Bureau, A., Berthelot, N., Ricard, J., Lafrance, C., Jomphe, V., Dioni, A., Fortin-Fabbro, É., Boisvert, M.-C., & Maziade, M. (2023). Heterogeneity in the longitudinal courses of global functioning in children at familial risk of major psychiatric disorders: Association with trauma and familial characteristics. Bipolar Disorders. Online Ahead of Print https://doi.org/10.1111/bdi.13386 CC BY

DOI: 10.1111/bdi.13386

ORIGINAL ARTICLE

BIPOLAR DISORDERS WILEY

Heterogeneity in the longitudinal courses of global functioning in children at familial risk of major psychiatric disorders: Association with trauma and familial characteristics

Alexandre Bureau[1,2] | Nicolas Berthelot[2,3] | Jasmin Ricard[2] | Camille Lafrance[2] | Valérie Jomphe[2] | Abdoulaye Dioni[1] | Énora Fortin-Fabbro[2] | Marie-Claude Boisvert[2] | Michel Maziade[2,4]

[1]Department of Social and Preventive Medicine, Faculty of Medicine, Université Laval, Québec, Quebec, Canada

[2]Cervo Brain Research Centre, Québec, Quebec, Canada

[3]Université du Québec à Trois-Rivières, Department of Nursing Sciences, Trois-Rivieres, Quebec, Canada

[4]Department of Psychiatry and Neuroscience, Faculty of Medicine, Université Laval, Québec, Quebec, Canada

Correspondence
Michel Maziade, Cervo Brain Research Centre, 2301 Av. D'Estimauville, Québec, QC G1E 1T2, Canada.
Email: michel.maziade@fmed.ulaval.ca

Funding information
Canada Research Chairs, Grant/Award Number: 950-200810; Canadian Institutes of Health Research, Grant/Award Number: MOP-114988, MOP-74430 and PCG-155471

Abstract

Objectives: The extent to which heterogeneity in childhood risk trajectories may underlie later heterogeneity in schizophrenia (SZ), bipolar disorder (BP), and major depressive disorder (MDD) remains a chief question. Answers may optimally be found by studying the longitudinal trajectories of children born to an affected parent. We aimed to differentiate trajectories of global functioning and their sensitive periods from the age of 6 to 17 years in children at familial risk (FHRs).

Methods: *First*, a latent class mixed model analysis (LCMM) was applied to yearly ratings of the Children's Global Assessment Scale (CGAS) from the age of 6 to 17 years in 170 FHRs born to a parent affected by DSM-IV SZ ($N=37$), BP ($N=82$) or MDD ($N=51$). Then, we compared the obtained Classes or trajectories of FHRs in terms of sex, parental diagnosis, IQ, child clinical status, childhood trauma, polygenic risk score (PRS), and outcome in transition to illness.

Results: The LCMM on yearly CGAS trajectories identified a 4-class solution showing markedly different childhood and adolescence dynamic courses and temporal vulnerability windows marked by a functioning decline and a degree of specificity in parental diagnosis. Moreover, IQ, trauma exposure, PRS level, and timing of later transition to illness differentiated the trajectories. Almost half (46%) of the FHRs exhibited a good and stable global functioning trajectory.

Conclusions: FHRs of major psychiatric disorders show heterogeneous functional decline during development associated with parental diagnosis, polygenic risk loading, and childhood trauma.

KEYWORDS
affected parents, bipolar disorder, childhood/adolescence risk trajectories, children at familial risk, longitudinal study, major depressive disorder, risk studies, schizophrenia

1 | INTRODUCTION

Increasing knowledge has been extracted from studies of children born to a parent affected by psychosis, bipolar, or major depressive disorders (MDDs)[1-6] and from developmental studies suggesting heterogeneity in pathways of risk and vulnerability windows.[1,7] Chief questions remain, particularly in the extent to which heterogeneity in childhood risk trajectories may underlie later heterogeneity in schizophrenia (SZ), bipolar disorder (BP), and MDD. Although the Clinical High-Risk (CHRs) individuals have been extensively studied mostly in a later period of life,[8] children at familial risk (FHRs) represent a key source of early childhood developmental information about the illness origin since they have a 10- to 20-fold increased risk of later developing the disorder of their parent or a spectrum disorder.[3,6,9,10,11] This situation is not negligible since these children amount to 10 million in the G7 nations alone.[5]

Recent longitudinal studies of bipolar offspring[1,2] have begun to define sequential preclinical stages in FHRs and suggested a degree of heterogeneity in the courses of these FHRs. For instance, the Canadian study of Duffy et al.[1] observed that the offspring of bipolar parents having a poor response to lithium had a different clinical profile than the offspring of parents who were good responders. This merits further investigation not only for bipolar offspring but also for MDD and SZ spectrum disorders given the recognized within-diagnosis heterogeneity of the three major psychiatric disorders which likely have roots in early development.[12,13] Most longitudinal studies investigated FHRs descending from only one parental illness and used solely clinical phenotypes as risk factors.[1-3] Relatedly, a new task force report[4] has recommended that future FHRs studies increase their power by combining clinical and biological markers and by including more than one parental psychiatric disorder within the same study since there is evidence of shared transmission and etiology for the three parental psychiatric illnesses.[6,9,14] Such advice might help to investigate differences among FHRs in their childhood developmental course.

The childhood trajectory of global functioning has been demonstrated as relevant for the understanding of the developmental roots of affective disorder and psychosis. A few bodies of data have looked at the progression of global functioning in childhood and adolescence as assessed by the Children Global Assessment Scale (CGAS) and consistently found general patterns consisting of three to four different longitudinal trajectories of global functioning in FHRs, in CHRs of psychosis individuals or in retrospective studies of SZ and BP patients. In brief, these results suggested that some FHRs would have a stable functioning trajectory with a good level of functioning, others show a stable trajectory with an intermediate functioning and one subgroup of FHRs displays a course characterized by a deteriorating functioning.[15-18] Similarly, in a 20-year study of patients having an affective or non-affective psychosis, Velthorst et al.[19] reported, by means of a latent class growth analysis of retrospective data, four different childhood functioning trajectories: a normally preserved functioning course, a moderately impaired course, a severely impaired course, and a profoundly impaired course.

Since these previous data on early course of global functioning justify a deeper characterization and the further digging into conceivable sources of developmental heterogeneity, since we had as a measure of global functioning, yearly ratings of the CGAS across childhood and adolescence, and since the field needs new longitudinal childhood studies of premorbid functioning, we were justified to undertake (i) a follow-up of FHRs from early childhood until late adolescence to better inspect vulnerability windows, (ii) the inclusion of both psychosis and mood disorders as parental diagnoses, and (iii) the combining of prospective measures of environmental, clinical, and biological risk variables.

Based on the above findings, we hypothesized that (i) we would find heterogeneity among FHRs functioning trajectories, particularly among abnormal functioning trajectories and (ii) heterogeneity would be marked by differences in parental diagnosis, FHRs' clinical characteristics, environmental adversity, and genetic factors.

Our first objective was to apply a latent class mixed modeling to the course of global functioning in FHRs from the age of 6 to 17 years based on the yearly rating of the CGAS.[20] We herein distinguished four global functioning trajectories with temporally different shapes. In a *second* step, we performed an external validity analysis by comparing the obtained trajectories in terms of sex, parental diagnosis, IQ, non-psychotic non-mood childhood DSM diagnoses, childhood trauma, polygenic risk score (PRS) as a genomic index of vulnerability, and outcome in transition to illness.

2 | METHODS

2.1 | Sample of offspring

Offspring *inclusion criteria* were having a parent with a DSM-IV diagnosis of SZ, BP, or MDD. The *exclusion criteria* were the presence of a diagnosis of DSM-IV psychotic disorder, BP or MDD, and spectrum disorders, autism, brain trauma, and metabolic disorders. The sample consisted of 170 FHRs that included 65 singletons, 36 sibling pairs, and 11 sibships of three children. All participants were Caucasians. The average age of FHRs at entry in the study was 14.9 years (range 5.2–27.6 years). The follow-up to assess clinical status and a transition to SZ, BP, or MDD extended to the average age of 21.0 years (range 8.5–36.5 years).

Out of the 170 offspring, 82 were offspring of an affected parent who were members of followed-up multigenerational kindreds densely affected by SZ and BP that were the object of several previously published reports.[21-23] The other 88 were offspring of an affected parent who were children referred to our regional youth mental health care from the CIUSSS de la Capitale Nationale, the institution that covers under a public health care system all child and family mental health services in the Quebec City area (800,000 population), Canada. These offspring have also been the subjects of previous reports.[24,25] To examine a possible bias created by the two

sampling sources, we looked at the distribution of the offspring from the two sampling sources in the four trajectory Classes obtained from the latent class mixed model (LCMM) and found a homogeneous distribution of the two subgroups of offspring in the Classes (see Table S7).

The sample characteristics are described in detail in Table S1. It included 48% of girls and 19% of these FHRs had transitioned to first episodes of psychosis or mood disorders at follow-up. The retention rate was 93%. Signed consent was obtained from all participants or the parents of participants under 18, as reviewed by our University Ethics Committee.

2.2 | Measures

2.2.1 | Global Assessment of Functioning

Global functioning was measured by means of the CGAS[20] for children under 18 that we rated year by year, from age 6 to 17 years according to the life chart procedure of Post et al.[26] that we used in previous studies.[27,28]

The yearly ratings were administered by experienced clinical professionals who then made a team consensus. Ratings relied on all available information, clinical interviews, family informants, and medical records, according to a method used in previous studies.[27,28] For the 67% of FHRs recruited before age 18, the yearly CGAS ratings were prospective or had a short recall period. Ratings were retrospective for the rest of the sample. Figure S1 in online supplement provides the distribution of the time span of yearly CGAS ratings obtained between the age 6 and 17 years (average span 9.12 years; SD 2.80 years). The Figure also shows that the majority of subjects (75%) had yearly CGAS measurements spanning 8 years or more. The sample had an average span of measurements of 9.12 years (SD 2.80 years).

2.2.2 | Clinical diagnoses of offspring and parents

For the parents, a consensus best estimate lifetime diagnostic procedure based on multiple sources of information was administered to the parents by experienced clinical professionnals[29] as previously described.[30] The procedure included the Structured Clinical Interview for DSM-IV disorders (*Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorder* [SCID]),[31,32] family interviews, and all available medical records across a lifetime according to a previous method showing reliability.[21,29,33,34] All medical charts were reviewed for each patient. The public universal health care in Québec makes easily available the out- and in-patient medical records across the patient's life. Based on this lifetime information (obtained from interview, medical records, and family informant's interviews), a DSM-IV diagnosis of SZ spectrum disorder, BP, or MDD was made by a panel of research psychiatrists or experienced clinicians who reached a consensus. When absence of consensus the case was rejected.

For the children, the same methods were applied except for the administration of the *Kiddie-Schedule for Affective Disorders and Schizophrenia*[35] with the parents of children under 18 in the presence of the child, or the SCID to offspring over 18 as we also have previously reported.[27,28,36]

The *presence of psychotic symptoms* in the lifetime diagnosis of bipolar parents or parents having a diagnosis of MDD was drawn from two sources: (i) the symptoms items of the SCID interview that explicitly inquires about psychotic symptoms (delusions, hallucinations, disorganized speech, disorganized or catatonic behavior, and negative symptoms), the SCID interview being done with the patient and a family informant and (ii) the review of the medical charts. The presence or absence of psychotic symptoms was then judged by consensus during the best estimate diagnosis consensus session.

The parents having SZ, BP with psychotic features and MDD with psychotic features were combined to form the subgroup of parents defined as having psychosis. In total, 12% of the MDD parents and 45% of BP parents had psychosis.

2.2.3 | Global IQ

We measured IQ at entry in the study by means of the *Wechsler Intelligence Scale for Children (WISC-III or WISC-V)* for subjects under 15 and with the *Wechsler Adult Intelligence Scale (WAIS-III or WAIS-IV) for subjects 18 to 27 years old*.

2.2.4 | Genotyping and genotype imputation

Whole-genome single nucleotide polymorphisms (SNPs) genotyping with Infinium Human OmniExpress24 Illumina microchips was made using DNA extracted from immortalized lymphocytes or fresh blood by affinity column (Midi prep Qiagen). Only SNPs with a minimum call rate of 98 percent were retained. We prepared genotype data for imputation using the HRC-1000G-check-bim.pl script (www.well.ox.ac.uk/~wrayner/tools/), which removed 5934 SNPs (0.9%) failing quality checks (see Data S1), leaving 635,147 SNPs. The imputation of all common variants was then made by the Michigan Imputation Server (imputationserver.sph.umich.edu) based on the Haplotype reference consortium panel.[37]

2.2.5 | Polygenic risk scores calculation

In addition to the genomic data, we obtained results on odds ratios (ORs) and *p*-values for the association of approximately 10 million autosomal SNPs with SZ, BP, and SZ and BP combined from the Psychiatric Genomics Consortium.[38] We performed LD clumping based on genotype data on the familial sample with plink (www.cog-genomics.org/plink2). We discarded SNPs within 500 kb and with an R-squared ≥0.1 with an SNP more significantly associated with SZ

and BP. Finally, we selected the SNPs that had *p*-values for association with SZ, BP, or SZ and BP under 0.10 in the calculation of the PRSs as in a previous report.[22] The PRS was dichotomized at the 75th percentile to form a high- and low-genetic risk group.

2.2.6 | Trauma

Five types of childhood trauma were assessed: physical abuse, sexual abuse, emotional abuse, neglect (physical and emotional), and witnessing domestic violence. As in previous studies,[28,39] we performed a semi-structured interview (Traumatic Event Screening Inventory)[40] with offspring or one of their parents and a rating of all available lifetime information: clinical interviews, contacts with families, research briefs of the home visits, and medical records collected throughout the longitudinal follow-up. This information was then rated consensually by two experts in childhood trauma blind to the other measures. Further details about the assessment are provided in Data S1.

2.3 | Statistical analysis

Our analysis of CGAS yearly rating trajectories followed the principles of growth mixture modeling of developmental trajectories[41] with the modification that, for the trajectory shape, instead of the usual polynomial curves,[42] we opted for linear B-splines with internal knots at 9, 11, 13, and 15 years of age, to capture potential abrupt changes in slope at these ages. The random effect for the intercept captures variation in the overall level within class and ensures that latent classes represent different trajectory shapes and not merely different mean functioning levels. This model is also known as a LCMM, a term we prefer in the present case given there is no notion of growth in functioning. LCMMs ranging from 1 to 8 classes were estimated by maximum likelihood, and the Bayesian information criterion (BIC) was computed as fit index. Posterior probabilities of class membership were computed for each subject from the LCMM. Analyses were performed using the LCMM R package.[43]

For descriptive purposes, mean IQ at entry in the study and Kaplan–Meier curves of survival free of a DSM-5 diagnosis of SZ, BP, or MDD or a spectrum disorder were estimated for each class, after assigning subjects to their most likely class.

In a subsequent external validity analysis to test differences among the obtained trajectories, we examined the association between the latent classes and the external variables such as childhood trauma, IQ, PRS, and parental diagnosis (with or without the presence of psychosis). We tabulated each variable in turn among the subjects assigned to each class based on maximum class membership probability for a descriptive purpose only. *Univariate analysis*: To formally estimate and test the association of each variable with class membership, we refitted LCMMs with each variable as an explanatory variable for both class membership and mean CGAS level given class membership, keeping the number of classes fixed, using all subjects with available measures for each variable. For dichotomous variables, we reported ORs of membership to a given class compared to the reference class between subjects with and without the characteristic of interest (e.g., presence of childhood trauma) with pointwise 95% confidence intervals. We tested variables influencing class membership using likelihood ratio (LR) tests. *Multivariable analysis*: We fitted a model with the four examined dichotomous predictors (sex, childhood trauma, parental psychosis, and dichotomized PRS) to explore the latent class distribution for different profiles of child and parental characteristics[44] on a reduced set of subjects with observed values on all predictors. Confidence intervals for the latent class distribution were computed using the delta method for multinomial probabilities.

3 | RESULTS

The BIC of LCMMs as a function of the number of classes is shown in Figure S2 in online supplement. The BIC declined rapidly from 1 to 4 classes, then more slowly to reach a minimum value at a solution of 7 classes. The 7-class solution included 2 classes that were the highest probability class for fewer than 10% of subjects (Figure S3 in supplement), thus representing rare trajectories. Three empirical reasons made us choose the 4-class solution: (i) it allowed a clearer clinical interpretation of each class; (ii) each of the four classes contained at least 15% of the sample and (iii) the 4-class solution BIC was only slightly higher than for the 7-class solution. The 4-class solution also satisfied recommended criteria of model adequacy (average posterior probabilities of class membership >0.7 and odds of correct classification based on these probabilities >5).[44]

The CGAS trajectories of the 4-class solution showed noticeably different courses depicted in Figure 1 with slopes reported in Table S2 in online supplement. Class 1 defined the largest subtype of FHRs (46%) that had a functional and stable CGAS score in the 80 range over the entire span from ages 6 to 17 (*Stable higher functioning trajectory*). Class 2 FHRs (15%) showed a trajectory marked by a fairly high average CGAS of 77 from age 6 to 11 years which then considerably declined in adolescence (from 11 to 15 years) down to a low average level of 57 (*Early adolescence decline trajectory*). The two last Classes had the most deterioration. Class 3 FHRs (19%) exhibited an overall very dysfunctional CGAS trajectory. They started at age 6 with a functioning below 70 and progressed down to an average CGAS under 55 in early adolescence which then tended to slightly increase from age 13 but remained below the 65 level (*Stable lower functioning trajectory*). Class 4 FHRs with *Preadolescence decline with recovery* (20%) started with the lowest average CGAS hovering around 63 from age 6 to 11 with a subsequent functioning increase from 13 to 15 years of age reaching a CGAS around 70.

We found no familial resemblance in class membership (Figure 1): the two siblings were assigned to the same class in 38% of the sibling pairs, a proportion not significantly higher than the 33% expected under the independence hypothesis ($Z = 0.83$,

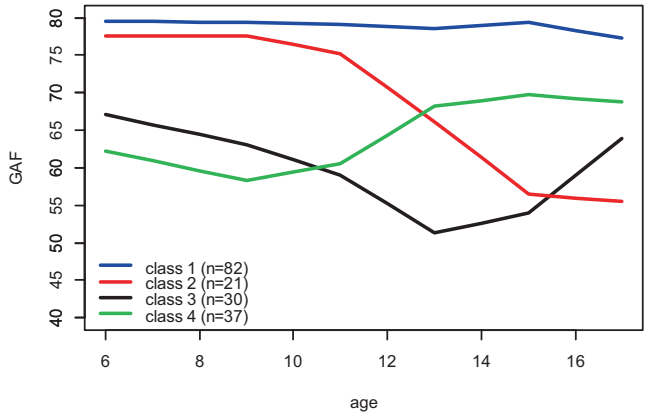

FIGURE 1 Mean class-specific CGAS trajectories from age 6 to 17 years detected by a latent class mixed model (LCMM) analysis with a 4-class solution. *n*: number of subjects assigned to each class based on highest posterior probability. The estimated proportions in each class were: 46% in Class 1, 19% in Class 2, 15% in Class 3, and 20% in Class 4. We found no evidence of *familial resemblance* of class membership: the two siblings were assigned to the same class in 38% of the sibling pairs, a proportion not significantly higher than the 33% expected under the independence hypothesis ($Z=0.83$, $p=0.41$). No statistically significant difference in class distribution or mean CGAS level within-class was found between the 33% of subjects with entirely *retrospective CGAS ratings* and the other subjects (LR test with 4 df, $p=0.08$).

$p=0.41$). Thus, it was not required to take into account family relatedness in the analyses.

No statistically significant difference in class distribution or mean CGAS level within-class was found between the 33% of subjects with entirely *retrospective* CGAS *ratings* and those with prospective ratings (LR test with 4 df, $p=0.08$). Adjusting for the span of yearly CGAS ratings revealed differences among the classes (Table S3 in supplement) but produced trajectory shapes almost identical to Figure 1 and similar class assignments (Figure S4 in supplement). Since interpreting results from a model conditioning on drop-out patterns is difficult,[45] we did not retain the span of CGAS ratings in our models.

Then, we inspected potential differences among the four classes in terms of parent or child characteristics in two related steps (Tables 1 and 2). We first presented more simply in Table 1 the LCMM derived OR for each of the external variables in univariate analyses. Then, we presented the latent class distribution for the four dichotomous external variable profiles in a multivariable analysis where the effect of one variable was controlled for the effect of the three others being entered in the model. Because of its good and steady longitudinal functioning, Class 1 was considered a reference group in some analyses. *Exposure to childhood trauma* was associated with class membership (Table 1; LR test, $p=0.002$). The odds of belonging to Class 3 versus Class 1 were nearly 8 times higher in children with childhood trauma than those without. There was no association of class membership with sex (LR test $p=0.87$) in the univariate analysis. We obtained in Table 1 a trend of differences ($p=0.10$) at the LR test with 3 degrees of freedom for the association of the SZ + BP PRS involving all the four classes membership. However, in Table 1 the odds of having a PRS in the top quartile for the FHRs belonging to Classes 3 (Stable Low Functioning) were more than 4 times higher (OR = 4.7; 95% CI = [1.18, 18.7]) than in Class 1 (Stable high functioning). Moreover, considering the model with multiple predictors estimated from LCMM, when one examines in Table 2 the distribution of class membership for various profiles of FHRs in terms of child and parental characteristics, we observed congruent results. Table 2 shows that in the children of parents with psychosis, both boys and girls having exposure to maltreatment and high PRS had close to 50% predicted probability of belonging to the *Stable Low functioning* Class 3. The confidence intervals for the latter two predicted probabilities [46%, 95% CI = (22, 72) and 50%, 95% CI = (22, 78)] exceeded the overall probability of Class 3, while the probabilities among children with low PRS were close to or lower than the overall Class 3 probability of 14%. Table 2 also suggests that certain subgroups of boys or girls are less likely to be part of specific classes. For instance, girls of parents without psychosis presenting trauma, high PRS or both were less likely to be in Class 1, whereas boys with psychotic parents were less likely to be in Class 2. We also performed the same LCMM when entering either the SZ PRS or the BP PRS, and the maximum log of the likelihood for each LCMM analysis was not higher than that from the LCMM using the combined SZ + BP PRS: respectively −4360 with the BP PRS, −4362 with the SZ PRS versus −4359 with the combined PRS. We thus pursued the following analyses with the LCMM using the combined PRS.

The presence of psychosis in parents was not found homogeneously distributed among the 4 Classes ($p=0.0012$; Table 1). Table 1 may suggest at a first glance a counter-intuitive finding, that is, Class 1 having a higher rate of psychotic parents. But when one considers that two ORs in Table 1 (Classes 3 vs. 1 and Classes 4 vs. 1) did not reach significance and the relatively similar proportions of psychotic parents in Class 1, Class 3, and Class 4, the observed heterogeneity would be mainly due to a lower presence of parental psychosis in Class 2 rather than an overproportion of psychotic parents in Class 1.

In Table S4, we observed a trend of association ($p=0.06$) with DSM-IV parental diagnoses suggesting that offspring of the parents with mood disorders, particularly with BP, might tend to be more represented in Class 1 having a *Stable higher functioning trajectory*. The presence of psychosis in parents was not found homogeneously distributed among the four Classes ($p=0.0012$; Table 1) which would be mainly due to a lower presence of parental psychosis in Class 2.

Global IQ at entry in the study showed that reference Class 1 had a mean IQ of 100.9, whereas Classes 2, 3, and 4 FHRs had, respectively, a mean IQ of 98.0, 90.3, and 92.9 ($F=8.98$, df = 3, $p<0.0001$).

We examined whether the *early timing and type of transitions* would also distinguish the four Classes, even though all participants had not reached the full age of illness incidence in this developmental study. Figure 2 illustrates the cumulative incidence of transitions

TABLE 1 Comparisons of latent class trajectories on parental and child characteristics.

Variable	Counts of subjects in latent trajectories[a] *N* (%)								Effect on class membership OR (95% CI)[b]						p[c]
	Class 1 (*N* = 82)		Class 2 (*N* = 21)		Class 3 (*N* = 30)		Class 4 (*N* = 37)		Class 2 versus Class 1		Class 3 versus Class 1		Class 4 versus Class 1		
Sex (*N* = 170)															
Male	43	(52)	6	(29)	19	(63)	21	(57)	0.49	(0.16, 1.52)	1.55	(0.51, 4.73)	1.14	(0.41, 3.17)	0.87
Female	39	(48)	15	(71)	11	(37)	16	(43)	—	—	—	—	—	—	—
Model-estimated % for Male	—	52	—	35	—	63	—	56	—	—	—	—	—	—	—
Parental psychosis (*N* = 170)[d]															
Yes	45	(55)	5	(24)	14	(48)	16	(43)	0.11	(0.03, 0.38)	0.70	(0.22, 2.24)	0.37	(0.13, 1.09)	0.0012
No	37	(45)	16	(76)	15	(52)	21	(57)	—	—	—	—	—	—	—
Model-estimated % for Yes	—	62	—	15	—	53	—	38	—	—	—	—	—	—	—
Childhood trauma[e] (*N* = 169)															
Yes	24	(29)	11	(55)	21	(70)	18	(49)	2.80	(0.97, 7.80)	7.80	(1.80, 34.9)	1.10	(0.35, 3.40)	0.0019
No	58	(71)	9	(45)	9	(30)	19	(51)	—	—	—	—	—	—	—
Model-estimated % for Yes	—	31	—	55	—	78	—	32	—	—	—	—	—	—	—
Polygenic risk score (SZ + BP) (*N* = 129)[f,g]															
>75th percentile	11	(18)	5	(33)	6	(29)	10	(32)	1.96	(0.48, 8.09)	4.70	(1.18, 18.7)	2.74	(0.81, 9.27)	0.10
<75th percentile	51	(82)	10	(67)	15	(71)	21	(68)	—	—	—	—	—	—	—
Model-estimated % for >75th	—	15	—	26	—	46	—	33	—	—	—	—	—	—	—

[a]Counts of subjects assigned to each class are for descriptive purposes only. Assignment based on highest posterior probability can distort proportions of characteristics for each class. The model-based percentages represent more accurately these proportions.

[b]Odds ratio of specified class compared to class 1 for the variable first level, with pointwise Wald 95% confidence interval constructed as exp{log-OR ± 1.96 SE(log-OR)}.

[c]*p*-value of likelihood ratio test with 3 degrees of freedom of the association of the variable to the classes membership.

[d]There were 12% of the MDD parents and 45% of BP had psychotic features. In all, the parents with SZ, with BP with psychosis and with MDD with psychosis were combined to form the subgroup of parents with psychosis.

[e]In addition, children exposed to childhood trauma had a CGAS on average 4 points lower than children without this exposure within the same class (Wald test, $p = 0.01$), the sole variable with such an effect above and beyond the association with class membership (Table S5 in online supplement).

[f]For a comparison of FHRs who were genotyped to FHRs who were not see footnote of Table 2.

[g]PRS was calculated as in Methods i.e., using odds ratios and *p*-values for the association of approximatively 10 million autosomal SNPs with SZ and BP combined from the Psychiatric Genomics Consortium.[38]

TABLE 2 Distribution of latent classes predicted by the LCMM model with multiple predictors for various profiles of child and parental characteristics.[a]

Profile	Class 1 Prob[b] (95% CI)	Class 2 Prob (95% CI)	Class 3 Prob (95% CI)	Class 4 Prob (95% CI)
Parents without psychosis				
Girls with no other risk factor	0.46 (0.23, 0.71)	0.32 (0.09, 0.70)	0.04 (0.01, 0.15)	0.18 (0.08, 0.35)
Girls with childhood maltreatment	**0.24 (0.09, 0.51)**	0.46 (0.14, 0.81)	0.11 (0.03, 0.37)	0.19 (0.07, 0.44)
Girls with high PRS[c]	**0.21 (0.07, 0.48)**	0.40 (0.09, 0.82)	0.10 (0.02, 0.35)	0.29 (0.10, 0.62)
Girls with childhood maltreatment and high PRS	**0.08 (0.02, 0.27)**	0.43 (0.10, 0.84)	0.25 (0.06, 0.64)	0.24 (0.07, 0.58)
Boys with no other risk factor	0.66 (0.45, 0.82)	**0.05 (0.02, 0.13)**	0.03 (0.01, 0.15)	0.25 (0.11, 0.48)
Boys with childhood maltreatment	0.43 (0.22, 0.67)	0.10 (0.03, 0.29)	0.14 (0.04, 0.39)	0.34 (0.15, 0.60)
Boys with high PRS	0.34 (0.13, 0.63)	0.08 (0.02, 0.25)	0.11 (0.02, 0.39)	**0.48 (0.21, 0.75)**
Boys with childhood maltreatment and high PRS	**0.15 (0.04, 0.42)**	0.09 (0.02, 0.33)	0.31 (0.08, 0.69)	0.44 (0.16, 0.77)
Parents with psychosis				
Girls with no other risk factor	**0.81 (0.59, 0.93)**	0.06 (0.01, 0.38)	0.05 (0.01, 0.19)	0.08 (0.03, 0.21)
Girls with childhood maltreatment	0.57 (0.34, 0.77)	0.11 (0.02, 0.45)	0.20 (0.07, 0.46)	0.11 (0.04, 0.26)
Girls with high PRS	0.52 (0.26, 0.77)	0.10 (0.01, 0.60)	0.19 (0.05, 0.50)	0.19 (0.06, 0.43)
Girls with childhood maltreatment and high PRS	**0.22 (0.09, 0.46)**	0.12 (0.02, 0.55)	**0.50 (0.22, 0.78)**	0.16 (0.06, 0.39)
Boys with no other risk factor	**0.87 (0.73, 0.95)**	**0.01 (0.00, 0.03)**	**0.03 (0.01, 0.13)**	0.09 (0.03, 0.23)
Boys with childhood maltreatment	0.68 (0.50, 0.82)	**0.02 (0.01, 0.05)**	0.17 (0.07, 0.34)	0.14 (0.05, 0.30)
Boys with high PRS	0.61 (0.35, 0.82)	**0.01 (0.00, 0.09)**	0.15 (0.04, 0.42)	0.22 (0.08, 0.49)
Boys with childhood maltreatment and high PRS	0.30 (0.13, 0.56)	**0.02 (0.00, 0.08)**	**0.46 (0.22, 0.72)**	0.22 (0.08, 0.48)
Overall	0.53	0.15	0.14	0.19

Note: Bold values refer to confidence intervals that do not contain the associated overall probability.

[a]Analysis performed on 128 subjects with complete data. The 42 excluded subjects were mainly subjects without genotype. Compared to the subjects with complete data, excluded subjects were not significantly different in terms of duration of follow-up, sex, presence of childhood maltreatment. They were significantly younger at the last visit (mean [SD] of 16.8 [4.8] years vs. 22.4 [7.8] years) and fewer had a parent with psychosis (32% vs. 52%).

[b]Model-estimated probability of class membership with 95% confidence interval.

[c]Polygenic risk score for SZ and BP combined.

to a major psychiatric disorder revealing that illness incidences in Class 2 FHRs with *Early adolescence decline* happened rather early, largely between 13 and 18 years of age, following by a few years their CGAS decline, and were mainly MDDs (Table S6). By contrast, transitions in Class 3 FHRs with *Stable lower functioning* were spread rather evenly from 8 to 28 years of age. Subjects in Class 1 Stable higher functioning and Class 4 *Preadolescence decline with recovery* were overall free from illness until age 17 up to which CGAS trajectories extend. Expectedly, Class 1 consisting of high-functioning offspring exhibited the lowest cumulative incidence which started rising only after 20 years of age, whereas Class 2 and Class 3 had the highest cumulative incidence. Table S6 in supplement displays the distribution of diagnoses.

As regards the presence of childhood non-psychotic non-mood DSM 5 diagnoses between 6 and 17 years of age, Table S8A presents the potential differences among the four FHRs Classes in rates of ADHD, neurodevelopmental disorders or anxiety disorders. Table S8B shows that Class 3 (*Stable lower functioning*) FHRs had more comorbid childhood diagnoses than Class 1 (*Stable higher functioning*) FHRs.

4 | DISCUSSION

The LCMM analysis of the yearly CGAS scores from age 6 to 17 detected four global functioning trajectories in children at risk of SZ and MDD. The distinctive trajectories differed in terms of temporal shape or vulnerability windows, IQ level, childhood trauma, genetic vulnerability, and timing and rate of ensuing transitions to illness. Our multivariate design including three parental diagnoses, the first of its kind to our knowledge, uncovered new dynamic information about potential developmental sources of illness heterogeneity that have methodological and clinical implications. Encouragingly, the present trajectories retain some architectural resemblance with the less defined patterns from earlier mentioned studies[15-19] which would increase the likelihood of future replication. Our study adds substantive evidence of specific timings in different functioning declines and suggests an involvement of both environmental and genetic factors in the distinction among outcomes.

Table 3 summarizes an interpretation of the contrasts in sensitive periods and clinical portrait among the four Classes or trajectories.

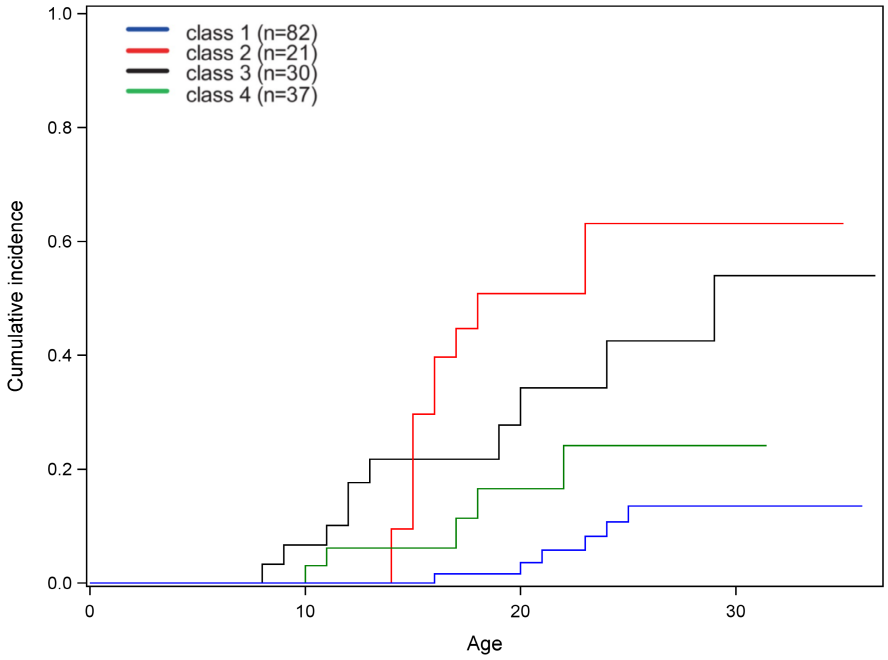

FIGURE 2 Cumulative incidence of transition to a DSM-5 diagnosis of SZ, BP or MDD. Cumulative incidence was estimated using the Kaplan–Meier estimator applied to subjects assigned to each class based on highest posterior probability. See legend of Figure 1 for color code. There was no significant difference in age at the last follow-up between subjects with and without transition ($p = 0.82$) suggesting no violation of the censoring-at-random hypothesis. Hazard of transition differed significantly among the classes (log-rank test chi-square = 29.4, df = 3, $p < 0.0001$). One must note that all participants had not reached the full age of illness incidence in this developmental study. This to an extent may limit the appraisal of outcome and exact later lifetime rate of transition.

In brief, a first Class (the *Stable Higher Functioning* trajectory) represented a majority (46%) of the FHR boys and girls of our sample who, even though they had undergone some of the highest risk conditions known in childhood,[5] had a good and stable longitudinal CGAS functioning through almost the peak period of risk of onset of illness. These FHRs would have a lower PRS and lesser exposure to trauma suggesting lower genetic and environmental liabilities. In all, almost half of the children born to an affected parent would fare well which may be an important message for the clinician toward some affected parents who worry too much about their children by overinterpreting the overall risk pending over them. However, it is also noteworthy that a small proportion of these FHRs would nevertheless transition to a major psychiatric disorder (13% cumulative incidence by age 25) which certainly deserves future investigation.

The three other trajectories (Table 3) exhibited distinct periods of decline and rates of transitions. Unlike Classes 3 and 4, the Class 2 (the *Early Adolescence Decline* trajectory) FHRs of whom mostly young girls more likely to be born to mothers having an affective disorder without psychosis experienced an abrupt CGAS decline in early adolescence, followed by transitions to first episodes of MDD in later adolescence. Previous studies of offspring MDD parents have reported, in the same life period, lower global functioning when compared to offpring of BP or control parents.[46] Weissman et al.[47] similarly reported in offspring of MDD parents a severe burden in terms of poor functioning and morbidity. Class 3 (the *Stable Lower Functioning* trajectory) FHRs exhibited the most deteriorated functioning trajectory from childhood with possible further descent in adolescence and had the poorest outcome (Table 3). Class 4 (the *Preadolescence Decline with Recovery* trajectory) to an extent resembled Class 3 in early childhood but subsequently differed by having a relative CGAS recovery in adolescence and an overall lower transition rate as outcome. Class 4 late functioning improvement needs replication but it could be compatible with our previously reported data suggesting that compensatory or protective mechanisms could be implicated in the development of major psychiatric disorders[27] and psychopathology.[7,48]

Noteworthy, although bipolar offspring would display a higher PRS than controls,[49] our findings suggest that both a higher PRS and trauma exposure would modulate the form, timing or transition outcome of specific trajectories such as the Class 3 FHRs with *Stable lower functioning* in comparison to the Class 1 FHRs with *Stable higher functioning*. Childhood trauma has been documented as having a major effect in major psychiatric disorders,[39,50] and an early effect that could, for instance, be mediated through an impact on cognitive dysfunctions in childhood[39] or on the accumulation of risk factors in FHRs.[25,28,51,52,53,54,55]

Methodologically, most previous studies of FHRs concentrated on only one parental diagnosis, whereas we sampled FHRs born from a parent affected by either one of the three major diagnoses which may explain differences in results with the former studies. However, the Duffy et al's Canadian longitudinal study[1] of FHRs of a BP parent compared the FHRs of parents with a good response

TABLE 3 FHRs profile in each of the four trajectory classes obtained by means of a LCMM analysis.

Class 1 stable higher functioning trajectory: These FHRs kept a good functioning course across childhood and adolescence, had higher IQs, were less likely to have been exposed to childhood trauma and tended to display a lower genetic load as indexed by the PRS. A small proportion nonetheless transitioned to an affective or non-affective disorder but at a later life period than the FHRs of the other classes.
Class 2 early adolescence decline trajectory: This trajectory would characterize mostly young FHR girls with a parent affected by a mood disorder who would be more vulnerable to a functioning decline in early adolescence followed in later adolescence by early transition to a major depressive disorder. These FHRs had higher IQs at the level of Class 1 FHRs, were more likely to be exposed to childhood trauma and to have a high-genetic vulnerability based on the PRS.
Class 3 stable lower functioning trajectory: These FHRs born to a parent having affective or non-affective psychosis, would carry a as high liability toward a transition as Class 2 FHRs but over a wider time span from childhood to young adulthood. They presented the most deteriorated functioning course with a CGAS under 60 all along childhood and adolescence, had lower IQs, were more likely to be exposed to childhood trauma and to have a high-genetic vulnerability as indexed the PRS.
Class 4 preadolescence decline with recovery: This peculiar trajectory exhibited a decline in childhood to a CGAS lower than 60 that would then slightly recuperate in adolescence. These FHRs had lower IQs and were exposed or not to childhood trauma.

Note: FHRs: children at familial risk born to a parent affected by schizophrenia, bipolar disorder, or major depressive disorder; LCMM: latent class mixed model; PRS: combined schizophrenia and bipolar disorder polygenic risk score.

to lithium to those of non-responder parents. They observed early global functioning declines (as measured by the GAF) but mainly in the offspring of lithium non-responder parents. This difference is congruent with our finding heterogeneous global functioning trajectories in FHRs. Moreover, as in our data, Duffy et al's findings suggest that a large proportion of FHRs would keep a fairly good functioning across development.

Our data would pinpoint that not only offspring of a BP parent but also those of parents with MDD or SZ might go through four possible functional decline trajectories with dissimilar developmental sequences and different vulnerability windows that may help early detection of the most at risk. Regarding future research, our data suggest that sampling methods could influence the results in variability among risk trajectories.

Our findings have clinical implications as they could inform about the practice of individualized surveillance among the siblings born to an affected parent. *First*, starting with simple serial measures of CGAS that most practitioners are familiar with, our study uncovered differing risk trajectories in terms of specific timings and outcomes, a finding concordant with hypotheses from the extensive review of Gee.[7] *Second*, as we previously argued,[5] the majority of affected parents are known in the clinic and can be interrogated about their children's functioning. *Third*, the presently observed limited inter-sibling resemblance in trajectories suggests asking questions about family or school functioning, or inquiring for change in functioning from one parental visit to the next. This might help distinguish among the siblings who would merit greater surveillance adjustment or an orientation toward child mental health services. *Fourth*, our findings raise the need of considering timing in the gathering and the interpretation of clinical information. Just as an example, regarding the Class 2 FHRs, the clinician should be alarmed when the child exhibits a functioning decline in preadolescence and be on the alert the following years for an emergence of first symptoms. An earlier timing of functioning decline might be particularly detrimental for later development since it may cause a child to miss social or academic opportunities, two protective factors that could contribute to mitigate the risk trajectory.

Our study has limitations and strengths. Among the strengths of our longitudinal study are the number of measures taken in the offspring and parents, both clinical and environmental that were combined with a genomic indicator.[4,48] A *first* limitation was that, despite the relatively large sample size, the possibility of type 2 errors in the detection of class predictors remains. A larger sample might also have increased the number of interpretable trajectories. *Second*, we did not include a control group. Our aim was to investigate the longitudinal trajectories in children living in a high-risk situation,[4] and not to compare the rates of risk indicators to those in the population, the latter having already been shown to be considerably lower.[27,30] *Third*, this is an early developmental study and several FHRs had not yet reached the full age of incidence of major psychiatric disorders. This to an extent may limit the appraisal of outcome and later lifetime rate of transition. *Fourth*, IQ was measured at entry of the study and unfortunately did not provide a longitudinal profile. *Fifth*, the characterization of the parental illness in high-risk studies such as ours has been concentrated on diagnosis only. Given the clear within-diagnosis heterogeneity among adult BP, SZ, and MDD, longitudinal high-risk studies should probably refine parental clinical and biological subtype measurements in an attempt to further delineate heterogeneity in FHRs trajectories and outcome. Refinement of parental illness definitions could help enhance relationships with the differences among FHRs observed in previous studies in terms of developmental, cognitive, and clinical antecedents, outcomes[30,48,53,56] and in FHRs neuronal endophenotypes.[24,57] Considering the parental diagnosis of affective or non-affective disorder when comparing results among FHRs studies would also be imperative. *Sixth*, our study is one of the rare long-term longitudinal risk studies extending over more than 20 years of follow-up and we consequently relied on the gold standard instrument of that time, that is, a yearly rating of global functioning using the CGAS. The possibility of using in our study the modern global functioning instruments now available could have modulated the results. *Finally*, caution is advised in interpreting the generalizability of our findings to the children at risk of the population even though studies have suggested that findings in

familial cases would not largely differ from those obtained in sporadic cases.[27,58,59]

ACKNOWLEDGEMENTS

This work was partly funded by a Canada Research Chair (#950-200810) in psychiatric genetics of which Maziade was the Chair and by Canadian Institute of Health Research grants (#MOP-74430, #MOP-114988 and #PCG-155471). The funding organizations had no role in the writing of this article.

CONFLICT OF INTEREST STATEMENT

All authors report no financial or competing interest in relation to the present research.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to ethical restrictions.

ORCID

Alexandre Bureau https://orcid.org/0000-0001-8220-9999
Michel Maziade https://orcid.org/0000-0001-6029-6702

REFERENCES

1. Duffy A, Goodday S, Keown-Stoneman C, Grof P. The emergent course of bipolar disorder: observations over two decades from the Canadian high-risk offspring cohort. *Am J Psychiatry*. 2019;176(9):720-729. doi:10.1176/appi.ajp.2018.18040461
2. Birmaher B, Merranko J, Hafeman D, et al. A longitudinal study of psychiatric disorders in offspring of parents with bipolar disorder from preschool to adolescence. *J Am Acad Child Adolesc Psychiatry*. 2021;60(11):1419-1429. doi:10.1016/j.jaac.2021.02.023
3. Mesman E, Nolen WA, Reichart CG, Wals M, Hillegers MH. The Dutch bipolar offspring study: 12-year follow-up. *Am J Psychiatry*. 2013;170(5):542-549. doi:10.1176/appi.ajp.2012.12030401
4. Faedda GL, Baldessarini RJ, Marangoni C, et al. An International Society of Bipolar Disorders task force report: precursors and prodromes of bipolar disorder. *Bipolar Disord*. 2019;21(8):720-740. doi:10.1111/bdi.12831
5. Maziade M. At risk for serious mental illness – screening children of patients with mood disorders or schizophrenia. *N Engl J Med*. 2017;376(10):910-912. doi:10.1056/NEJMp1612520
6. Song J, Bergen SE, Kuja-Halkola R, Larsson H, Landen M, Lichtenstein P. Bipolar disorder and its relation to major psychiatric disorders: a family-based study in the Swedish population. *Bipolar Disord*. 2015;17(2):184-193. doi:10.1111/bdi.12242
7. Gee DG. Early adversity and development: parsing heterogeneity and identifying pathways of risk and resilience. *Am J Psychiatry*. 2021;178(11):998-1013. doi:10.1176/appi.ajp.2021.21090944
8. Carpenter WT. Clinical high risk controversies and challenge for the experts. *Schizophr Bull*. 2018;44(2):223-225. doi:10.1093/schbul/sbx182
9. Rasic D, Hajek T, Alda M, Uher R. Risk of mental illness in offspring of parents with schizophrenia, bipolar disorder, and major depressive disorder: a meta-analysis of family high-risk studies. Meta-analysis research support, non-U.S. Gov't. *Schizophr Bull*. 2014;40(1):28-38. doi:10.1093/schbul/sbt114
10. Axelson D, Goldstein B, Goldstein T, et al. Diagnostic precursors to bipolar disorder in offspring of parents with bipolar disorder: a longitudinal study. *Am J Psychiatry*. 2015;172(7):638-646. doi:10.1176/appi.ajp.2014.14010035
11. Post RM, Altshuler LL, Kupka R, et al. Multigenerational transmission of liability to psychiatric illness in offspring of parents with bipolar disorder. *Bipolar Disord*. 2018;20(5):432-440. doi:10.1111/bdi.12668
12. Murray RM, Bhavsar V, Tripoli G, Howes O. 30 years on: how the neurodevelopmental hypothesis of schizophrenia morphed into the developmental risk factor model of psychosis. *Schizophr Bull*. 2017;43(6):1190-1196. doi:10.1093/schbul/sbx121
13. Vandeleur C, Rothen S, Gholam-Rezaee M, et al. Mental disorders in offspring of parents with bipolar and major depressive disorders. *Bipolar Disord*. 2012;14(6):641-653. doi:10.1111/j.1399-5618.2012.01048.x
14. Oquendo MA, Ellis SP, Chesin MS, et al. Familial transmission of parental mood disorders: unipolar and bipolar disorders in offspring. *Bipolar Disord*. 2013;15(7):764-773. doi:10.1111/bdi.12107
15. Weintraub MJ, Schneck CD, Walshaw PD, et al. Longitudinal trajectories of mood symptoms and global functioning in youth at high risk for bipolar disorder. *J Affect Disord*. 2020;277:394-401. doi:10.1016/j.jad.2020.08.018
16. Lee EJ, Hower H, Jones RN, et al. Course of longitudinal psychosocial functioning in bipolar youth transitioning to adults. *J Affect Disord*. 2020;268:109-117. doi:10.1016/j.jad.2020.03.016
17. Salagre E, Grande I, Sole B, et al. Exploring risk and resilient profiles for functional impairment and baseline predictors in a 2-year follow-up first-episode psychosis cohort using latent class growth analysis. *J Clin Med*. 2020;10(1):73. doi:10.3390/jcm10010073
18. Lyngberg K, Buchy L, Liu L, Perkins D, Woods S, Addington J. Patterns of premorbid functioning in individuals at clinical high risk of psychosis. *Schizophr Res*. 2015;169(1–3):209-213. doi:10.1016/j.schres.2015.11.004
19. Velthorst E, Fett AJ, Reichenberg A, et al. The 20-year longitudinal trajectories of social functioning in individuals with psychotic disorders. *Am J Psychiatry*. 2017;174(11):1075-1085. doi:10.1176/appi.ajp.2016.15111419
20. Shaffer D, Gould MS, Brasic J, et al. A children's global assessment scale (CGAS). *Arch Gen Psychiatry*. 1983;40(11):1228-1231. doi:10.1001/archpsyc.1983.01790100074010
21. Maziade M, Roy MA, Chagnon YC, et al. Shared and specific susceptibility loci for schizophrenia and bipolar disorder: a dense genome scan in eastern Quebec families. *Mol Psychiatry*. 2005;10(5):486-499. doi:10.1038/sj.mp.4001594
22. Boies S, Merette C, Paccalet T, Maziade M, Bureau A. Polygenic risk scores distinguish patients from non-affected adult relatives and from normal controls in schizophrenia and bipolar disorder multi-affected kindreds. *Am J Med Genet B Neuropsychiatr Genet*. 2018;177(3):329-336. doi:10.1002/ajmg.b.32614
23. Bureau A, Chagnon YC, Croteau J, et al. Follow-up of a major psychosis linkage site in 13q13-q14 reveals significant association in both case-control and family samples. *Biol Psychiatry*. 2013;74(6):444-450. doi:10.1016/j.biopsych.2013.03.004
24. Gagne AM, Moreau I, St-Amour I, Marquet P, Maziade M. Retinal function anomalies in young offspring at genetic risk of schizophrenia and mood disorder: the meaning for the illness pathophysiology. *Schizophr Res*. 2020;219:19-24. doi:10.1016/j.schres.2019.06.021
25. Berthelot N, Garon-Bissonnette J, Jomphe V, Doucet-Beaupré H, Bureau A, Maziade M. Childhood trauma may increase risk of psychosis and mood disorder in genetically high-risk children and adolescents by enhancing the accumulation of risk indicators. *Schizophr Bull Open*. 2022;3(1):sgac017.
26. Post RM, Roy-Byrne PP, Uhde TW. Graphic representation of the life course of illness in patients with affective disorder. *Am J Psychiatry*. 1988;145(7):844-848. doi:10.1176/ajp.145.7.844

27. Maziade M, Paccalet T. A protective-compensatory model may reconcile the genetic and the developmental findings in schizophrenia. *Schizophr Res*. 2013;144(1–3):9-15. doi:10.1016/j.schres.2012.12.022
28. Paccalet T, Gilbert E, Berthelot N, et al. Liability indicators aggregate many years before transition to illness in offspring descending from kindreds affected by schizophrenia or bipolar disorder. Research support, non-U.S. Gov't. *Schizophr Res*. 2016;175(1–3):186-192. doi:10.1016/j.schres.2016.04.038
29. Maziade M, Roy MA, Fournier JP, et al. Reliability of best-estimate diagnosis in genetic linkage studies of major psychoses: results from the Quebec pedigree studies. *Am J Psychiatry*. 1992;149(12):1674-1686. doi:10.1176/ajp.149.12.1674
30. Maziade M, Rouleau N, Mérette C, et al. Verbal and visual memory impairments among young offspring and healthy adult relatives of patients with schizophrenia and bipolar disorder: selective generational patterns indicate different developmental trajectories. *Schizophr Bull*. 2011;37(6):1218-1228. doi:10.1093/schbul/sbq026
31. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders: DSM-IV*. 4th ed. American Psychiatric Press; 1994.
32. Spitzer RL. The structured clinical interview for DSM-III-R (SCID). *Arch Gen Psychiatry*. 1992;49(8):624-629. doi:10.1001/archpsyc.1992.01820080032005
33. Maziade M, Roy MA, Martinez M, et al. Negative, psychoticism, and disorganized dimensions in patients with familial schizophrenia or bipolar disorder: continuity and discontinuity between the major psychoses. *Am J Psychiatry*. 1995;152(10):1458-1463. doi:10.1176/ajp.152.10.1458
34. Roy MA, Lanctot G, Merette C, et al. Clinical and methodological factors related to reliability of the best-estimate diagnostic procedure. *Am J Psychiatry*. 1997;154(12):1726-1733. doi:10.1176/ajp.154.12.1726
35. Kaufman J, Birmaher B, Brent D, et al. Schedule for affective disorders and schizophrenia for school-age children-present and lifetime version (K-SADS-PL): initial reliability and validity data. Research support, non-U.S. Gov't research support, U.S. Gov't, P.H.S. *J Am Acad Child Adolesc Psychiatry*. 1997;36(7):980-988. doi:10.1097/00004583-199707000-00021
36. Maziade M, Gingras N, Rouleau N, et al. Clinical diagnoses in young offspring from eastern Québec multigenerational families densely affected by schizophrenia or bipolar disorder. *Acta Psychiatr Scand*. 2008;117(2):118-126. doi:10.1111/j.1600-0447.2007.01125.x
37. McCarthy S, Das S, Kretzschmar W, et al. A reference panel of 64,976 haplotypes for genotype imputation. *Nat Genet*. 2016;48(10):1279-1283. doi:10.1038/ng.3643
38. Bipolar Disorder and Schizophrenia Working Group of the Psychiatric Genomics Consortium, Electronic address: douglas.ruderfer@vanderbilt.edu, Bipolar Disorder and Schizophrenia Working Group of the Psychiatric Genomics Consortium. Genomic dissection of bipolar disorder and schizophrenia, including 28 subphenotypes. *Cell*. 2018;173(7):1705-1715.e16. doi:10.1016/j.cell.2018.05.046
39. Berthelot N, Paccalet T, Gilbert E, et al. Childhood abuse and neglect may induce deficits in cognitive precursors of psychosis in high-risk children. *J Psychiatry Neurosci*. 2015;40(5):336-343. doi:10.1503/jpn.140211
40. Choi KR, McCreary M, Ford JD, Rahmanian Koushkaki S, Kenan KN, Zima BT. Validation of the traumatic events screening inventory for ACEs. *Pediatrics*. 2019;143(4):e20182546. doi:10.1542/peds.2018-2546
41. Muthen B, Muthen LK. Integrating person-centered and variable-centered analyses: growth mixture modeling with latent trajectory classes. *Alcohol Clin Exp Res*. 2000;24(6):882-891.
42. Nagin DS. Analyzing developmental trajectories: a semiparametric, group-based approach. *Psychol Methods*. 1999;4(2):139-157. doi:10.1037/1082-989X.4.2.139
43. Proust-Lima C, Philipps V, Liquet B. Estimation of extended mixed models using latent classes and latent processes: the R package lcmm. *J Stat Softw*. 2017;78(2):1-56. doi:10.18637/jss.v078.i02
44. Nagin DS, Odgers CL. Group-based trajectory modeling in clinical research. *Annu Rev Clin Psychol*. 2010;6:109-138. doi:10.1146/annurev.clinpsy.121208.131413
45. Dantan E, Proust-Lima C, Letenneur L, Jacqmin-Gadda H. Pattern mixture models and latent class models for the analysis of multivariate longitudinal data with informative dropouts. *Int J Biostat*. 2008;4(1):Article 14. doi:10.2202/1557-4679.1088
46. Anderson CA, Hammen CL. Psychosocial outcomes of children of unipolar depressed, bipolar, medically ill, and normal women: a longitudinal study. *J Consult Clin Psychol*. 1993;61(3):448-454. doi:10.1037//0022-006x.61.3.448
47. Weissman MM, Talati A, Gameroff MJ, et al. Enduring problems in the offspring of depressed parents followed up to 38 years. *EClinicalMedicine*. 2021;38:101000. doi:10.1016/j.eclinm.2021.101000
48. Duffy A, Malhi GS, Carlson GA. The challenge of psychiatric diagnosis: looking beyond the symptoms to the company that they keep. *Bipolar Disord*. 2018;20:410-413. doi:10.1111/bdi.12686
49. Birmaher B, Merranko J, Hafeman D, et al. The role of bipolar polygenic risk score in the familial transmission of bipolar disorder-an updated analysis. *Bipolar Disord*. 2022;24(4):437-440. doi:10.1111/bdi.13205
50. Teicher MH, Gordon JB, Nemeroff CB. Recognizing the importance of childhood maltreatment as a critical factor in psychiatric diagnoses, treatment, research, prevention, and education. *Mol Psychiatry*. 2021;27:1331-1338. doi:10.1038/s41380-021-01367-9
51. Birmaher B, Merranko JA, Goldstein TR, et al. A risk calculator to predict the individual risk of conversion from subthreshold bipolar symptoms to bipolar disorder I or II in youth. *J Am Acad Child Adolesc Psychiatry*. 2018;57(10):755-763.e4. doi:10.1016/j.jaac.2018.05.023
52. Carpenter WT. Early detection of psychosis vulnerability: Progress, opportunity, and caution. *Am J Psychiatry*. 2016;173(10):949-950. doi:10.1176/appi.ajp.2016.16060746
53. Keown-Stoneman CDG, Goodday SM, Preisig M, et al. Development and validation of a risk calculator for major mood disorders among the offspring of bipolar parents using information collected in routine clinical practice. *EClinicalMedicine*. 2021;39:101083. doi:10.1016/j.eclinm.2021.101083
54. Cannon TD, Yu C, Addington J, et al. An individualized risk calculator for research in prodromal psychosis. *Am J Psychiatry*. 2016;173(10):980-988. doi:10.1176/appi.ajp.2016.15070890
55. Worthington MA, Cao H, Cannon TD. Discovery and validation of prediction algorithms for psychosis in youths at clinical high risk. *Biol Psychiatry Cogn Neurosci Neuroimaging*. 2020;5(8):738-747. doi:10.1016/j.bpsc.2019.10.006
56. Rudaz D, Vandeleur CL, Gholam M, et al. Psychopathological precursors of the onset of mood disorders in offspring of parents with and without mood disorders: results of a 13-year prospective cohort high-risk study. *J Child Psychol Psychiatry*. 2021;62(4):404-413. doi:10.1111/jcpp.13307
57. Maziade M, Bureau A, Jomphe V, Gagne AM. Retinal function and preclinical risk traits in children and adolescents at genetic risk of schizophrenia and bipolar disorder. *Prog Neuropsychopharmacol Biol Psychiatry*. 2022;112:110432. doi:10.1016/j.pnpbp.2021.110432
58. Roy MA, Crowe RR. Validity of the familial and sporadic subtypes of schizophrenia. *Am J Psychiatry*. 1994;151(6):805-814. doi:10.1176/ajp.151.6.805

59. Esterberg ML, Trotman HD, Holtzman C, Compton MT, Walker EF. The impact of a family history of psychosis on age-at-onset and positive and negative symptoms of schizophrenia: a meta-analysis. *Schizophr Res*. 2010;120(1–3):121-130. doi:10.1016/j.schres.2010.01.011

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Bureau A, Berthelot N, Ricard J, et al. Heterogeneity in the longitudinal courses of global functioning in children at familial risk of major psychiatric disorders: Association with trauma and familial characteristics. *Bipolar Disord*. 2023;00:1-12. doi:10.1111/bdi.13386