prevalence of childhood maltreatment than an overestimation (46). Finally, as other studies using a MZ-twin differences design (22, 24), we can not rule out the possibility that some unmeasured non-genetic factor could have contributed to our findings. Therefore, further research in larger samples is needed to better understand under which

circumstances childhood adversity environmentally increases the risk or frequency of psychotic experiences.

5. Conclusion

Our findings shed new light regarding the role of childhood adversity as an environmental risk factor involved in the development of psychotic experiences. We found a significant environmental effect of childhood adversity on the development of positive and negative psychotic experiences using a MZ-twin differences approach, suggesting that the association cannot be solely attributed to genetic confounding. Therefore, although some individuals may be genetically vulnerable to the impact of childhood adversity (15), our findings indicate that childhood adversity can independently contribute to the development of psychotic experiences. Further research in larger samples is needed to better understand under which circumstances childhood adversity environmentally increases the risk or frequency of psychotic experiences.

Conflict of interest

None.

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Table 1. *Sociodemographic characteristics of the MZ-twin subsample (n=172 individuals; 86 MZ twin pairs). Number of individuals varies in function of the measure.*

	MZ-twins subsample
Male sex	31.8% (n=27)
Age in years, mean (SD)	33.7 (12.8) (n=172)
Education Level	
Elementary School	16.9% (n=28)
High School	31.3% (n=52)
University	51.8% (n=86)
IQ, mean (SD)	102.9 (12.5) (n=166)
SES	
Low	39.0% (n=46)
Average	61.0% (n=72)
Birht place	
Urban	41.2% (n=70)
Rural	58.8% (n=100)

SD, Standard Deviation; **IQ**, Intelligence Quotient; **SES**, Sociodemographic Status

Table 2. In the left side of the table, association between Childhood Adversity (CA) score and positive and negative PLEs and negative PLE in the whole sample (n=226). In the right side of the table, association between intrapair scores (twin 1- twin 2) for CA and intrapair scores for positive and negative PLE in a subample of MZ twin pairs (n=85 pairs). All analyses were adjusted by sex and age.

	Positive PLEs				Intrapair Positive PLEs		
	β	SE	p		β	SE	p
CA Score	.45	.16	.008*	Intrapair CA Score	.71	.29	.016*
	Negative PLEs				Intrapair Negative PLEs		
	β	SE	p		β	SE	p
CA Score	.77	.18	.000**	Intrapair CA Score	.95	.38	.014*

β , unstandardized coefficient; SE, standard error; *p<.05; **p<.01.

Appendix

Childhood Adversity Questionnaire

While you were growing up, during your first 18 years of life:

1. Did a parent or other adult in the household swear at you, insult you, put you down or humiliate you?
2. Did a parent or other adult in the household act in a way that made you feel that you might be physically hurt?
3. Did a parent or other adult in the household push, slap or throw something at you?
4. Did a parent or other adult in the household hit you so hard that you had marks or were injured?
5. Have your mother or father ever left home for a long period of time for any reason?
6. Did a parent or other adult in the household touch your body or fondle you in a sexual way?
7. Did a parent or other adult in the household attempt or had any sexual activity with you (oral, anal or vaginal)?
8. Did you often or very often feel that no one in your family loved you or thought you were special or important?
9. Did you often or very often feel that your family look out for each other, feel close to each other, or support each other?
10. Did you often or very often feel that you didn't have enough to eat, had to wear dirty clothes, and had no one to protect you?
11. Did you often or very often feel that your parents were too drunk or high to take you to the doctor if you needed it?
12. Were your parents ever separated or divorced?
13. Was your mother or stepmother ever pushed, grabbed, slapped, or had something thrown at her?

14. Was your mother or stepmother ever kicked, bitten, hit with a fist, or hit with something hard?
15. Did you live with anyone who was a problem drinker or alcoholic or who used to use street drugs?
16. Was a household member depressed or mentally ill, or did a household member attempt to suicide?
17. Did a household member go to prison?
18. At the school, did one or more peers make fun of you, call you by nicknames or bully you?
19. At the school, did one or more peers insult, threat, steal or hit you?