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Emerging psychopathology and clinical staging in adolescent offspring of parents with bipolar disorder or schizophrenia—A longitudinal study

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Abstract

Objectives: Offspring of parents with bipolar disorder (BDo) and schizophrenia (SZo) are at increased risk for these disorders and general psychopathology. Little is known about their (dis)similarities in risk and developmental trajectories during adolescence. A clinical staging approach may help define the developmental course of illness.

Methods: The Dutch Bipolar and Schizophrenia Offspring Study is a unique cross-disorder and prospective cohort study, established in 2010. In total, 208 offspring (58 SZo, 94 BDo, and 56 control offspring [Co]) and their parents participated. Offspring were 13.2 years (SD = 2.5; range: 8–18 years) at baseline and 17.1 years (SD = 2.7) at follow-up (88.5% retention rate). Psychopathology was assessed using the Kiddie Schedule for Affective Disorders and Schizophrenia for School Age Children Present and Lifetime Version, and Achenbach System of Empirically Based Assessment parent-, self- and teacher-reports. Groups were compared on (1) the presence of categorical psychopathology, (2) timing and development of psychopathology using a clinical staging perspective, and (3) dimensional psychopathology using a multi-informant approach.

Results: SZo and BDo showed more categorical psychopathology and (sub)clinical symptoms, as compared to Co. SZo have, compared to BDo, an increased risk for developmental disorders, a younger age of onset, and more (sub)clinical symptoms of the mood and behavioral spectrum as reported by multiple informants.

Conclusions: Our study shows that the phenotypical risk profile overlaps between SZo and BDo, although an earlier onset of developmental psychopathology was found specifically in SZo, suggesting of a potentially different ethiopathophysiology. Longer follow-up and future studies are needed.

KEYWORDS
adolescent, bipolar disorder, child, psychiatry, psychopathology, risk, schizophrenia

Nikita Setiaman and Esther Mesman is contributed equally to this work.

1 | INTRODUCTION

Schizophrenia (SZ) and bipolar disorder (BD) are severe mental illnesses. SZ affect 0.33%–0.7%[1,2] and BD affect 0.81%–1.29%[3] of the worldwide population. A positive family history of SZ or BD is the strongest predictor for the development of these severe mental illnesses.[4] Prospective familial high-risk studies may inform us on the early trajectories and general risk of psychopathology. In addition to genetic predisposition, having a parent with SZ or BD has been associated with an increased burden of environmental stressors in childhood that further increases the risk of developing a psychiatric disorder.[5] Using a prospective cross-disorder approach, studies on offspring of parents with SZ (SZo) or BD (BDo) can inform us on the similarities and dissimilarities in neurodevelopmental trajectories of their risk for psychopathology.[6]

The development of psychopathology during adolescence is of great interest since it is known that neurodevelopmental deviation prior to clinical onset plays an important role in the pathophysiology of the severe mental illnesses. Additionally, the risk for developing psychopathology is high during adolescence[7] and prodromal symptoms start even earlier.[8] Moreover, during adolescence, typical adolescent behavior and prodromal symptoms of severe mental illness overlap and are difficult to differentiate.[9,10] Familial high-risk studies show that both SZo and BDo have an elevated risk to develop homotypic psychopathology, that is psychotic and mood disorders, as well as heterotypic psychopathology, that is anxiety or developmental disorders.[4,11] Importantly, subthreshold symptoms of mania and depression are highly predictive of future manic and depressive episodes in BDo,[12,13] as well as anxiety disorders, which is confirmed by the clinical staging perspective.[14]

To date, four studies using a cross-disorder approach have compared the risk of psychopathology in offspring at familial risk for SZ or BD (see Table S1). Overall, these studies showed that psychopathology was more prevalent in SZo and BDo than in control offspring (Co).[15–20] Some studies reported higher prevalence rates of mood[15] or more anxiety symptoms in BDo compared to SZo.[17] Psychotic experiences and developmental and disruptive disorders were more prevalent in SZo compared to BDo.[15,16,21] Others found no significant differences between these groups,[18,20] although one of these studies showed an overall increase in dimensional psychopathology in 7-year-old SZo compared to BDo at baseline.[19] The mean age of these studies varied from 7.8 to 17.5 (see Table S1). Although a higher prevalence of psychopathology in both familial risk groups is evident in these studies, whether developmental trajectories are similar across groups or diverge during adolescence is not fully understood due to the relatively young age[15–17,19] and/or lack of longitudinal design[17,18] of these cross-disorder studies.

Clinical staging models have the potential to improve the logic and timing of interventions in psychiatry but are rarely used to enhance early recognition in mental illnesses,[22–24] despite the known benefits from its use for physical illnesses.[25] They define the progression of illness rather than the diagnosis itself.[22] Studies on the current clinical staging models for SZ or BD focused on the clinical implications of the models, cognitive and neurobiological biomarkers, and on offspring at familial risk[26–32] but do not use a cross-disorder approach and rarely have a developmental perspective. Moreover, among present cross-disorder studies, a clinical staging model perspective is lacking. Incorporating both approaches may shed light on (dis)similarities in illness age of onset, course/progression and hetero/homotypic development of psychopathology.

This study aims to investigate the natural trajectories of psychopathology in SZo, BDo, and Co from late childhood/early adolescence onward (mean age of 13.2 years; range: 8–18 years) up to a mean age of 17.1 years (range 11–22), using a unique prospective cohort study. We will examine the natural course of emerging psychopathology by comparing the three groups, using three approaches. First, the presence of lifetime categorical psychopathology will be compared between groups. Second, studying the timing and development of these diagnoses using a clinical staging model will help identify windows of opportunity for early interventions in both at risk groups. Finally, as (young) adolescent offspring may show increased symptomatology without a full-blown diagnoses, we will also compare levels of (sub)clinical symptoms by taking a dimensional approach.

2 | PATIENTS AND METHODS

2.1 | Participants and procedure

The Dutch Bipolar and Schizophrenia Offspring study (DBSOS) is an ongoing prospective cohort study, investigating the development of brain, genetics, cognitive functioning, and environment, that contribute to risk and resilience in SZo and BDo. In total, 58 SZo (38 families), 94 BDo (60 families), and 56 Co (34 families), aged 8–18 years old, were included between 2010 and 2017. Data at baseline has been partly presented before.[33–35] Figure S1 presents detailed recruitment and drop-out characteristics. Overall, 88.5% of the offspring participated at 4-year follow-up: 51 SZo (87.9%), 84 BDo (89.4%), and 49 Co (87.5%). Families with at least one first-degree relative (mostly one affected parent; one family with two parents affected with BD-I and two families with a BD sibling), or two second-degree relatives with SZ (four families) or BD (one family) were recruited via adult psychiatrists and child-and-adolescent psychiatrists in the Netherlands, advertisements (e.g., lectures, patient advocacy groups, and study website) or hear-say (e.g., hospital staff or other participants). Control families were recruited via advertisements on schools and leisure clubs (i.e., lectures and flyers) or hear-say. Parental diagnoses were confirmed with the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I[36]). In case of psychiatric admission, death or unknown whereabouts of the index parent (15.8% of BD and 14.7% of SZ), parental diagnosis was retrieved from the Family Interview for Genetic Studies (FIGS).[37,38] Co-parents and control parents were interviewed using the mini Schedule for Clinical Assessment in Neuropsychiatry (mini-SCAN) interview,[39] followed by the SCID-I in case of reported psychopathology.

Exclusion criteria were an IQ < 70, a major medical history or history of neurological illness, and additionally for Co, a first-degree relative with a severe mood or psychotic disorder.

Written informed consent was obtained from all offspring older than 12 years and both parents or legal caregivers of children younger than 18 years old. The study was conducted at the University Medical Center Utrecht (UMCU) in the Netherlands. The medical ethics committee of the UMCU approved the study protocol. All participants received a financial compensation for their time participating in several measurements (i.e., interviews, questionnaires, neuropsychological tests, blood withdrawal, and MRI) and travel expenses were reimbursed.

2.2 | Measures

Clusters of Lifetime DSM-IV axis-I disorders: The presence of current and lifetime DSM-IV diagnoses in offspring was examined with the Kiddie Schedule for Affective Disorders and Schizophrenia for School Age Children Present and Lifetime Version (K-SADS-PL).[40] This interviewer-oriented semi-structured face–to-face interview was administered to offspring and parents separately. Screen items cover symptoms of depression, mania, psychosis, anxiety, developmental, substance, and other non-mood disorders, allowing severity scores of 1 (absent), 2 (mild), and 3 (severe). Supplementary items were always administered for the depression, mania, and psychosis domains, and for the remaining domains when at least one of the screen items in that specific domain was scored with a severity score of 3. Symptoms were assessed using specific criteria of the instrument,[40] based on the criteria of the DSM-IV.

Consensus scores were based on both child and parent perspectives to establish lifetime DSM-IV axis-I diagnoses, giving a greater weight to the parent's report for observed behavior and to the child's report for subjective experiences in case of disagreement. Autism spectrum diagnoses were based on psychiatric evaluations from outpatient clinics. During the K-SADS interview, information on age of onset, medication use, and treatment history was obtained. The Children's Global Assessment Scale (CGAS) was used to assess the level of functioning (i.e., social, school/occupational, and personal functioning).[41]

Clinical Staging Model: Duffy[29] proposed a staging model for BDo with stages that take into account the developmental perspective and early precursors of the classical episodic BD as well as psychotic features of the bipolar spectrum: 0 (well, with familial risk); 1 (non-specific syndromes/non-specific syndromes and developmental disorders); 2 (mild mood or single depressive episode/negative syndrome); 3 (recurrent major depressive disorder/attenuated psychotic syndrome); and 4 (BD/mixed [mania/psychotic/cyclic] or psychotic disorder). This study slightly adapted this model, not only profiting from the offspring approach, but also allowing a cross-disorder approach that acknowledges the heterotypic nature of SZ and BD.[42] Stage 0 (well) was divided into stage 0_a (well, without familial risk) and 0_b (well, with familial risk). Stage 1 is referred to as the non-mood stage. Within stage 1, we distinguished "developmental," "anxiety," "alcohol/substance," and "other non-mood" disorders. Psychosis was clustered with manic episodes in stage 4. Each transition through the stages and corresponding age of onset were based on the DSM-IV diagnoses retrieved from the K-SADS-PL interviews (at either baseline, follow-up, or both). The absence of lifetime DSM-IV diagnoses at either baseline or both waves was registered as stage 0_a (Co) or 0_b (SZo and BDo). Comorbid diagnoses with the same age of onset are registered as the highest stage according to the hierarchy of this model.

(Sub)clinical symptoms: In order to evaluate the symptomatology that may precede the onset of categorical psychopathology, summary scores for (sub)clinical symptoms were calculated at baseline and follow-up of both screen and supplementary items. To prevent missing values, we only summarized data that was administered to all participants; thus, both screen and supplementary items were used for depression, mania, and psychosis domains, and only screen items were used for anxiety and behavioral problems.

Additionally, parent-, self-, and teacher-reports of the Achenbach System of Empirically Based Assessment (ASEBA)[43,44] questionnaires were administered at both waves. Parents reported on their offspring's behavior using the Child Behavior Checklist (CBCL: 8–18 years) or the Adult Behavior Checklist (ABCL; 19+). Offspring filled out the Youth Self Report (YSR; 12–18 years) or the Adult Self Report (ASR; 19+). The Teacher's Report Form (TRF) was administered to primary or secondary school teachers of participants. T-scores of internalizing and externalizing scales were calculated with *ASEBA PC* (https://aseba.org/aseba-pc/). Both parents of SZo and BDo and one parent (by choice) of Co were asked to fill out the parent-report. Mothers were included as main informant in this study and fathers were included in the absence of the mother's questionnaire (baseline: 4% SZo, 2% BDo, and 2% Co; follow-up: 9% SZo, 12% BDo, and 24% Co).

IQ: Four subtasks of the Wechsler Intelligence Scale for Children-III (WISC-III)[45] for participants aged 8–16 or Wechsler Adult Intelligence Scale-III (WAIS-III)[46] for participants 17 years or older were administered (i.e., picture arrangement, block design, vocabulary, and information) to estimate IQ.

All assessments were conducted by trained interviewers with a Bachelor's or Master's degree in medicine/psychology, supervised by a licensed psychologist (EM) and a psychiatrist certified in adult and child-and-adolescent psychiatry (MH).

2.3 | Statistical analyses

Statistical analyses were checked for assumptions and replaced with appropriate alternatives in case of violations.

Demographic information: Group differences at baseline and follow-up on dichotomous demographic variables, treatment and level of functioning were tested with chi-squared (X^2) tests. Differences on continuous demographic variables were tested with one-way ANOVA's, or their non-parametric equivalents. Post hoc pairwise

comparisons were done with a Tukey's HSD in case of significant main effects for group.

Clusters of Lifetime DSM-IV axis I disorders: Lifetime prevalence of DSM-IV axis I disorders in each cluster was compared between groups with chi-squared (X^2) tests. Survival curves using Kaplan–Meier survival analyses[47] were calculated for each cluster, determining the probability of illness onset, given the age of the latest known information. Survival analyses were extended using cox proportional hazard regression analyses including a correction for age. Finally, the number of comorbid diagnoses was compared between groups with a Kruskal–Wallis test.

Clinical staging: We registered all lifetime DSM-IV psychopathology and corresponding ages of onset for all subjects, assigning each of them to the stages in our clinical staging model. First, the prevalence of each latest known stage and number of transitions was compared between groups with chi-squared (X^2) tests. Second, survival curves using Kaplan–Meier survival analyses were calculated for the prevalence of stage 1 (non-mood), stage 2 (single/mild mood), and stage 3 and 4 combined (recurrent depressive mood and manic/psychotic), thereby determining the probability of transitions to a later stage. Cox proportional hazard analyses, correcting for age at the interview and sex were done to calculate the hazard ratio. Finally, exploratory analyses were done to investigate the differences in precursors of stage 2 (i.e., first single mood episode) between SZo and BDo.

(Sub)clinical symptoms: K-SADS-PL summary scores of depression, mania, psychosis, anxiety, and behavioral problems (i.e., symptoms of attention-deficit [hyperactivity], oppositional defiant or conduct disorders), and t-scores from the ASEBA questionnaires were compared between groups using linear mixed models, with group and age at the waves as fixed factors and subject-id as random factor. Evaluation of AIC showed that an additional age*group interaction effect did not improve the models.

Sensitivity analyses: All analyses were repeated after excluding subjects with multiple second-degree family members, but without an affected parent (BDo: $N=4$, three families; SZo: $N=6$, four families). Additionally, to correct for the effect of age and sex, the analyses for the cluster of DSM-IV categories *any diagnosis*, *any non-mood and any mood diagnosis* are repeated for offspring below and above the age of 17.5 years (median age at follow-up), and for the sexes separately.

Statistical analyses were done in SPSS v28.0.1.0 and R v3.6.3. Correction for multiple testing was done for 32 analyses (main analyses of lifetime diagnoses, clinical staging model, and (sub)clinical symptoms) using the false rate discovery—Benjamini–Hochberg procedure, with a false discovery rate of 5% ($\alpha < 0.034$ for main analyses and $\alpha < 0.05$ for post hoc pairwise comparisons).

3 | RESULTS

3.1 | Demographic information

Demographic and clinical characteristics of participating families and offspring are summarized in Table 1. In total, 58 SZo (38 families), 94 BDo (60 families), and 56 Co (34 families), aged 8–18 years old participated at baseline. At 4-year follow-up (mean age = 17.1, SD = 2.7), the overall retention rate was 88.5%. Across groups, BDo were slightly older than SZo and Co. Mean IQ was significantly lower in the familial high-risk groups than Co.

3.2 | Clusters of lifetime DSM-IV axis I disorders

The prevalence of each cluster of DSM-IV psychopathology at baseline and follow-up is presented in Table 2. Overall, an increase of psychopathology is seen between baseline and follow-up. At the mean age of 17.1 years, the lifetime prevalence of any DSM-IV axis-I disorder was highest in SZo (72.5%), followed by BDo (64.3%) and Co (30.6%); the difference between SZo and BDo was not significant ($X^2 = 0.99$, $p = 0.349$). Significant differences were found in the "non-mood cluster" and "mood cluster." The "non-mood cluster" was most prevalent in SZo (70.6%) and significantly more prevalent than BDo (47.6%; $X^2 = 6.81$, $p < 0.012$). Subsequent analyses within the "non-mood cluster" showed significantly more developmental disorders in SZo (43.1%) as compared to controls (16.3%) ($X^2 = 8.55$, $p = 0.004$). Substance disorders were more frequent in BDo (10.7%) as compared to Co (0.0%) ($X^2 = 5.63$, $p = 0.026$). Both SZo and BDo reported more comorbidity (49.0% and 50.0%) compared to Co.

Taking into account age of onset, survival distributions per group and DSM-IV clusters were plotted using Kaplan–Meier survival curves (Figure 1). As shown in Figure 1, for both clusters, the survival distributions of the familial high-risk groups were significantly different from Co. Only in the "non-mood cluster" SZo (median age of onset: 18.0; CI95%: 16.6–19.4), survival distribution was significantly different from BDo (median age of onset: 18.0; CI95%: 16.6–19.4) ($Exp(B) = 2.17$, $p < 0.001$) after correction for age and sex.

3.3 | Clinical staging

The distribution of stages and number of transitions are presented in Table 2. At the mean age of 17.1 years, stage $0_a/0_b$ was most common in Co (69.4%) followed by BDo (35,7%) and SZo (27.5%). We found no significant difference in prevalence of stage 1–4 at this age. As shown in Table 2, the total number of transitions between age 13.2 and 17.1 was significantly higher in SZo (One transition: 52.9%, two or more: 19.6%) and BDo (One transition: 35.7%, two or more: 28.6%) as compared to Co (One transition: 24.5%, two or more: 6.1%). Individual transitions between stages over time are depicted in Figure 2. Exploratory analyses showed no significant difference in prevalence of precursors of stage 3 (mild or single mood) between SZo and BDo (data not shown). Figure 1B shows the survival distribution per stage and group. Significant group differences were found for stage 1 and stage 2, indicating that the timing and risk to reach one of these stages differed between groups during adolescence. Again, differences between BDo and SZo were only significant for stage 1.

TABLE 1 Demographic variables.

	SZo	BDo	Co	Statistics	*p*	Pairwise
Family characteristics						
Families at baseline/ follow-up, *n*	38/33	60/52	34/29			
Sex index parent, *n* (% female)	14 (41.2)	37 (64.9)	–			
Bipolar disorder I/II[a], *n*	–	47/10	–			
Schizophrenia/psychotic disorder[a,b], *n*	26/8	–	–			
Age of onset, M(SD)	24.4 (8.7)	22.3 (8.7)	–			
Number of episodes, M(SD)	4.4 (5.0)	17.0 (14.4)	–			
Range	1–20	2–60				
Number of psychiatric hospitalizations, M(SD)	2.1 (1.8)	2.2 (2.3)	–			
Range	0–7	0–7				
Highest level of parental education						
- Primary, %	8.8	5.2	3.2	$X^2(4)=6.87$	.143	
- Secondary, %	38.2	20.7	16.1			
- Continued education, %	52.9	74.1	80.6			
Co-parent						
- Mood disorder	13	13	3			
- Anxiety disorder	1	3	2			
- Substance abuse	1	1	1			
- Other disorder[c]	–	2	1			
Offspring characteristics						
Offspring at baseline/ follow-up, *n*	58/51	94/84	56/49			
Retention rate at follow-up	87.9	89.4	87.5			
Age at baseline, *M(SD)*	12.8 (2.7)	13.7 (2.4)	12.9 (2.2)	F (2,205) = 3.12	**0.046**	**n.s.**
Age at follow-up, *M(SD)*	16.6 (2.8)	17.8 (2.6)	16.6 (2.4)	F (2,181) = 4.81	**0.009**	**BDO >SZo $p = 0.02$ and BDo > Co $p = 0.04$**
Years between baseline and follow-up, *M(SD)*	3.9 (0.8)	4.1 (0.7)	3.8 (1.0)	F (2,181) = 2.89	0.058	
Sex, % girls at baseline	65.5	46.8	48.2	$X^2(2) = 5.57$	0.062	
IQ baseline, *M(SD)*	101.0(18.3)	105.4 (18.8)	115.7 (12.8)	F (2,126) = 14.82	**<0.001**	**SZo <Co $p<0.001$ and BDo <Co $p=0.001$**
C-GAS, *M(SD)*	6.1(1.5)	6.5 (1.5)	7.8 (1.2)	F (2,205) = 23.87	**<0.001**	**SZo < Co $p<0.001$ and BDo <Co $p<0.001$**
Psychological treatment, n (%)	35 (60.3)	47 (50.0)	11 (19.6)	$X^2(2)= 21.03$	**<0.001**	**SZo > Co $p<0.001$ and BDo >Co $p<0.001$**
Hospitalization, n(%)	5 (8.6)	5 (5.3)	–	Fisher's exact	0.069	
Offspring lifetime medication use, *n (%)*[d]						
- *Antidepressant*	2 (3.4)	1 (1.1)	–			
- *Lithium*	Na	3 (3.2)	–			
- *Antipsychotics*	5 (8.6)	6 (6.4)	–			

TABLE 1 (Continued)

	SZo	BDo	Co	Statistics	*p*	Pairwise
- *Stimulants*	8 (13.8)	14 (14.9)	6 (10.7)			
- *Benzodiazepine*	2 (3.4)	–	–			

Bold indicates statistically significant *p*-values

Abbreviations: BDo, bipolar disorder offspring; SZo, schizophrenia offspring; Co, Control offspring; C-GAS, Children's Global Assessment Scale; M, mean; SD, standard deviation; n.s., not significant.

[a]9 BD diagnoses and 6 SZ diagnoses were based on the Family Interview for Genetic Studies; There are four families with two second degree family members affected with schizophrenia, one family with two second degree family members affected with BD, and two families with first degree family members (sisters) affected with BD that were not included in this table; one family had two affected parent with BD, only the parent with the highest number of episodes was included in this table.

[b]Psychotic disorders were schizoaffective disorder ($n=6$) or unspecified psychotic disorder ($n=2$).

[c]Co: one co-parent with a chronic pain disorder; BDo: one co-parent with a gambling addiction and one co-parent with a adjustment disorder; comorbidities are not included in this table.

[d]6.9% of SZo and 5.3% of BDo used a combination of two types of medication.

3.4 | (Sub)clinical symptoms

Table 3 presents the dimensional psychopathology at age 13.2 and 17.1 per group and domain using a multi-informant approach. Both SZo and BDo reported significantly more symptoms than co, independent of age, on the interview-based summary scales as well as the internalizing and externalizing scales of the ASEBA questionnaires as reported by all informants (offspring, parent, and teacher). BDo scored significantly higher on the mania scale than Co ($t(205)=3.43$, $p<0.001$). Compared to BDo, SZo reported higher levels on the depression ($t(205)=2.08$, $p=0.039$) and behavioral problems ($t(205)=2.13$, $p=0.034$) scales of the K-SADS-PL. Interestingly, self-report showed no significant differences between the familial high-risk groups on both internalizing or externalizing problem scales. Parent-report indicated that SZo experienced more internalizing symptoms than BDo ($t(199)=2.23$, $p=0.027$). Also, more externalizing problems were observed by parents ($t(199)=2.27$, $p=0.025$) and teachers ($t(151)=3.14$, $p=0.0.002$) in SZo than in BDo.

3.5 | Sensitivity analyses

Results after the sensitivity analyses excluding subjects with multiple second-degree family members did not alter findings (data not shown). The results of the sensitivity analyses for age and sex are presented in Table S2. Sensitivity analyses for age suggest that the higher prevalence rates for the different types of psychopathology was only statistically significant between BDo and Co in the subgroups older than 17.5 years old. Differences between SZo and Co for any diagnosis and non-mood disorders was statistically significant in the subgroups younger as well as older than 17.5 years old. Sensitivity analyses for sex suggest that especially male offspring at familial risk are more vulnerable for psychopathology. These results should be interpreted with care due to small sample sizes per subgroup.

4 | DISCUSSION

This prospective study among offspring of parents with SZ (SZo) or BD (BDo) cover the window of early childhood until late adolescence using a longitudinal design. The aim was to examine the (dis) similarities in the course of emerging psychopathology and clinical staging among this high-risk population. In sum, this study showed that both SZo and BDo are at increased risk for psychopathology. Moreover, compared to BDo, SZo were more likely to develop non-mood psychopathology at young age. At a dimensional level, more (sub)clinical symptoms of developmental and mood disorders were present in SZo as compared to BDo and Co. The multi-informant approach showed that information gathered via interviews, parents, or teachers, in addition to the self-report, were important, especially for externalizing symptoms.

Higher prevalence rates in the non-mood and depressive mood clusters in familial high-risk groups during adolescence have been reported in previous high-risk studies.[16,18,48–50] In contrast to Maziade et al.,[18] we did find differences between SZo and BDo. Importantly, Maziade and authors included a sample of selected families with high familial load for SZ and BD, while our sample may have been more heterogeneous. The higher risk of non-mood psychopathology in SZo as compared to BDo, confirms findings of the Spanish cross-diagnostic cohort study that developmental and disruptive disorders were more prevalent in SZo compared to BDo.[15,16] Unlike, De la Serna, et al.[15] this study did not replicate higher prevalence rates of mood disorders in BDo than in SZo. However, the Spanish cohort is approximately 3 years younger than the DBSOS cohort, and within their study, SZo were significantly younger than BDo (see Table S1). The survival distribution of the mood cluster in Figure 1 illustrates that age may be a possible explanation for this divergent finding. Finally, this study did not replicate the finding of higher levels of anxiety[17] in prevalence rate nor in the dimensional data. Cultural or methodological factors may explain the difference in findings.[51,52]

TABLE 2 The development of psychopathology and staging at baseline and follow-up.

	SZo				BDo				Co						
	Baseline ($n=58$)		Follow-up ($n=51$)		Baseline ($n=94$)		Follow-up ($n=84$)		Baseline ($n=56$)		Follow-up ($n=49$)		Group differences at follow-up		
DSM-IV axis I clusters	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	**Statistic**	***p***	**Pairwise**
Any diagnosis	35	(60.3)	37	(72.5)	50	(53.2)	54	(64.3)	10	(17.9)	15	(30.6)	X^2 (2) = 20.82	**<0.001**	**SZo <Co $p<0.001$ and BDo > Co**
Any non-mood	31	(53.4)	36	(70.6)	36	(38.3)	40	(47.6)	7	(12.5)	13	(26.5)	X^2 (2) = 19.46	**<0.001**	**SZo > BDo $p=0.01$ and SZo > Co $p<0.001$ and BDo > Co $p<0.001$**
- *Anxiety*	10	(17.2)	11	(21.6)	10	(10.6)	12	(14.3)	3	(5.4)	3	(6.1)	X^2 (2) = 4.92	0.083	
- *Developmental*[a]	18	(31)	22	(43.1)	22	(23.4)	26	(31.0)	1	(1.8)	8	(16.3)	X^2 (2) = 8.50	**0.014**	**SZo > Co $p=0.004$**
• *AD(H)D*	11		12		15		17		1		8				
• *Autism spectrum disorders*	11		10		6		7		–		–				
• *Disruptive behavior disorder*	5		5		7		7		–		–				
- *Other non-mood*[b]	10	(17.2)	10	(19.6)	16	(17.0)	18	(21.4)	4	(7.1)	6	(12.2)	X^2 (2) = 1.79	0.422	
- *alcohol/substance*	1	(1.7)	3	(5.9)	2	(2.1)	9	(10.7)	–		–		Fisher's exact	**0.041**	**BDo > Co $p=0.03$**
Any mood[c,d]	11	(19.0)	17	(33.3)	26	(27.7)	34	(40.5)	5	(8.9)	6	(12.2)	X^2 (2) = 11.72	**0.003**	**SZo >Co $p=0.02$ and BDo > Co $p<0.001$**
- *bipolar spectrum*[d]	1	(1.7)	1	(2.0)	4	(4.3)	3	(3.6)	–		–		Fisher's exact	0.589	
Psychosis	–		1	(2.0)	–		1	(1.2)	–		–		Fisher's exact	1.00	
Comorbidity	24	(41.4)	25	(49.0)	33	(35.1)	42	(50.0)	5	(8.9)	6	(12.2)	X^2 (2) = 21.07	**<0.001**	**SZo <Co $p<0.001$ and BDo > Co $p<0.001$**
- *1 diagnosis*	14	(24.1)	6	(11.8)	18	(19.1)	11	(13.1)	3	(5.4)	2	(4.1)			
- *> 2 diagnoses*	10	(17.2)	19	(37.3)	15	(16.0)	31	(36.9)	2	(3.6)	4	(8.2)			
Clinical staging															
Stage 0_a/0_b: well with(out) familial risk	23	(39.7)	14	(27.5)	44	(46.8)	30	(35.7)	46	(82.1)	34	(69.4)	X^2 (2) = 20.82	**<0.001**	**SZo <Co $p<0.001$ and BDo < Co $p<0.001$**
Stage 1: non-mood	24	(41.4)	20	(39.2)	24	(25.5)	20	(23.8)	5	(8.9)	9	(18.4)	X^2 (2) = 6.19	0.045	
Stage 2: mild or single mood	9	(15.5)	12	(23.5)	17	(18.1)	20	(23.8)	3	(5.4)	4	(8.2)	X^2 (2) = 5.52	0.064	
Stage 3: recurrent mood	1	(1.7)	3	(5.9)	5	(5.3)	10	(11.9)	2	(3.6)	2	(4.1)	Fisher's exact	0.305	

TABLE 2 (Continued)

	SZo				BDo				Co						
	Baseline ($n=58$)		Follow-up ($n=51$)		Baseline ($n=94$)		Follow-up ($n=84$)		Baseline ($n=56$)		Follow-up ($n=49$)		Group differences at follow-up		
DSM-IV axis I clusters	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	Statistic	*p*	Pairwise
Stage 4: (hypo)mania/psychosis	1	(1.7)	2	(3.9)	4	(4.3)	4	(4.8)	–		–		Fisher's exact	0.425	
Number of transitions between stages															
0			14	(27.5)			30	(35.7)			34	(69.4)	X^2 (2) = 31.22	**<0.001**	**SZo > Co $p<0.001$ and BDo > Co $p<0.001$**
1			27	(52.9)			30	(35.7)			12	(24.5)			
2			6	(11.8)			20	(23.8)			3	(6.1)			
3			4	(7.8)			4	(4.8)	–						

Bold indicates statistically significant *p*-values

Abbreviations: BDo, bipolar disorder offspring; SZo, schizophrenia offspring; Co, Control offspring; AD(H)D, attention-deficit (hyperactivity) disorder.

Note: Corrected for multiple testing using false discovery rate—Benjamini–Hochberg procedure; with α, 0.034.

[a]Attention-deficit (hyperactivity)disorder, disruptive behavioral disorders (not otherwise specified), autism spectrum disorder.

[b]Enuresis/encopresis, adjustment disorder, tic disorder, and eating disorders.

[c]Major depressive disorder, dysthymia, depression not otherwise specified, mood disorder not otherwise specified.

[d]Bipolar disorder, and type I/II, cyclothymia.

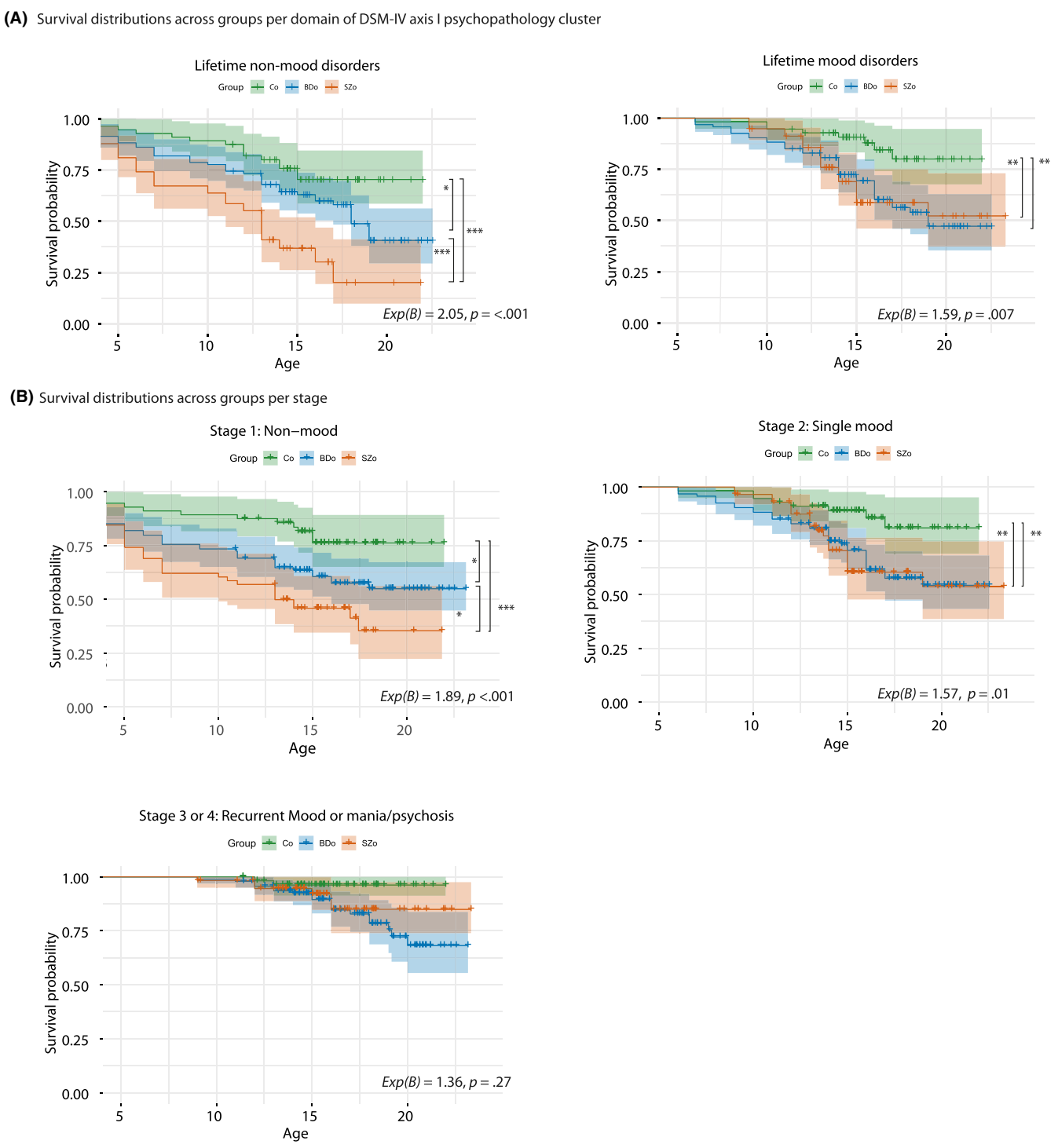

FIGURE 1 (A) Survival distributions across groups per domain of DSM-IV axis I psychopathology cluster. (B) Survival distributions across groups per stage. Cox regressions, corrected for age at interview and sex. Asterisks depict significant pairwise comparisons: $^{*}p < 0.05$, $^{**}p < 0.01$, and $^{***}p < 0.001$.

The clinical staging approach allowed us to explore differences in disorders or stages preceding first mood episodes between groups, which may provide a tool for prognostic orientation or opportunities for intervention. As expected, both familial risk groups have showed more transitions between stages, but staging did not reveal clear differences between SZo and BDo. By evaluating survival curves of the DSM-IV diagnoses clusters as well as clinical stages, we could confirm that non-mood disorders are more prevalent at younger age in SZo than BDo. Although the rates of non-mood disorders (stage 1) did not differ in frequency, our staging perspective revealed the importance of risk profiling using a longitudinal course. Taken together, this study underscores the heterotypic character of

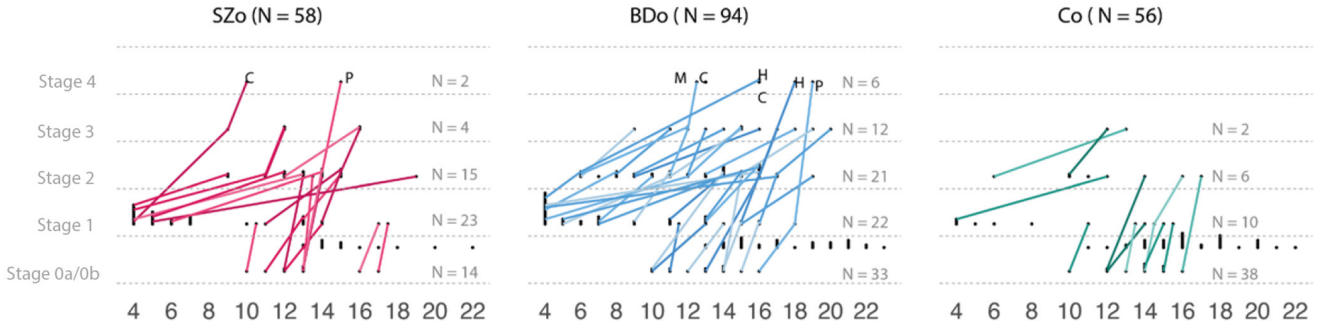

FIGURE 2 Individual trajectories of clinical staging. Stage 0a = control offspring, no diagnosis; stage 0b= at risk, no diagnosis; stage 1 = non mood disorders; stage 2 = single mood disorders; stage 3 = recurrent mood disorders; stage 4 = manic/psychotic disorders; C = cyclothymic; H = hypomania; M = Mania; P = psychotic; each connecting line between dots represents a transition between stages, offspring without any diagnosis at both waves are represented by a single dot at their latest know ages (i.e., at follow-up or at baseline in case of drop-outs).

psychopathology in offspring at familial high risk and suggests that problems (especially developmental disorders) occur at a younger age in SZo than in BDo, well before the onset of a first mood episode. As expected, between the mean age of 13 and 17 years, the majority of Co remained at the same stage, and SZo and BDo progressed one or two stages.

SZ and BD have been identified as life-course illnesses with different clinical manifestations from an at-risk to a late stage.[28] Whether regression to previous stages, as a result of remission of symptoms, is possible is still under debate in the literature. Although symptoms can go in remission (current clinical state), as underlying disease processes may be irreversible, clinical staging is considered unidirectional.[42] Offspring will therefore retain their risk for progression to further stages, irrespective of their current clinical state.

In line with previous studies,[16,18,19] both SZo and BDo reported more (sub)clinical symptoms in the domains of depression, psychosis, anxiety, and developmental symptoms than Co. SZo reported more symptoms of developmental disorders and depression than BDo; this was reflected in interviewer-based-, parent-, and teacher-, but not self-report, stressing the importance of a multi-informant approach. Mania symptoms were most prevalent in BDo, and have been previously marked as important risk factor for BD in BDo.[12,13,53] Mania symptoms may belong to the specific prodrome for BD, yet longer follow-up of these cross-disorder studies are needed.

Overall, results show that SZo and BDo follow a similar developmental course of emerging psychopathology, although SZo are more vulnerable for non-mood disorders at a younger age and for symptoms of developmental and mood disorders. This may point toward a different ethiopathophysiology. In an earlier study on brain structure in a subsample of the current cohort, we found evidence of smaller intracranial volumes in SZo compared to BDo (a difference of 1%).[33] As ICV is considered a marker for neurodevelopment,[54,55] a smaller ICV is suggestive of neurodevelopmental factors that are likely more at play in relation to familial risk for SZ than BD.[56] Future studies are essential to further address the relationship between brain developmental and clinical trajectories. Long-term follow-up of these offspring is essential to provide a complete and reliable prediction of the developmental course toward SZ and BD.

Several limitations should be considered. First, we described developmental trajectories during childhood/adolescence in offspring at familial risk. We included offspring with a broad age range (8–18 years old) at baseline. Unfortunately, due to the relatively small sample size, correction for age could not be applied to all analyses. The prevalence rates should be interpreted with care, as age is an important factor in the onset of disorders and especially the younger offspring may still develop (more) psychopathology after our follow-up measurement. Additionally, as peak onset age for both disorders (in the general population) is approximately 20 years,[7] definite conclusions about the development of SZ or BD in the current cohort would be premature. Follow-up studies at an older age, as well as studies with larger sample sizes, are still needed to better understand the effect of age and in the risk for SZ or BD. Second, we adapted the staging model by Duffy[29] to compare the developmental trajectories between SZo and BDo. Importantly, other staging models suggest the perspective of cognitive development and the importance of biomarkers.[23,26,57] The model by Duffy was chosen here, because of its focus on bipolar disorder and the psychotic features of the bipolar spectrum. Additionally, its developmental perspective includes symptoms that are not disorder-specific. It has been argued that variabilities in clinical outcome, prodrome and onset, and comorbid disorders complicate the predictive use of clinical staging models for SZ and BD.[58] Additionally, clinical staging models that include pre-onset stages for individuals at risk are non-specific, therefore caution is needed to prevent inappropriate (early) treatment that are not proven to prevent severe mental illnesses and may increase fear and stigma.[59] However, this study used the clinical staging framework to further unravel the developmental course of BD and SZ in at-risk offspring, rather than to predict the clinical outcome of offspring at familial risk for mental illness. Finally, the majority of BDo had a parent with BD-I (82%), while genetic overlap with SZ is greater for BD-I than BD-II.[60] Differences between SZo and BDo may have been more pronounced with a more heterogeneous BDo sample.

TABLE 3 Dimensional psychopathology reported at baseline and follow-up.

	SZo		BDo		Co				
	Baseline ($n=58$)	Follow-up ($n=51$)	Baseline ($n=94$)	Follow-up ($n=84$)	Baseline ($n=56$)	Follow-up ($n=49$)			
KSADS-PL summary scores per cluster	**M (SD)**	**M (SD)**	**M (SD)**	**M (SD)**	**M (SD)**	**M (SD)**	***Statistic***	***p***	***Pairwise***
Mood, 31 items	41.0 (10.8)	47.9 (13.7)	39.3 (9.2)	45.0 (12.0)	34.1 (4.1)	37.0 (7.2)	$F(2,205)=12.92$	**<0.001**	**SZo >BDo $p=0.04$ and SZo > Co $p<0.001$ and BDo > Co $p<0.001$**
Mania, 9 items	9.7 (2.3)	10.1 (2.4)	10.1 (3.1)	11.3 (4.0)	9.1 (0.3)	9.1 (0.4)	$F(2,205)=6.08$	**0.003**	**BDo > Co $p < 0.001$**
Psychosis, 33 items	36.1 (4.7)	37.2 (5.0)	35.1 (3.6)	36.1 (4.0)	33.5 (1.2)	33.6 (1.5)	$F(2,205)=11.88$	**<0.001**	**SZo > Co $p<0.001$ and BDo > Co $p<0.001$**
Anxiety, 16 items	20.2 (3.9)	22.6 (5.2)	19.3 (3.9)	21.1 (4.6)	17.8 (2.3)	18.9 (3.3)	$F(2,205)=9.49$	**<0.001**	**SZo >Co $p<0.001$ and BDo > Co $p=0.005$**
Behavioral problems, 14 items	19.2 (4.9)	20.9 (6.0)	18.0 (3.9)	19.5 (4.9)	15.6 (2.3)	16.7 (3.5)	$F(2,205)=11.02$	**<0.001**	**SZo >BDo $p=0.03$ and SZo > Co $p<0.001$ and BDo > Co $p=0.003$**
ASEBA Questionnaires, *t*-score									
Self-report	**$n=27$**	**$n=40$**	**$n=61$**	**$n=80$**	**$n=35$**	**$n=44$**			
Internalizing problems	51.1 (10.7)	49.7 (13.1)	50.8 (11.1)	46.1 (11.7)	44.0 (7.8)	44.3 (10.7)	$F(2,186)=6.21$	**0.003**	**SZo >Co $p<0.001$ and BDo > Co $p=0.02$**
Externalizing problems	50.7 (9.4)	46.7 (10.1)	48.9 (11.4)	46.7 (9.3)	43.2 (8.7)	44.4 (8.9)	$F(2,186)=4.68$	0.010	
Parent-report	**$n=50$**	**$n=46$**	**$n=85$**	**$n=81$**	**$n=47$**	**$n=45$**			
Internalizing problems	56.4 (10.3)	54.2 (12.9)	53.6 (12.3)	49.3 (10.3)	45.7 (9.5)	43.2 (9.8)	$F(2,199)=18.97$	**<0.001**	**SZo >BDo $p=0.03$ and SZo > Co $p<0.001$ BDo > Co $p<0.001$**
Externalizing problems	52.0 (12.4)	52.0 (11.9)	49.9 (11.0)	46.3 (10.2)	44.3 (10.3)	41.4 (8.9)	$F(2,199)=13.10$	**<0.001**	**SZo >BDo p 02 and SZo > Co $p<0.001$ and BDo > Co $p<0.001$**
Teacher-report	**$n=42$**	**$n=16$**	**$n=64$**	**$n=29$**	**$n=41$**	**$n=23$**			
Internalizing problems	55.0 (10.5)	60.0 (13.2)	54.3 (9.8)	52.5 (5.8)	48.9 (7.9)	47.4 (7.3)	$F(2,151)=11.94$	**<0.001**	**SZo >Co $p<0.001$ and BDo > Co $p<0.001$**
Externalizing problems	54.8 (10.5)	56.0 (10.6)	50.8 (8.0)	50.6 (7.8)	46.6 (6.5)	48.5 (7.7)	$F(2,151)=12.30$	**<0.001**	**SZo >BDo $p=0.002$ and SZo > Co $p<0.001$ and BDo > Co $p=0.02$**

Bold indicates statistically significant *p*-values

Abbreviations: BDo, bipolar disorder offspring; SZo, schizophrenia offspring; Co, Control offspring; M, mean; SD, standard deviation.

Note: Statistics are based on latest known information (baseline or follow-up) and corrected for multiple testing using false discovery rate—Benjamini–Hochberg procedure, with $\alpha=0.034$.

To conclude, SZo and BDo show a comparable course of emerging psychopathology during childhood/adolescence. However, the earlier onset of developmental disorders and elevated developmental and mood symptoms in SZo as compared to BDo suggest a more severe early course in SZo compared to BDo that may reflect a difference in the at-risk phenotype. Having an affected parent has great impact on the development of offspring's mental well-being. Both offspring groups could benefit from close monitoring of clinical symptoms, to assess their clinical risk and provide early interventions to prevent illness transitions.

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DATA AVAILABILITY STATEMENT

The participant consent forms restrict data sharing on a public repository. Anonymous data and code are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

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

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