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Childhood Trauma May Increase Risk of Psychosis and Mood Disorder in Genetically High-risk Children and Adolescents by Enhancing the Accumulation of Risk Indicators

Nicolas Berthelot*[,1,2,3,4], Julia Garon-Bissonnette[2,3,4,5], Valérie Jomphe[2], Hélène Doucet-Beaupré[2,6], Alexandre Bureau[2,6], and Michel Maziade[2,6]

[1]Department of Nursing Sciences, Université du Québec à Trois-Rivières, Trois-Rivières, QC, Canada; [2]CERVO Brain Research Center, Centre intégré de santé et de services sociaux de la Capitale-Nationale, Quebec City, QC, Canada; [3]Centre d'études interdisciplinaires sur le développement de l'enfant et la famille, Trois-Rivières, QC, Canada; [4]Interdisciplinary Research Center on Intimate Relationship Problems and Sexual Abuse, Montreal, QC, Canada; [5]Department of Psychology, Université du Québec à Trois-Rivières, Trois-Rivières, QC, Canada; [6]Department of Psychiatry and Neurosciences, Faculty of Medicine, Université Laval, Quebec City, QC, Canada

*To whom correspondence should be addressed; Université du Québec à Trois-Rivières, Department of Nursing Sciences, 3351 boul. des Forges, PO Box 500, Trois-Rivières, QC, Canada; tel: 1-819-376-5011, ext. 3487, e-mail: Nicolas.berthelot@uqtr.ca

Background: **Genetically high-risk children carry indicators of brain dysfunctions that adult patients with schizophrenia or bipolar disorder display. The accumulation of risk indicators would have a higher predictive value of a later transition to psychosis or mood disorder than each individual risk indicator. Since more than 50% of adult patients report having been exposed to childhood trauma, we investigated whether exposure to trauma during childhood was associated with the early accumulation of risk indicators in youths at genetic risk.** ***Methods:*** **We first inspected the characteristics of childhood trauma in 200 young offspring (51% male) born to a parent affected by DSM-IV schizophrenia, bipolar disorder, or major depressive disorder. A subsample of 109 offspring (51% male) had measurements on four risk indicators: cognitive impairments, psychotic-like experiences, nonpsychotic nonmood childhood DSM diagnoses, poor global functioning. Trauma was assessed from direct interviews and reviews of lifetime medical and school records of offspring.** ***Results:*** **Trauma was present in 86 of the 200 offspring (43%). The relative risk of accumulating risk indicators in offspring exposed to trauma was 3.33 (95% CI 1.50, 7.36), but more pronounced in males (RR = 4.64, 95% CI 1.71, 12.6) than females (RR = 2.01, 95% CI 0.54, 7.58).** ***Conclusion:*** **Childhood trauma would be related to the accumulation of developmental precursors of major psychiatric disorders and more so in young boys at high genetic risk. Our findings may provide leads for interventions targeting the early mechanisms underlying the established relation between childhood trauma and adult psychiatric disorders.**

Key words: child abuse/maltreatment/offspring/schizophrenia/bipolar disorder/major depressive disorder/cumulative/risk studies/vulnerable

Introduction

Childhood trauma is a key risk factor for the development of psychopathology.[1–5] Among the patients having schizophrenia, bipolar disorder, or major depressive disorder, more than 45% report having been exposed to childhood trauma.[3,6–8] Moreover, exposure to trauma would be associated with a less favorable psychiatric illness course[9–12] and poorer response to treatment.[13,14] There also is some evidence that trauma would precede the clinical-high-risk syndrome[15] and contribute to inducing the onset of illness.[16–18] However, the early mechanisms through which childhood trauma increases the vulnerability to major psychiatric disorders are little known.[5,12,19–21] Longitudinal studies of high-risk children and adolescents (i.e., children born to a parent affected by schizophrenia, bipolar disorder, or major depressive disorder) can shed light on how childhood trauma may have a developmental effect across the early risk trajectory heading to a later appearance of a major psychiatric illness.

Six main leads drawn from longitudinal studies of genetically high-risk children can help investigate the developmental influence of childhood trauma. First, many indicators of brain dysfunctions that adult patients display are detectable in children born to an affected parent

and can be seen as illness precursors.[22] We, and others, have previously reported in genetically high-risk children that these risk indicators or endophenotypes can be found among different modalities such as neurocognitive deficits,[23–25] psychotic-like experiences,[26] poor social functioning,[27] and DSM nonpsychotic nonmood diagnoses during childhood.[28,29] Second, many risk endophenotypes have been shown to be shared by offspring of parents affected by any one of the diagnoses of schizophrenia (SZ), bipolar disorder (BP), or major depressive disorder (MDD),[25,30,31] which is congruent with the genetic and phenotypic commonalities otherwise observed in adult patients.[32–35] Third, these risk indicators would tend to progressively accumulate along the risk trajectory from childhood to young adulthood.[36] Fourth, this progressive accumulation in genetically high-risk children would be a better predictor of a later transition to any of the three disorders (SZ, BP, and MDD) than any single risk indicator taken alone.[24,36,37] Of relevance, later along the trajectory, in referred Clinically High-Risk individuals, the aggregation of similar risk indicators also better predicted transition to illness in the following years than all indicators taken individually.[24,38,39] Fifth, this recent knowledge concerning the predictive value of the aggregation of risk factors has supported the development of risk calculators aiming to identify the youths that are the most at-risk of developing a major psychiatric disorder (see review of Worthington et al[40]). Sixth, studies of children and adolescents at genetic risk have suggested that childhood trauma is associated with cognitive deficits,[23] psychotic-like experiences,[26] impairments in functioning,[15] and general symptoms.[41] These studies investigated each of these clinical features individually which raises the possibility that childhood trauma serves as a catalyst for the process of accumulation of such risk indicators in children at risk.

It is also of relevance that a vast literature has shown sizeable sex differences in childhood vulnerability, young boys being at higher risk,[42,43] which may be reflected in the consistent observations of considerable sex differences in major psychiatric disorders.[12,44] The mechanisms explaining the latter remain largely unknown and deserve to be directly approached in developmental studies involving childhood trauma.[21]

Based on this body of data, *our main objective* was to evaluate whether exposure to childhood trauma was associated with an accumulation of risk indicators in genetically high-risk children, adolescents, and young adults. Our secondary objective was to test whether males would be more prone to accumulate risk indicators under exposure to childhood trauma. We began by estimating the rate and characteristics of childhood trauma in our sample of genetically high-risk youths who were born to a parent affected by schizophrenia, bipolar disorder, or major depressive disorder.

Methods

Sample of Offspring

Offspring *inclusion criteria* were (1) having a parent with a DSM-IV diagnosis of schizophrenia (SZ), bipolar disorder (BP), or major depressive disorder (MDD) and (2) being between 6 and 27 years old, which remains within the vulnerability window preceding the average age of onset of the three parental diagnoses. The *exclusion criteria* were the presence of a diagnosis of DSM-IV psychotic disorder, BP, or MDD at assessment, and brain or metabolic disorders. Signed consent was obtained from all participants and their parents when children were under 18, as reviewed by our University Ethics Committee. The sample of 200 offspring had two sources: 86 were enrolled from the younger generations of kindred densely affected by schizophrenia and bipolar disorder,[35] and 114 were referred to our regional mental health care institution. All participants were Caucasians. Forty-one offspring (20.5%) had a parent with SZ and 159 (79.5%) had a parent with an affective disorder (94 BP; 65 MDD). The 200 offspring included 65 singletons, 44 sibships of 2, and 15 of 3 or more participants. Mean age at assessment was 15.1 years (67 were aged between 5 and 11, 68 between 12 and 17, and 65 between 18 and 27 years old; $SD = 5.52$) and 51% were males.

Measures

Childhood Trauma. Childhood trauma was assessed using a method described previously.[23] Five types of childhood trauma were assessed: physical abuse, sexual abuse, emotional abuse, neglect (emotional and physical), and witnessing domestic violence. These categories of abuse and neglect were comparable to those reported in meta-analytic work on childhood trauma[3,41] and in widely used instruments.[45,46] The presence or absence of childhood trauma was rated year by year on a life chart inspired by the Post et al[53] method which allowed us to get a good estimate of participants' age at first exposure to trauma. Ratings were made blind to the goals of the study as to the aggregation scores by a clinical PhD psychologist specialized in childhood trauma (NB) and a PhD student (JGB), using all information collected through two complementary sources: (1) a semi-structured interview developed to assess childhood trauma and having sounded psychometric properties (Traumatic Event Screening Inventory[47,48]) administered to the offspring, one of their parents and relatives (when available), (2) the review of all medical records, clinical interviews and research briefs of the home visits by research assistants throughout the longitudinal follow-up. Again blindly, discordances between raters were reviewed to obtain a consensus on the presence of childhood trauma. In the current study, we used a dichotomous score of exposure to any one of the five

Table 1. The Quantitative and Categorical Definitions of Aggregation of Risk Indicators

Categories of Risk Indicators	Quantitative Definition[a]	Categorical Definition
Cognitive deficits[b]	Sum of deficits among episodic memory, processing speed, executive functions and working memory (scores ranging from 0 to 4 deficits)	Absence or presence of 2 deficits or more[f] (absence = 0 or presence = 1)
Childhood nonpsychotic nonmood DSM IV diagnosis[c]	Sum of different DSM-IV disorders (scores ranging from 0 to 4 diagnoses)[e]	Absence or presence of 2 diagnoses or more (absence = 0 or presence = 1)
Psychotic-like experiences	Sum of attenuated symptoms[d] (scores ranging from 0 to 4 symptoms)[e]	Absence or Presence of 2 attenuated symptoms or more (absence = 0 or presence = 1)
Functioning in childhood	GAF had four classes: 0 = 81–100; 1 = 71–80; 2 = 61–70; 3 = 51–60; 4 = ≤50	GAF > 60 = 0 GAF ≤ 60 = 1
Total score of risk aggregation	**Sum of the scores in each of the 4 categories of indicators (total from 0 to 16)**	**Sum of scores in each of the 4 categories of indicators (total from 0 to 4)**

[a]Scores for each domain were recoded (0–4) so that each domain had an equivalent relative weight to the equation.
[b]Cognitive impairments were measured using the following tests:1) Processing speed—*Digit symbol Substitution Task (WISC/WAIS)* and *Category Fluency: animal naming*; 2) Episodic memory—*California Verbal Learning Test (CVLT-II)* delayed recall and *Rey Complex Figure (RCF)* delayed recall; 3) Working memory—*Digit span (WISC/WAIS)* and *Spatial Span*; 4) Executive functioning—*Wisconsin Card Sorting Test total errors* and *Tower of London (TOL)* number of problems solved in minimum moves. Standardized scores were used from each test, based on normative samples balanced for age and sex. For each domain, the two z-scores were averaged and a cognitive deficit was defined as a z = score of −1.0 or below percentile 16th.
[c]Axis 1 disorders were assessed using the *Kiddie-Schedule for Affective Disorders and Schizophrenia* (K-SADS) administered to parents of children <18 and the *Structured Clinical Interview for DSM-IV Disorders* (SCID-I) administered to youth ≥18.
[d]Psychotic like experiences were assessed using three instruments: a semi-structured interview with the youths and their parents adapted from the Dunedin Study interview methods; the DIS-C (Shaffer et al., 2000); the questionnaire used by Laurens et al. (2007). The nine symptoms focused on three key domains: perceptual abnormalities (visual and auditory hallucinations), delusions (persecutory, suspiciousness, reading thoughts, idea of reference, control, grandiosity), and bizarre behavior.
[e]When a participant had more than four diagnoses or attenuated symptoms, he/she received the maximum score of 4.
[f]The cut-off of two indicators is based on our previous report that this threshold was distinguishing the high-risk offspring from controls (Paccalet et al., 2016).

types of childhood trauma before 18 years old (exposed vs not exposed).

Neuropsychological Assessments. We selected the cognitive domains previously reported as impaired in high risk offspring in comparison to healthy controls,[25,30] i.e., processing speed, episodic memory, working memory, and executive functions (Measures are detailed in Supplementary Methods and in table 1). Assessments were made blind to all other measures by a certified psychologist or PhD students supervised by a senior neuropsychologist.

Clinical Ascertainment of Offspring and Parents. A best estimate lifetime diagnostic procedure based on multiple sources of information was administered to the parent.[49] The Kiddie-Schedule for Affective Disorders and Schizophrenia (K-SADS)[50] was administered to the parents of children under 18 in the presence of the child, or the SCID to participants over 18. Medical charts were also reviewed. Our diagnostic methods have already been reported several times (see Supplementary Methods).[25,36,51]

Global Social Functioning. The Children's Global Assessment Scale[52] was used to assess global functioning (GAF) year by year as inspired by the life chart from Post et al,[53] a method we used in previous studies, relying on all available information, clinical interviews, contacts with families and medical records. The average GAF score was calculated from 6 to 11 years of age to have a measure of functioning that would not be concurrent with the occurrence of cognitive deficits or DSM childhood diagnoses.

Psychotic-like Experiences. Psychotic-like experiences were measured with several instruments: a direct semi-structured interview with the youths and their parents adapted from the Dunedin Study interview methods,[54] the DIS-C,[55] and the questionnaire used by Laurens et al.[56] The nine core items focused on three key domains: perceptual abnormalities (visual and auditory hallucinations), delusions (persecutory, suspiciousness, reading thoughts, idea of reference, control, grandiosity), and bizarre behavior. The clinical interviewers probed to rule out irrelevant symptoms. In a second step, using all available information, two experienced clinical professional assistants coded each experience as 0: absent or probable; 1: definite psychotic-like experience.

Statistical Analysis

We used two complementary methods to define the *score of aggregation of risk indicators*, a first one using a quantitative variable having the advantage of relying on a lower number of arbitrary decisions on different cut-offs, and a second one using a categorical variable. By doing so, we had two goals: (1) to test whether the two methods would yield congruent results in the study and (2) to use a categorical definition that could better fit translation into the clinic by being closer, for instance, to recent methods of "risk calculators" reported in the field.[24,36,37,39] The two methods are described in table 1.

Statistical analyses were conducted with SAS/STAT software, version 9.4 for Windows (SAS Institute Inc., Cary, NC, USA). We first reported the rate and descriptive statistics of childhood trauma in the sample of 200 offspring aged 5 to 27. We compared males and females on the types, severity, and timing of trauma by means of chi-square tests for categorical variables and Wilcoxon tests for ordinal variables.

To meet our main objective of assessing the relationship between childhood trauma and the aggregation of the four risk indicators, we then analyzed the subsample of 109 offspring who had completed the measures for the four indicators (table 1). The association with the *quantitative score of aggregation* was assessed with a linear regression analysis including an interaction term (*trauma* × *sex*), given our hypothesis about a sex modifying effect. As regards the *categorical aggregation score*, we used a binomial generalized linear model with an identity link function to test the interaction between childhood trauma and sex on the presence of accumulation of risk indicators using the additive risk scale. To obtain relative risks (RR) with confidence intervals comparing each combination of childhood trauma and sex to the given reference group (female without childhood trauma), a second binomial generalized model was fitted with a log link function. We also did the analysis by including age as a covariate.

To evaluate a potential effect of the sibships on the results, the model using generalized estimating equations was refitted with the sibship ID as subject and an exchangeable working correlation structure. Finally, even though we could have presented one-tailed *P* values given our unidirectional a priori hypotheses, two-tailed values were presented in Results and in table 2.

Results

Characteristics of Childhood Trauma in the Whole Sample

Out of the 200 offspring, 43% (n = 86) had been exposed to childhood trauma. The exposed offspring experienced on average two subtypes of childhood trauma among physical abuse, sexual abuse, emotional abuse, exposure to intimate partner violence and neglect (M = 1.99, SD = 1.07). The mean age at first trauma was of 4.41 years old (SD = 4.54; table 2). Boys and girls had similar ages at first trauma and similar frequency of subtypes of childhood trauma with the exception of sexual abuse that was more frequent in girls (2.0% vs 13.3%; table 2). More exposure to trauma was seen in offspring of schizophrenia parents than in offspring of mood disorder parents [respectively 68% vs 37%; $\chi 2(1) = 13.46$, $P < .001$] and this

Table 2. Characteristics of Trauma in the Sample of 200 Genetically High-Risk Youths

Variables	Total (N = 200)[a] n (%)	Male Only (n = 102) n (%)	Female Only (n = 98) n (%)	Group Differences (Males vs Females) P-Value[b]
Any trauma[c]	86 (43)	41 (40.2)	45 (45.9)	.41
Single type	33 (16.5)	15 (14.7)	18 (18.4)	.56
2 types	33 (16.5)	18 (17.7)	15 (15.3)	
3 types or more	20 (10.0)	8 (7.8)	12 (12.3)	
Physical abuse	38 (19)	20 (19.6)	18 (18.4)	.82
Sexual abuse	15 (7.5)	2 (2)	13 (13.3)	.002
Emotional abuse	37 (18.5)	21 (20.6)	16 (16.3)	.44
Neglect	33 (16.5)	13 (12.7)	20 (20.4)	.14
Domestic violence	48 (24)	20 (19.6)	28 (28.6)	.14
Age at first trauma				.95
0–2 years old	45 (22.5)	21(20.6)	24 (24.5)	.96
3–5 years old	13 (6,6)	7 (6.9)	6 (6.1)	
6–11 years old	20 (10.0)	9 (8.8)	11 (11.2)	
12–17 years old	8 (4.0)	4 (3.9)	4 (4.1)	
	Mean (SD)	**Mean (SD)**	**Mean (SD)**	**Group differences (males vs females)[a]**
Sum of traumas[d]	1.99 (1.07)	1.85(0.79)	2.11 (1.26)	.26
Age at first trauma (in years)[c]	4.41 (4.54)	4.36 (4.62)	4.47 (4.52)	.92

[a]The 109 offspring included in the analyses on the aggregation of risk indicators were not significantly different from the remaining 91 offspring included only in the analyses on the characteristics of exposure to trauma in terms of rate of childhood trauma [respectively 42% and 44%; $\chi 2(1) = 0.06$, $P = .80$] and sex (51% males).
[b]Two-sided P-values are obtained from Mann–Whitney U tests for continuous variables and from Chi-square tests for categorical variables.
[c]Trauma was evaluated using interviews with offspring, or their parents for younger participants, and blind rating of all available lifetime information, clinical interviews, contacts with families, and medical records collected throughout the longitudinal follow-up.
[d]Sum of traumas and age at first trauma were computed in the subgroup of 86 offspring exposed to childhood trauma.

was observed for all types of trauma except for physical abuse ($\chi 2(1) = 2.05$, $P = .15$) (Supplementary Table S1).

Childhood Trauma and the Aggregation of Risk Indicators

Our main objective was to test the potential association of trauma with two complementary definitions of the aggregation of risk indicators aggregation. In the multiple regression analysis in which the dependent variable was the quantitative definition of aggregation, and the independent variables were trauma and sex, we observed a significant effect of trauma ($\beta_{trauma} = 2.08$, 95% C.I. = [0.99, 3.16], $P = .0003$) on risk aggregation. As a covariate, sex was also associated with the aggregation score ($\beta_{sex} = 1.17$, 95% C.I. = [0.09, 2.24], $P = .03$). The addition of age as a covariate in the analysis yielded a similar significant main effect of childhood trauma ($\beta_{trauma} = 2.15$, 95% C.I. = [1.09, 3.21], $P = .0001$). The association of childhood trauma with aggregation scores was observed as early as in childhood and adolescence (offspring aged 11 to 18 years; $\beta_{trauma} = 2.56$, 95% C.I. = [0.98, 4.14]; $P = .002$) as it was found in the older offspring aged 19 to 26 years ($\beta_{trauma} = 1.49$, 95% C.I. = [0.21, 2.76]; $P = .02$). To address our secondary objective, we redid the analysis by entering the *trauma* × *sex* interaction term and the interaction term was not found significant ($P = .44$).

The analysis on the categorical definition of aggregation congruently showed an association with childhood trauma. The offspring exposed to childhood trauma had a greater probability of accumulating risk indicators (36.96%) than nonexposed offspring (11.11%) with a relative risk of 3.33 (95% C.I. = [1.50, 7.36]; $P = .001$) (Supplementary Table S2). The association between trauma and aggregation was apparent in younger offspring (RR = 83, 95% C.I. = [1.24, 6.49]; $P = .009$) as well as in older offspring (RR = 6.59., 95% C.I. = [0.83, 52.46]; $P = .04$). On the additive risk scale, a statistically significant effect of the *trauma* × *sex* interaction was found on the accumulation of risk indicators ($P = .04$): the relative risk of aggregation was 5.28 (95% C.I. = [1.69, 16.4]; $P = .004$) in exposed males vs 2.01 (95% C.I. = [0.53, 7.58]; $P = .30$) in exposed females when compared to the reference group of nonexposed females (figure 1). The relative risk of aggregation in boys with childhood trauma in comparison to boys without trauma was 4.64 (95% CI 1.71, 12.6). The reanalysis entering age as a covariate yielded similar results with a *trauma* × *sex* interaction remaining close to significance ($P = .059$). The reanalyses accounting for the nonindependence of observations within the sibships also yielded similar results. The *trauma* × *sex* interaction remained close to significance ($P = .056$) and the relative risk of aggregation remained in the same range: 5.33 (95% C.I. = [1.70, 16.8]; $P = .004$) in exposed males versus 2.08 (95% C.I. = [0.54, 7.99]; $P = .28$) in exposed females when compared to the reference group of nonexposed females. Finally, the relative risk of aggregation in boys with childhood trauma in comparison to boys without trauma was 4.60 (95% CI = [1.69, 12.5]; $P = .003$).

Discussion

Our findings suggest that exposure to childhood trauma in genetically high-risk youths, chiefly in young boys would be associated with the accumulation process of risk indicators across childhood, adolescence, and young adulthood. Considering the high predictive value of the risk accumulation on a later transition to illness,[36] and the human and economic burden carried by families in which one parent is affected by schizophrenia, bipolar or major depressive disorder,[22] our study has implications not only for the understanding of the developmental risk mechanisms but also for prevention research and intervention.

The *first* main finding is the association of childhood trauma with the accumulation of four risk indicators (e.g., cognitive impairments, psychotic-like experiences, nonpsychotic nonmood childhood DSM diagnoses, poor global functioning) in genetically high-risk youths. This finding was supported by two complementary estimates of risk indicators aggregation: one drawing on a quantitative definition and the other on a categorical definition that may better accommodate, for instance, a clinical translation in upcoming risk calculators or in defining pre-clinical staging of child risk status. The relevance of our finding is strengthened by previous evidence that risk clusters would be a better predictor of a later transition to illness than any individual risk indicator taken alone, both in genetically high-risk children and in older "clinical high-risk" (CHRs) individuals.[24,36,37] A second basis of relevance is that the accumulation of risk indicators may not be exclusive to psychiatry since it

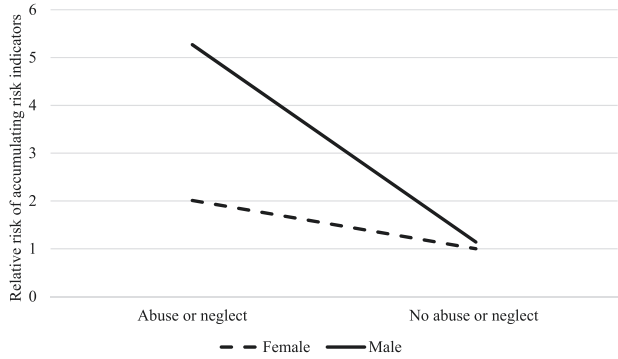

Fig. 1. Relative risk of accumulating risk indicators under trauma exposure separately in male and in female offspring. Young boys and girls had a similar risk of accumulation in absence of trauma, but boys had a greater risk than girls in presence of trauma (*trauma* × *gender* under the additive binomial model reached: $P = .039$). Relative risks were computed using females without trauma as the reference group.

also characterizes children at risk of metabolic cardiovascular disorders.[57,58] Interestingly, childhood trauma may be involved in the development of atherogenesis.[59] This calls for more research focussing on the relation between trauma and risk clusters in both psychiatric and cardiovascular disorders.[60] Drawing information from both sets of complex disorders may accelerate the understanding of shared risk mechanisms.[60]

The *second* finding is that young boys would be more vulnerable to aggregating risk indicators after exposure to childhood trauma than girls, thus making them more at risk or differently at risk of a later incidence of major psychiatric disorder. The greater vulnerability of males was more apparent in the categorical analysis in which the relative risk of boys exposed to childhood trauma (RR = 4.64) doubled that of exposed girls (RR = 2.01). The currently observed greater vulnerability to trauma in young boys could also offer a developmental explanation for the more severe impact of childhood trauma on symptoms and functioning in male patients having a first episode of psychosis,[12] and for the sex differences in outcome where females showed a later onset of illness yet less severe disorders than males.[44,61]

Our results also advocate for further research on the basic mechanisms underlying the potential effect of childhood trauma on the vulnerability to accumulate risk indicators. For instance, previous studies suggested that childhood trauma dysregulates the hypothalamic-pituitary-adrenal (HPA) axis which may become either chronically over-activated or under-responsive following trauma.[62–66] This dysregulation might impact brain areas such as the hippocampus,[65] the amygdala, and the prefrontal cortex.[67] which in turn could contribute to the early emergence of affective dysregulation, cognitive dysfunctions, and attenuated symptoms of psychosis as we observed in our study. Interestingly, sex is an important biological determinant of vulnerability to psychosocial stress.[68] For example, previous studies have reported a down-regulation of diurnal cortisol in girls exposed to pervasive maltreatment, while an over-activation of diurnal cortisol was observed in boys.[69] Recent findings also suggest a sex-specific neural activation model underlying the central stress response featuring asymmetric prefrontal activity in males and primarily limbic activation in females.[68] The present greater vulnerability of males in their early trajectory stresses the importance of sex-sensitive developmental research among genetically high-risk youths having experienced childhood trauma.

Our study presents limitations and strengths that must be considered when interpreting the findings. One of our main strengths is that our measure of abuse and neglect had the advantage of drawing information from multiple sources, including direct interviews and reviews of contemporary medical records, instead of relying only on retrospective questionnaires as in most studies. Our method also allowed us to observe that trauma occurred before 11 years old in 91% of the participants and before 5 years old in 67% of them (see table 2), suggesting that trauma would precede the onset of DSM-IV diagnoses, cognitive deficits, psychotic-like experiences, and poor functioning. One limitation may be that our results, stemming from youths born to an affected parent, would entail, from a stringent point of view, that they would be generalizable only for that high-risk population. However, we and others have previously reported that genotype, phenotype, and developmental findings drawn from highly familial patients, families and high-risk offspring had a substantial resemblance with those extracted from sporadic cases or high-risk children from birth cohorts.[51,70,71] Another limitation is that our longitudinal sample included subjects older than 10 years of age. Since the accumulation of risk indicators following trauma would already be apparent in the younger offspring of our sample, future studies should also include younger children.

Concluding Comments on Clinical Implications

Our findings have several clinical implications. *First,* we found that 43% of the offspring of our sample experienced at least one type of abuse or neglect before the age of 18. This figure is not surprisingly high given that more than 50% of patients affected by schizophrenia or bipolar disorder have consistently reported having experienced childhood trauma,[3,6,8] and given that a parental history of childhood trauma would be among the most important risk factors for child maltreatment.[72] These figures clearly point to the need of inquiring about childhood trauma in the regular medical or psychiatric monitoring of the children born to an affected parent, children who number in the millions in the G7 nations alone.[22] *Second*, the place of exposure to childhood trauma in the *clinical staging* of the risk status, or in algorithms of risk calculators, should definitely be addressed in future research on personalized preventive interventions that would in part be sex specific as our findings suggest.

The present findings may, indeed, orient research towards new targets in preventive interventions, namely trauma focused interventions aiming to delay or block the accumulation of risk factors in high-risk offspring exposed to childhood trauma. Such interventions may, for instance, target emotion regulation, acceptance, interpersonal skills, trauma re-processing, mentalization, and the integration of dissociated ego states.[73] Whereas evidence-based treatments for trauma-exposed children and adolescents are available[74] and widely disseminated,[75] the efficacy of such interventions in genetically high-risk youths has to be better investigated.[15,21] Future intervention studies should also probably evaluate other preventive actions targeting domains that would remain impaired, such as additional cognitive remediation therapy for a child having cognitive deficits. It is noteworthy that several clinical experts consider trauma interventions

appropriate and applicable to patients with an early psychotic disorder and a comorbid trauma-related disorder.[73,76] Therefore, there is no indication that genetically high-risk youths would not be good candidates for such treatments.

Supplementary Material

Supplementary data are available at *Schizophrenia Bulletin Open* online.

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