Association of sociocultural stressors with bipolar disorder onset in Puerto Rican youth growing up as members of a minoritized ethnic group: results from the Boricua Youth Longitudinal Study

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Summary

Background The development of bipolar disorder is currently explained by a complex interaction of genetic and environmental factors. Less is known regarding the influence of sociocultural factors. This study aims to evaluate the incidence and impact of sociocultural factors on bipolar disorder onset in two comparable samples of youth growing up in different social settings.

Methods We leveraged data from two urban population-based cohorts representative of Puerto Rican children growing up in either San Juan (Puerto Rico) or the South Bronx (NYC) and followed up for 17 years. Bipolar disorder diagnoses were based on retrospective self-reports on the World Health Organization Composite International Diagnostic Interview. We used a causal inference approach to estimate associations of sociocultural factors with bipolar disorder onset after adjusting for potential confounders.

Findings We found that South Bronx children, who grew up as a minoritized group, had twice the risk of bipolar disorder onset as young adults, with an incidence rate of 2.22 new cases per 1000 person-years compared to 1.08 new cases in San Juan (incidence rate difference, 1.13; 95% CI, 0.09–1.20). After adjusting for potential confounders, South Bronx children had the same lifetime hazard of bipolar disorder onset compared to San Juan children. However, our analysis demonstrated that caregivers' exposure to societal cultural stress partially explained the increased risk of bipolar disorder onset in the South Bronx, in addition to the potential contribution of genetics.

Interpretation Our results provide evidence that societal cultural stress can increase the risk of lifetime bipolar disorder onset in youth growing up as a minoritized group. Addressing stress in minoritized groups might reduce the risk of bipolar disorder onset.

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Research in context

Evidence before this study

Bipolar disorder has been considered one of the most heritable mental illnesses and most research on the aetiology of the disease focuses on finding genetic markers and understanding the polygenic architecture of the disease. Recently, several stress theories have been suggested to better understand the additional contributing mechanisms to the development of the disease. However, very few longitudinal studies have examined the role of environmental factors, particularly sociocultural stressors in minoritized populations, that potentially influence the development of bipolar disorder.

We searched in MEDLINE for studies published from January 1, 1980 to January 5, 2022, using the terms "bipolar disorder" AND ("incidence" OR "onset") AND "risk factors" AND ("environmental factors" OR "sociocultural factors") without language restrictions. This approach identified original studies or reviews of the literature on the topic with an emphasis on exposure to stress as a risk factor for developing bipolar disorder. A recent meta-analysis showed that stressors associated with the onset of bipolar disorder included exposure to adverse events during childhood, urbanicity, ethnic minority status and substance misuse. Some of these were general epidemiological longitudinal studies with subgroup analysis including ethnicity, observational cross-sectional studies of individuals with bipolar disorder and associations with retrospective exposure to adverse events and/or substance use. Two longitudinal studies performed in the UK and France reported a higher incidence of bipolar disorder among ethnic minorities and immigrant populations, respectively. Yet, epidemiological studies reporting the incidence and prevalence of bipolar disorder rarely considered sociocultural factors. Those studies looking at the impact of sociocultural stressors are potentially biased because they are either (1) cross-sectional, substantially limiting causal inference; (2) have focused solely on subthreshold symptoms and not on clinical symptoms of the disease; (3) do not include an appropriate comparison group when studying minoritized or immigrant populations (e.g., non-immigrant populations or a comparable sample living as a "non-minoritized" group); or (4) do not control simultaneously for other known risk factors of bipolar disorder."

Added value of this study

This study used data from two urban population-based cohorts representative of Puerto Rican children who grew up as either a minoritized group or an ethnic majority. We used rigorous methods with careful attention to bias and confounding to overcome the limitations of previous studies. Propensity score weighting was used to create an appropriate counterfactual for children in the minoritized group, which included key covariates such as family history of mood disorder, gender, and parental age at child's birth. We found that Puerto Rican youth growing up as a minoritized group had twice the risk of developing bipolar disorder compared to similar youth growing up as an ethnic majority. In addition, factors related to parental acculturation stress increased the hazard of lifetime bipolar disorder onset more among youth from the minoritized group. These results support the hypothesis of a multifactorial cause of bipolar disorder.

Implications of all the available evidence

Acculturation stress in an ethnic minoritized group was associated with an increased risk of bipolar disorder onset. Variables related to being a member of an ethnic minoritized group along with other sociocultural stressors should be included when researching the development and course of bipolar disorder. Interventions targeting sociocultural stress at the policy and systemic levels should be incorporated to reduce excess risk of bipolar disorder among minoritized groups.

Introduction

Bipolar disorder (BD) represents a great burden to patients, healthcare systems, and society.[1,2] The epidemiology and presentation of the disease varies across different regions, with 12-month prevalence estimates ranging from 1.5% to 2.4%, although the reason for this variance is still unknown.[2] The development of BD depends substantially on genetic factors, with heritability estimates ranging between 60 and 85%.[3] Life stress and its repeated exposure to stressors are well recognised as prominent contributors to disease, including to the development of affective disorders such as BD.[4] Within the stress theory, many environmental factors might potentially impact the risk of BD development. Variables such as neurodevelopmental stressors, childhood trauma, substance use, and the accumulation of adverse life events have been associated with the development of BD.[5] Yet, stressors arising from the social and cultural life experiences remain understudied. Prior studies evidenced an increased incidence and earlier age of onset of BD among ethnic minorities in the UK.[6] Stress exposure related to being part of a minoritized group has been recognized as a risk factor for physical and mental illnesses.[7,8] Yet, compared to other mental disorders like schizophrenia,[9] anxiety, and depression,[10] few studies have rigorously examined how sociocultural stressors related to being a member of a minoritized ethnic group, including distress from adapting to a

dominant culture and discrimination, might contribute to developing BD.[5] For example, there is consistent evidence of an increased risk for psychotic disorders among immigrants and members of minoritized groups compared to those from the dominant culture.[11]

Evaluating the impact of sociocultural stressors in severe mental illnesses—particularly those related to being part of a minoritized group—presents conceptual and methodological challenges.[12] Previous studies looking at the impact of sociocultural stressors on BD are limited in scope since they are either (1) cross-sectional, substantially limiting causal inference;[13,14] (2) have focused solely on subthreshold symptoms;[14,15] (3) do not include samples comparing those who belong to a minoritized group and those sharing the dominant culture within the same country;[13] or (4) do not control simultaneously for other known BD risk factors.[13,15] Overall, the paucity of research and the methodological challenges in assessing the association of sociocultural stressors with BD have led to inconclusive findings.[13,15,16] Thus, disentangling the impact of sociocultural stressors—such as discrimination or acculturation stress—while considering the contribution of other recognized environmental factors in the development of BD would allow to identify at-risk populations and implement early detection systems to develop preventive interventions that reduce BD onset and/or subsequent disability.

Here, we used representative samples of two urban populations of Puerto Rican children from the Boricua Youth Study (BYS):[17] one in the South Bronx in New York City (the minoritized group) and another in Metropolitan San Juan and Caguas in Puerto Rico (the majority group). A prior study using BYS data indicated that sociocultural stressors related to being a member of the minoritized group (e.g., cultural stress and perceived discrimination) and social context stress (e.g., exposure to violence) were associated with the development of depression and anxiety.[10,18] We examined the effect of growing up as a minoritized ethnic group, and subsequent related exposure to sociocultural stressors (societal cultural stress, family cultural stress, perceived discrimination, and perceived social position), on lifetime BD onset compared to growing up in a dominant ethnic group. We compared the incidence rate of lifetime BD diagnoses between groups and evaluated whether differences in lifetime BD onset could be explained by previously recognized environmental factors and/or sociocultural stressors in minoritized groups. We also examined whether the effect of any of these stressors on lifetime BD onset was significantly different between groups. Based on previous findings,[10,18] we hypothesized that both incidence and lifetime BD onset would be higher in the South Bronx and that the excess risk would be associated with variables related to growing up as a minoritized ethnic group.

Methods

Design and sample

We used data from the BYS,[17] a four-wave longitudinal study of Puerto Rican children followed-up from childhood/early adolescence to late adolescence/young adulthood. Participants were selected through multistage probability sampling to be representative of two urban populations of Puerto Rican children: one in the South Bronx in New York City (the minoritized ethnic group) and another in the Metropolitan Areas in San Juan and Caguas in Puerto Rico (the majority group). Primary sampling units were household clusters (Census blocks) randomly selected from those defined in the 1990 US Census and subsequently updated using the 2000 US Census. Secondary sampling units were random households from the selected blocks. Households were eligible if at least one child 5–13 years old and one of the child's primary caretakers were identified as being of Puerto Rican ancestry (with up to three eligible children per household selected at random). Children and one primary caretaker were interviewed at Wave 1 in the year 2000 (N = 2491 dyads), and two more times at about one-year intervals (Wave 2 and Wave 3) between 2001 and 2004. Participants were interviewed one last time at Wave 4 between 2013 and 2017, when children were mostly young adults (N = 2004, aged 15–29 years [median, 22; interquartile range, 17–27]; 82.8% follow-up rate among eligible children).[19] Children ages 7 years and older signed assent forms, while caregivers and youth ages 18 years and older in the South Bronx and 21 years and older in Puerto Rico signed informed consent for participation in the study. Forms and procedures were approved by the Institutional Review Boards of all participating institutions (Registration Number # 2015P001490) and followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Measures

Outcomes

Lifetime BD diagnoses at Wave 4—youth aged 15–29 years—were based on retrospective self-reports on the World Health Organization's Composite International Diagnostic Interview (CIDI, v.3),[20] a fully structured lay-administered diagnostic interview. We calculated and analysed the incidence rates of lifetime BD (as number of cases per person-years) and age at onset (AAO) within the statistical framework described below. We classified respondents as having lifetime BD type I (BD-I) if they ever had a manic episode, and as having lifetime BD type II (BD-II) if they ever had a hypomanic but not manic episode and ever had a Major Depressive Episode (MDE).[21] Manic episode (duration 1+ week), hypomanic episode (duration 4+ days), and MDE were operationalized using DSM-IV criteria. CIDI criteria for manic/hypomanic episodes include symptoms not being the direct physiological effect of a substance. Age at onset of

BD-I and BD-II was assessed using AAO of manic/hypomanic episodes and of MDE from retrospective self-reports at the syndrome level.

Environmental and sociocultural stressors

Many factors might potentially impact the risk of BD development.[2] The current study particularly focused on those that have shown consistent evidence of association with BD development.

Neurodevelopmental stressors were assessed using caregiver self-reports at Wave 1 and included four variables: whether the biological mother smoked during pregnancy, premature birth of the child, low birthweight, and occurrence of caesarean birth.

Substance use prior to BD onset was assessed using youth self-reports at Wave 4 on the CIDI substance use module. We included five indicators of ever using each of the following substances and the age at first use being younger than AAO of BD: cocaine, marijuana, painkillers/opioids, sedatives/tranquilizers, and stimulants.

Parental loss and child maltreatment were assessed using six events that have been previously associated with BD and that were part of the Adverse Childhood Experiences Study:[22] Parental death and divorce/separation, child emotional abuse, neglect, and physical abuse (based on the Parent-Child Conflict Tactics Scale),[23] and child sexual abuse (based on the Sexual Victimization Scale).[24] Each event was coded as present if reported at Waves 1, 2, or 3.

Social context was measured using three variables for caregiver-reported past-year household income below the federal poverty line, exposure to violence,[17] and neighbourhood characteristics,[17] which were assessed using caregiver reports of neighbourhood problems. Each variable was coded as present if reported at Waves 1, 2, or 3.

Stress related to minoritized ethnic group was characterized using youth- and caregiver-reported past-year societal cultural stress (e.g., experiencing problems making friends because they do not speak English well or feeling they didn't belong either in Puerto Rico or the US), caregiver-reported past-year family cultural stress (e.g., you feel like some family members are losing their religion or moral values), and youth-reported past-year perceived discrimination (been treated poorly due to race, skin colour, where they came from, language/accent, and/or social class), based on adapted subscales of the Cultural Stress module of the Hispanic Stress Inventory.[25] The stressors were coded as present if participants responded "sometimes or often" to any question at Wave 1, 2, or 3, and as absent if they responded "rarely or never" at all waves.[26] We also included perceived social position, assessed through youth self-report at Wave 4 on the MacArthur Scale of Subjective Social Status-Youth Version,[27] which retrospectively asked the youth to place themselves where they think they stood socioeconomically ten years prior relative to other people in their community. Details regarding specific questions for the evaluated stressors, psychometrics of the used scales, and bivariate correlations between each pair of stressors can be found in the Supplement and published elsewhere.[19,26]

Statistical analysis

Comparison group for the minoritized group

Since place of residence (i.e., San Juan and Caguas or the South Bronx) is subject to selection bias, the minoritized group may differ in unknown exposures limiting the understanding of potential differences. We applied propensity score weighting (PSW)[28] to create a comparison group that can provide an appropriate counterfactual for the developmental trends of children growing up in the minoritized group. Specifically, we estimated the conditional probability of residing in the minoritized context (South Bronx) using Wave 1 data to weight all subsequent analyses to account for selection assignment differences between the groups. This strategy aimed to turn children of the majority group into a representative sample of children in the minoritized group with respect to the distribution of the baseline variables used to estimate the propensity score. Although no significant differences were observed between groups in the balancing variables, PSW substantially improved this balance by bringing the small differences close to zero (Table S2). See further details on our PSW strategy in the Supplement.

Incidence rate of lifetime BD

We evaluated if the incidence rate of BD in adolescence and young adulthood in the minoritized group significantly differed from those in the majority group after creating an appropriate counterfactual. Because participants could still develop BD later in life, data were "censored" at their age at Wave 4 for those with no history of BD. Thus, we calculated differences in the incidence rate of BD to measure the difference in the number of new BD cases relative to the total time participants were observed "at risk" and used the standard error of the difference to construct the 95% confidence interval (95% CI). We then evaluated its significance at the $\alpha = 0.05$ level. Thus, our null hypothesis of no difference included zero within the 95% CI (further details are provided in the Supplement).

Lifetime BD onset and the role of environmental and sociocultural stressors

We also examined whether differences in lifetime BD onset between groups could be explained by differences in environmental and sociocultural stressors (including ethnic minority stress) using discrete-time survival models with person-year as the unit of analysis. Data were censored at the AAO of BD or age at Wave 4 for those with no history of the disorder. We estimated six different models: Model 0 evaluated unadjusted

differences in lifetime BD onset between the minoritized and majority groups; Model 1 added the neurodevelopmental stressors; Model 2 added substance use prior to BD onset; Model 3 added parental loss and child maltreatment; Model 4 added social context; and Model 5 added ethnic minoritized stress. To examine whether the effect of each stressor differed by groups, we included two-way interactions between minoritized group and each stressor in the fully adjusted Model 5 separately to prevent over-specification. We could not determine whether all youth experienced some of the stressors (parental loss and child maltreatment, social context, and ethnic minoritized stress) prior to the onset of BD; thus, all survival models excluded youth whose AAO of BD was younger than their age at Wave 3 (see full sample estimates in Table S3). Hazard Ratios (HR) and 95% CI were estimated using survey methods in Stata 15,[29] and standard errors were adjusted for intraclass correlations induced by the multistage probability sampling, with children nested within households and households nested within Census blocks. In each model, we adjusted for fall discovery by using an omnibus test for the hypothesis that all model coefficients were zero. Further, although we conducted a secondary analysis using data from the BYS, using results from a recent study[30] we determined that our sample size of 2004 youth was adequate in terms of the number of participants and outcome events relative to the number of predictor parameters. This minimizes the risk of overfitting and ensures precise estimates of overall outcome risk (detailed calculations are provided in the Supplement). Missing data was handled using multiple imputation by chained equations.[31] See Supplement for further details.

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Results

From all young adults interviewed at Wave 4 (N = 2004), 921 grew up in the minoritized group (South Bronx) and 1083 resided as the majority (San Juan and Caguas). Other demographics and relevant characteristics were previously published.[10] Lifetime BD diagnoses were identified in 79 participants, resulting in a weighted prevalence of 3.92%. Nine of these participants were excluded from our analysis since their AAO was younger than their age at Wave 3, and we could not identify whether they were exposed to some stressors prior to BD onset (see Table S4 for a breakdown of lifetime BD diagnoses and AAO by age at Wave 4). From the remaining 70 youth with lifetime BD diagnosis, 42 grew up in the South Bronx and 28 in Puerto Rico. As shown in Table 1, compared to their majority counterparts, young adults from the minoritized group with a BD diagnosis were more likely to have experienced stressors related to parental divorce/separation, neighbourhood problems, and family cultural stress. In contrast, young adults from the minoritized group with a BD diagnosis were less likely to have reported societal cultural stress. This last result was driven by youth from the majority group being more likely to report societal cultural stress related to knowing, understanding, or speaking English well, given that they grew up speaking Spanish.

Incidence rates of lifetime BD

The incidence rate of lifetime BD in the minoritized group roughly doubled the one from the majority group (Table 2), with 2.22 cases in the South Bronx compared to 1.08 cases per 1000 person-years in San Juan and Caguas (incidence rate difference, 1.13; 95% CI, 0.42–1.85). When disaggregated by type, the incidence rate difference appeared to be driven by new BD-I cases: 1.31 and 0.66 cases per 1000 person-years in the minoritized and majority group, respectively (incidence rate difference, 0.65; 95% CI, 0.09–1.20).

Survival models

Consistent with the incidence rate estimates, youth from the minoritized group had a higher hazard—and therefore a shorter survivor time—of lifetime BD onset than majority youth. Our HR estimates in unadjusted Model 0 (Table 3) indicated that, at any particular age, almost twice as many youths from the minoritized group had developed BD compared to the majority youth (HR, 1.97; 95% CI, 1.13–3.46). This higher hazard remained unchanged in Model 1, which adjusted for neurodevelopmental stressors (HR, 1.94; 95% CI, 1.10–3.40), although we could not reject the null hypothesis that all model coefficients were zero ($F_{(5,252.19)}$, 1.44; p, 0.21). The difference in hazard between minoritized and majority youth became smaller and nonsignificant after accounting for substance use prior to BD onset (Model 2), parental loss and child maltreatment (Model 3), social context (Model 4), and ethnic minoritized stress (Model 5). Further, we could reject the null hypothesis that all model coefficients were zero in Models 4 and 5 only. In the fully adjusted Model 5, caregiver-reported societal cultural stress was the only stressor independently associated with a higher hazard of lifetime BD onset (HR, 2.15; 95% CI, 1.18–3.89), while the effect of marijuana use was near significance (HR, 1.90, 95% CI, 1.00–3.63, p, 0.051). In addition, youth from the minoritized group remained about 1.55 times as likely to develop BD at any particular age compared to majority youth (HR, 1.55; 95% CI, 0.80–3.02).

Stressor	Without BD (N = 1925)			With BD (N = 70)[b]		
	Minoritized Group (South Bronx)	Majority Group (Puerto Rico)	p	Minoritized Group (South Bronx)	Majority Group (Puerto Rico)	p
	N = 873	N = 1052		N = 42	N = 28	
	Mean (SE)	Mean (SE)		Mean (SE)	Mean (SE)	
Neurodevelopmental stressors (from W1)						
Mother smoked during pregnancy (caregiver)	20.5% (1.8%)	8.3% (1.3%)	<0.00001	16.4% (6.8%)	18.1% (7.9%)	0.87
Premature birth (caregiver)	23.6% (2.0%)	14.7% (1.3%)	0.00024	20.9% (7.4%)	22.5% (8.2%)	0.88
Low birth weight (<2500 g; caregiver)	13.3% (1.3%)	10.5% (1.1%)	0.10	6.4% (4.7%)	10.1% (5.9%)	0.62
Caesarean birth (caregiver)	19.4% (1.5%)	31.6% (1.9%)	<0.00001	10.2% (6.1%)	37.3% (11.1%)	0.034
Substance use prior to BD onset (from W4)						
Cocaine (youth)	2.4% (0.5%)	1.3% (0.5%)	0.11	13.3% (6.7%)	3.5% (3.5%)	0.19
Marijuana (youth)	54.0% (1.7%)	26.2% (1.7%)	<0.00001	68.0% (7.5%)	43.6% (11.2%)	0.072
Pain killers/opioids (youth)	9.0% (0.9%)	12.7% (1.4%)	0.025	9.5% (5.6%)	19.5% (8.9%)	0.34
Sedatives (youth)	3.3% (0.7%)	4.8% (0.7%)	0.13	6.0% (5.6%)	9.2% (6.3%)	0.71
Stimulants (youth)	6.2% (0.9%)	4.3% (0.7%)	0.075	9.6% (4.3%)	9.9% (6.6%)	0.97
Parental loss and child maltreatment (from W1-3)						
Parental death (caregiver)	6.8% (1.0%)	3.8% (0.7%)	0.019	0.0% (0.0%)	0.0% (0.0%)	NA
Parental divorce/separation (caregiver)	68.6% (2.2%)	47.5% (2.7%)	<0.00001	80.2% (6.5%)	49.8% (10.6%)	0.015
Emotional abuse (youth and caregiver)	42.3% (1.9%)	24.5% (1.7%)	<0.00001	47.1% (8.4%)	26.2% (9.2%)	0.093
Neglect (youth and caregiver)	20.6% (1.8%)	22.3% (1.6%)	0.48	26.0% (7.3%)	23.8% (9.1%)	0.85
Physical abuse (youth and caregiver)	35.3% (2.0%)	27.2% (1.8%)	0.0028	35.9% (8.7%)	34.4% (9.6%)	0.91
Sexual abuse (youth and caregiver)	10.0% (1.2%)	6.9% (1.0%)	0.046	12.6% (5.7%)	6.1% (4.1%)	0.36
Social context (from W1-3)						
Income below poverty line (caregiver)	46.1% (2.6%)	38.7% (2.8%)	0.055	55.9% (7.4%)	44.0% (10.8%)	0.36
Exposure to violence (youth)	28.0% (1.6%)	29.0% (2.2%)	0.71	37.2% (8.1%)	26.7% (9.0%)	0.38
Neighbourhood characteristics (caregiver)	86.7% (1.7%)	67.2% (2.8%)	<0.00001	87.9% (5.6%)	54.8% (10.5%)	0.0059
Ethnic minoritized stress (from W1-3)						
Societal cultural stress (youth)	52.6% (1.9%)	85.9% (1.3%)	<0.00001	40.7% (9.3%)	85.6% (7.7%)	0.00022
Societal cultural stress (caregiver)	35.4% (2.3%)	56.2% (2.4%)	<0.00001	57.7% (8.1%)	43.9% (11.5%)	0.33
Family cultural stress (caregiver)	88.5% (1.2%)	72.0% (1.9%)	<0.00001	92.8% (3.8%)	57.6% (9.6%)	0.00074
Discrimination (youth)	36.2% (1.9%)	36.6% (2.0%)	0.90	32.0% (8.7%)	43.5% (11.5%)	0.43
Perceived social position (youth)[c]	4.14 (0.07)	5.43 (0.09)	<0.00001	3.26 (0.35)	5.64 (0.46)	0.000046

Notes: Mean and Standard Error (SE) based on 50 imputed datasets. BD, Bipolar Disorder; W1, Wave 1; W4, Wave 4; W1-3, Waves 1 to 3; NA, Not Applicable. [a]Final survey weights were rescaled using the propensity score as described in the Supplement. [b]Excludes N = 9 participants whose age at onset of BD was younger than their age at Wave 3. [c]Perceived social position was assessed retrospectively at Wave 4 (youth were asked to place themselves where they think they stood ten years prior relative to other people in their community).

Table 1: **Differences in the distribution of environmental and sociocultural stressors by lifetime bipolar disorder (BD) diagnosis across minoritized and majority groups (propensity score weighted).[a]**

The cumulative hazard function, a graphical representation of the estimates in Table 3, is depicted in Fig. 1. In correspondence to the estimates from Models 0 and 1, Fig. 1 shows that about 6.0% of youth from the minoritized group had developed BD by age 25 compared to about 3.0% of youth in the majority group.

Incidence Rate (IR) per 1000	Total	Minoritized group (South Bronx)	Majority group (Puerto Rico)	Test South Bronx = Puerto Rico	
	N = 2004	N = 921	N = 1083		
	IR	IR	IR	Difference	[95% CI]
BD (BD-I or BD-II)	1.65	2.22	1.08	1.13	[0.42, 1.85]
BD-I	0.98	1.31	0.66	0.65	[0.09, 1.20]
BD-II	0.66	0.89	0.42	0.47	[−0.01, 0.89]

Notes: BD, Bipolar Disorder; BD-I, Bipolar Disorder Type I; BD-II, Bipolar Disorder Type II. [a]Final survey weights were rescaled using the propensity score as described in the Supplement.

Table 2: **Difference in the incidence rate of BD across minoritized and majority groups (propensity score weighted).[a]**

Predictor	Model 0		Model 1		Model 2	
	HR [95% CI]	p>|t|	HR [95% CI]	p>|t|	HR [95% CI]	p>|t|
Group membership (from W1)						
Minoritized group (majority group reference)	1.97 [1.13, 3.46]	p = 0.02	1.94 [1.10, 3.40]	p = 0.02	1.69 [0.95, 3.02]	p = 0.07
Neurodevelopmental factors (from W1)						
Mother smoked during pregnancy (caregiver)			0.90 [0.39, 2.06]	p = 0.80	0.85 [0.37, 1.95]	p = 0.70
Premature birth (caregiver)			1.29 [0.59, 2.81]	p = 0.52	1.25 [0.58, 2.72]	p = 0.56
Low birth weight (<2500 g; caregiver)			0.38 [0.10, 1.39]	p = 0.14	0.39 [0.11, 1.45]	p = 0.16
Caesarean birth (caregiver)			0.84 [0.38, 1.84]	p = 0.65	0.86 [0.39, 1.87]	p = 0.69
Substance use prior to BD onset (from W4)						
Cocaine (youth)[c]					–	–
Marijuana (youth)					1.76 [0.99, 3.13]	p = 0.06
Pain killers/opioids (youth)					1.08 [0.39, 3.01]	p = 0.89
Sedatives (youth)					1.43 [0.30, 6.78]	p = 0.65
Stimulants (youth)					1.21 [0.46, 3.24]	p = 0.70
Overall model omnibus test	F (1, 258.87) = 5.71	p = 0.02	F (5, 252.19) = 1.44	p = 0.21	F (9, 257.61) = 1.63	p = 0.11

Predictor	Model 3		Model 4		Model 5	
	HR [95% CI]	p>|t|	HR [95% CI]	p>|t|	HR [95% CI]	p>|t|
Group membership (from W1)						
Minoritized group (majority group reference)	1.55 [0.89, 2.68]	p = 0.12	1.54 [0.88, 2.69]	p = 0.13	1.55 [0.80, 3.02]	p = 0.19
Neurodevelopmental factors (from W1)						
Mother smoked during pregnancy (caregiver)	0.82 [0.35, 1.91]	p = 0.64	0.90 [0.38, 2.16]	p = 0.81	0.86 [0.35, 2.11]	p = 0.74
Premature birth (caregiver)	1.25 [0.57, 2.75]	p = 0.58	1.24 [0.56, 2.77]	p = 0.59	1.29 [0.59, 2.82]	p = 0.51
Low birth weight (<2500 g; caregiver)	0.40 [0.11, 1.47]	p = 0.16	0.39 [0.10, 1.50]	p = 0.17	0.42 [0.11, 1.58]	p = 0.20
Caesarean birth (caregiver)	0.90 [0.42, 1.95]	p = 0.79	0.85 [0.39, 1.88]	p = 0.69	0.90 [0.41, 1.98]	p = 0.80
Substance use prior to BD onset (from W4)						
Cocaine (youth)[c]	–	–	–	–	–	–
Marijuana (youth)	1.92 [1.04, 3.54]	p = 0.04	1.87 [0.99, 3.56]	p = 0.054	1.90 [1.00, 3.63]	p = 0.051
Pain killers/opioids (youth)	1.05 [0.38, 2.89]	p = 0.92	1.06 [0.38, 2.94]	p = 0.91	1.13 [0.41, 3.09]	p = 0.81
Sedatives (youth)	1.42 [0.31, 6.51]	p = 0.65	1.40 [0.31, 6.42]	p = 0.66	1.37 [0.31, 6.01]	p = 0.67
Stimulants (youth)	1.13 [0.42, 3.08]	p = 0.80	1.11 [0.42, 2.96]	p = 0.83	1.10 [0.41, 2.91]	p = 0.85
Parental loss and child maltreatment (from W1-3)						
Parental death (caregiver)[d]	–	–	–	–	–	–
Parental divorce/separation (caregiver)	1.26 [0.69, 2.31]	p = 0.45	1.36 [0.74, 2.48]	p = 0.32	1.37 [0.74, 2.55]	p = 0.31
Emotional abuse (youth and caregiver)	1.41 [0.67, 2.99]	p = 0.37	1.41 [0.67, 2.94]	p = 0.36	1.44 [0.72, 2.88]	p = 0.31
Neglect (youth and caregiver)	0.27 [0.03, 2.11]	p = 0.21	0.25 [0.03, 1.94]	p = 0.19	0.26 [0.03, 2.03]	p = 0.20
Physical abuse (youth and caregiver)	0.94 [0.39, 2.28]	p = 0.90	0.91 [0.38, 2.20]	p = 0.83	0.93 [0.38, 2.24]	p = 0.86
Sexual abuse (youth and caregiver)	1.20 [0.17, 8.39]	p = 0.86	1.21 [0.16, 8.81]	p = 0.85	1.18 [0.17, 8.38]	p = 0.87
Social context (from W1-3)						
Income below poverty line (caregiver)			1.49 [0.84, 2.65]	p = 0.17	1.61 [0.93, 2.78]	p = 0.09
Exposure to violence (youth)			1.05 [0.56, 1.95]	p = 0.88	1.03 [0.54, 1.96]	p = 0.93
Neighbourhood characteristics (caregiver)			0.77 [0.40, 1.47]	p = 0.43	0.69 [0.36, 1.32]	p = 0.26
Ethnic minority stress (from W1-3)						
Societal stress (youth)					0.68 [0.32, 1.44]	p = 0.31
Societal stress (caregiver)					2.15 [1.18, 3.89]	p = 0.01
Family stress (caregiver)					0.66 [0.36, 1.22]	p = 0.19
Discrimination (youth)					1.06 [0.51, 2.20]	p = 0.88
Perceived social position (youth)[e]					0.94 [0.82, 1.08]	p = 0.38
Overall model omnibus test	$F_{(14,\ 257.84)}$ = 1.52	p = 0.10	$F_{(17,\ 258.06)}$ = 2.05	p = 0.0094	$F_{(22,\ 257.81)}$ = 2.16	p = 0.0024

Notes: BD, Bipolar disorder; PSW, Propensity score weighting; HR, Hazard Ratio; CI, Confidence Interval; W1, Wave 1; W4, Wave 4; W1-3, Waves 1 to 3; estimates based on 50 imputed datasets. [a]Final survey weights were rescaled using the propensity score as described in the Supplement. [b]Excludes N = 9 participants whose age at onset of BD was younger than their age at Wave 3. [c]Cocaine use was perfectly positively correlated with marijuana use; cocaine use was thus excluded from the analyses. [d]No participant with a BD diagnosis experienced parental death at Waves 1 to 3; parental death was thus excluded from the analyses. [e]Perceived social position was assessed retrospectively at Wave 4 (youth were asked to place themselves where they think they stood ten years prior relative to other people in their community).

Table 3: **Minoritized and majority groups differences in lifetime bipolar disorder (BD) onset explained by differences in environmental and sociocultural stressors (propensity score weighted).**[a,b]

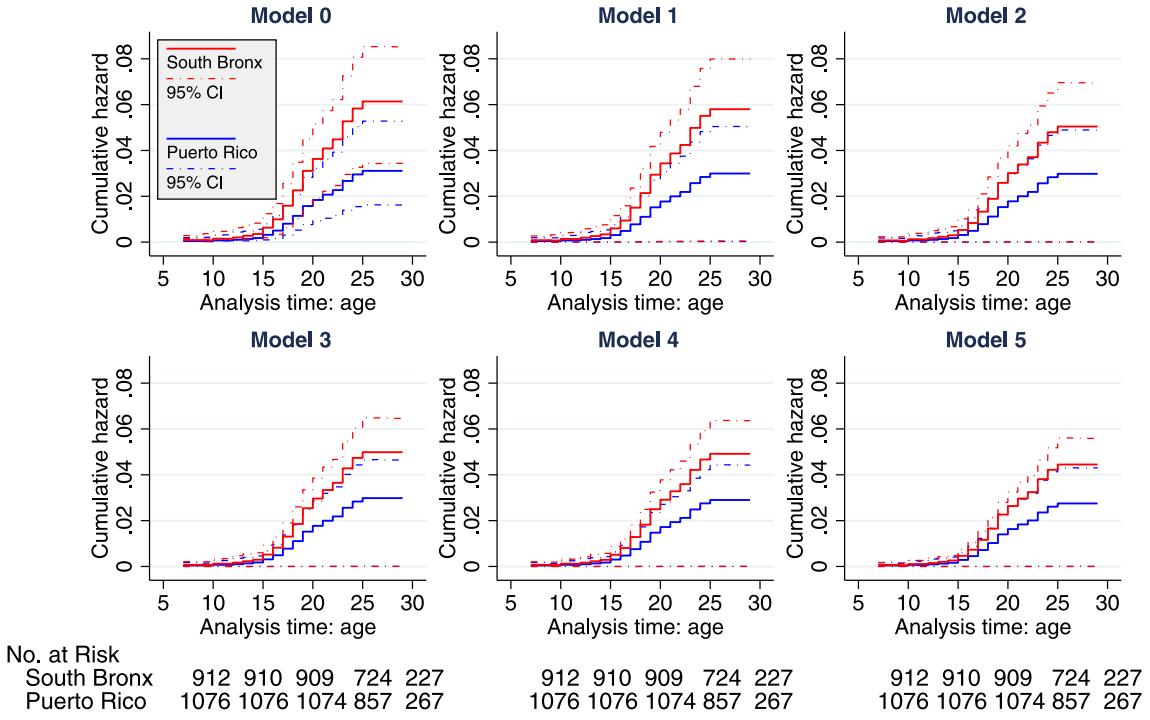

Fig. 1: **Cumulative hazard function for South Bronx (minoritized group) and Puerto Rico (majority group).** *Notes:* Model 0 evaluated unadjusted site differences in BD onset. Model 1 added to Model 0 the neurodevelopmental stressors, Model 2 added substance use prior to BD onset, Model 3 added parental loss and child maltreatment, Model 4 added social context, and Model 5 added minoritized ethnic stress.

This difference decreased in Models 2–4, where about 4.9% of youth from the minoritized group had developed BD by age 25 compared to about 2.9% of youth in the majority group. This difference was further decreased in the fully adjusted Model 5, where about 4.4% of youth from the minoritized group had developed BD by age 25 compared to about 2.8% of youth in the majority group.

Our results from the discrete-time survival analysis using two-way interactions between the minoritized group and environmental and sociocultural stressors are presented in Fig. 2. We display the HR estimates associated with the interactions. These HR estimates represent the effect of each stressor on the hazard of lifetime BD onset in the minoritized group relative to the majority. If a particular stressor increases the hazard of lifetime BD onset, a HR for the interaction above one would indicate that such stressor increases this hazard more among youth from the minoritized group compared to the majority. A HR below one would indicate that the stressor increases the hazard of lifetime BD onset less among youth from the minoritized group compared with the majority. Analogously, if a particular stressor decreases the hazard of lifetime BD onset, a HR for the interaction above one would indicate that such stressor decreases this hazard less among youth from the minoritized group compared with the majority. A HR below one would indicate that the stressor decreases the hazard of lifetime BD onset more among youth from the minoritized group compared with the majority. As shown in Fig. 2, only the effect of two stressors (both related to ethnic minoritized stress) on lifetime BD onset differed by group: a unit increase in caregiver-reported societal cultural stress increased the hazard of lifetime BD onset more among youth from the minoritized group than from the majority group (HR, 3.49; 95% CI, 1.03–11.78), while a unit increase in youth-reported perceived social position decreased this hazard more among youth from the minoritized group than from the majority group (HR, 0.76; 95% CI, 0.59–0.99).

Discussion

Lifetime prevalence of BD in our two urban populations of Puerto Rican youth ages 15–29 years old, one in the South Bronx in New York City (the minoritized ethnic group) and another in the Metropolitan Areas in San Juan and Caguas in Puerto Rico (the majority group), was estimated at around 3.92%. This prevalence is consistent with previous US population-based estimates among young adults of similar ages. Based on diagnostic interview data from the same assessment tool as in our study, lifetime prevalence of bipolar spectrum

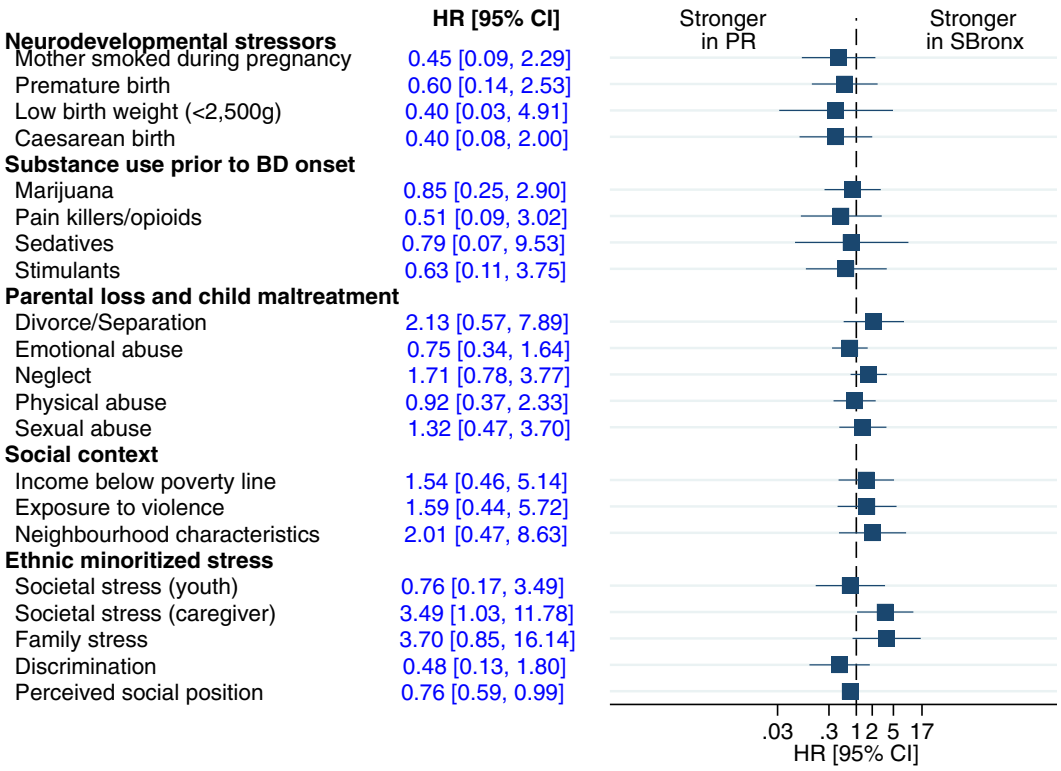

Fig. 2: **Hazard ratios for the two-way interaction between group membership and environmental and sociocultural factors.** *Notes:* HR, Hazard Ratio; CI, Confidence Interval; PR, Puerto Rico; SBronx, South Bronx.

disorder (which includes sub-threshold disorder) among young adults 18–29 years old was 7.0% in the National Comorbidity Survey Replication (NCS-R).[32] Further, lifetime prevalence of BD-I and BD-II in the National Comorbidity Survey Adolescent (NCS-A) was 3.1% among youth 15–16 years old and 4.3% among youth 17–18 years old. However, we found that Puerto Rican youth growing up as a minoritized ethnic group in the South Bronx had doubled incidence rates of lifetime BD than those in Puerto Rico, despite an assumed share of similar genetic background. These results are consistent with higher rates of other affective disorders (e.g., depression) in Puerto Ricans growing up as a minoritized group compared to those youth living as the majority in Puerto Rico.[10] While many risk factors for development of BD have been proposed, after adjusting for a variety of well-recognized risk factors (including neurodevelopmental stressors, childhood trauma, and substance use), differences between the minoritized and majority groups were no longer statistically significant, which suggested that these well-known risk factors might indeed play causal roles in the observed differences in risk of BD. However, in contrast with prior research, we found that caregiver-reported societal cultural stress was the only stressor independently associated with a higher hazard of lifetime BD onset, a stressor not previously related to the development of BD,[33] and a potentially preventable risk factor. Further, our results suggested that an increased risk of BD among youth from the minoritized group could be partially attributed to caregiver-reported societal cultural stress, which increased the hazard of lifetime BD onset more among youth from the South Bronx compared to youth from Puerto Rico. This result suggested that ethnic stress might be an important risk factor for the development of BD among Puerto Rican youth from the minoritized group.

Previous research described higher incidence of BD among second-to third-generation but not among first-generation migrants (born outside of the country of residence).[13] The increased incidence of BD among second-to third-generation migrants is consistent with our results, where over 85% of South Bronx youth were second- or third-generation migrant-residents (in this case, meaning their parents/grandparents had been born in Puerto Rico). This highlights the impact of post-migration stress factors (such as social defeat,[11] achievement-expectation mismatch,[34] and acculturation stress[35]) rather than selective migration or migration, per se, as risk factors on BD development.[36] Although the migration process of Puerto Ricans does not involve a change in legal status, post-migration factors related to

experiencing minoritized status, acculturation to a distinct context, and discrimination are still present.[37,38] They can lead to harsh parenting styles that could potentially affect disease development in their children.[39] Acculturation stress levels among Puerto Ricans living in Puerto Rico are also high in this sample and have been related to American cultural dominance and social pressures impacting cultural norms and expectations on the island.[26] Overall, these results add to hypotheses exploring multifactorial drivers leading to BD onset,[40] including the contribution of chronic stress.[41] Individuals exposed to a hostile context with high levels of psychological distress (e.g., racism, acculturation, harsh parenting style, adverse childhood events, or early moderate-to-severe substance use) are at higher risk of developing BD than populations that are not exposed.[4] However, more research is needed for understanding the mechanisms and potential targets of these exposures. Finally, we found that other well-known risk factors were not associated with BD onset. This lack of significant association could be explained by the specific characteristics of our sample (e.g., young age, Puerto Rican ethnicity) that have not been previously studied. Further research looking at specific ethnic groups, immigrant populations, and young adults is needed to replicate these findings.

Study limitations include assessment of BD diagnosis based on lay-administrated retrospective symptom self-report, not a clinician-based diagnosis. The CIDI is a diagnostic interview that has been validated in different populations. However, unfortunately, it has not been validated in a Latinx immigrant sample yet. Compared to clinical appraisals, the diagnostic test has shown high validity (positive predictive value, 0.88; negative predictive value, 1.0) in the general population.[42] Thus, under this performance we would have correctly classified on average around 90% of the BD cases on both cohorts. Further, the average time between the first BD episode and the reporting date was less than five years for both groups, limiting recall biases. Even though the sample size was relatively small to identify BD cases, as expected given the population level incidence of the disorder, the uniqueness of the homogenous sample and the methodology employed were sufficient to detect differences between cohorts. Using cohorts from the same country, both from urban settings, and with similar quality of care and adding PSW to balance the sample for crucial variables allowed us to assume groups were interchangeable. However, this assumption might hide potential selection bias such as urbanity levels in each site, higher in the South Bronx,[43,44] mental healthcare quality of care differences,[45] or specific attitudes towards reporting mental health symptoms. For instance, stigma towards mental health could be lower in Puerto Ricans living in the South Bronx, potentially affecting self-reported BD symptoms, as it has been found in other countries.[46] Further, prior research suggests that prevalence estimates of BD using the CIDI might be conservative (i.e., they might represent a lower bound),[21] which could potentially bias our results in two ways. First, one of our main findings was a higher incidence and earlier age at onset of BD in the South Bronx compared to Puerto Rico. Suppose the CIDI underestimates the prevalence of BD in Puerto Rico only. In that case, it is possible that no differences between the two sites would be observed if BD was measured with a different instrument. Thus, there would be no need to examine risk factors that might explain differences between the minoritized and majority group in the first place, including sociocultural stressors. Second, even if the CIDI underestimates the true prevalence of BD equally in both sites, if there is a relationship between sociocultural stressors and failure to detect BD symptoms using the CIDI (e.g., the CIDI failing to detect BD symptoms in participants with low levels of sociocultural stress), it is possible that no relationship between sociocultural stressors and risk for BD would be observed if BD was also measured with a different instrument. Future research might thus benefit from assessing BD symptoms within the same sample using more than one method. With the PSW we balanced for family history of depression and accounted for family risk among both cohorts. However, we could not balance for full BD-specific history which might limit the assumption that samples are similar relative to genetic vulnerability. Yet, under the assumption that BD-specific family history is randomly distributed over the cohorts, our finding should hold.

It is also possible that caregivers' migration from Puerto Rico to the South Bronx was associated with risk factors for BD and/or BD itself. Data limitations did not allow us to include some of these factors in our PSW. For example, childhood trauma has been found to be associated with BD, and many migrant children face a multitude of traumatic experiences prior to, during, and following migration.[47] However, history of childhood trauma experienced by the caregivers was not available in our data, and thus could not be included in our PSW. Furthermore, stressors related to the social context were included in the model to differentiate between potential increased risk of BD due to disadvantaged social condition from minoritized status. However, to better study postmigration factors the analysis could include other variables related to social stress or social defeat (e.g., exposure to aggressions or social cohesion).[11] Data collection procedures did not allow assessing perceived social position prospectively at Waves 1–3; thus, our analysis involved retrospective perceived social position at Wave 4, limiting its interpretation and validity. Further, our results are limited by data collection censored at Wave 4 (ending in 2017) when some participants were only 15 years old and can present BD later. Therefore, these results, including the higher rates of BD in the South Bronx compared to prior population-

based estimates in youth and young adults,[48] indicate an earlier onset of the disease in the South Bronx compared to Puerto Rico. However, they might not represent a higher lifetime incidence of BD, and subsequent prevalence, in Puerto Rican populations. Longitudinal studies with a longer observation period are needed to answer this question. Finally, overall, this is a secondary analysis of the Boricua Youth Study focusing on the incidence of BD and on exploring the effect of well-established environmental factors and factors related to being minoritized on the onset of BD. The research plan was limited to the available variables in the original dataset and the specific populations included in the study.

Despite these limitations, we believe the major implications of our findings are three-fold. First, variables related to being a member of an ethnic minoritized group along with other sociocultural stressors should be included when researching the development and course of BD. Replication of this approach in cohorts including other minoritized populations will help uncover the mechanisms behind the BD risk differences and consolidate the importance of understanding sociocultural factors in BD development. Second, interventions that reduce sociocultural stress and its impact might subsequently reduce the excess of BD incidence for the minoritized youth.[49] Lastly, our findings support evidence for public health interventions aiming to improve identification and management of BD cases among socially disadvantaged populations, particularly among minoritized groups, who already face greater gaps in their access to care worldwide.[50]

Conclusions

The surveyed cohort of Puerto Rican youth growing up in the South Bronx present higher rates of BD compared to their counterparts growing up in San Juan, Puerto Rico. Research should incorporate sociocultural stressors when studying BD onset and development in the future. Interventions targeting sociocultural stress reduction at the policy and systemic level should be incorporated to reduce BD risk excess among minoritized groups.

Contributors

Irene Falgas-Bague, performed the literature search, study design, data interpretation, writing of the original draft, reviewing and editing the final manuscript. She shared final responsibility for the decision to submit for publication along with M.C-G, M.A. and P.M.D.

Mario Cruz-Gonzalez, had access to raw data, worked on the study design and statistical plan, conducted the data analysis and verified the data, contributed to the data interpretation, the figures and the writing of the original draft and multiples revisions of it. He shared final responsibility for the decision to submit for publication along with I.F-B., M.A. and P.M.D.

Jenny Zhen-Duan, contributed to the data interpretation, writing, reviewing, and editing of the manuscript.

Arundati Nagendra, worked on the literature search, writing the original draft and reviewing of the manuscript.

Kiara Alvarez contributed to the data curation, data verification, project administration, writing of the original draft and reviewing and editing of the manuscript.

Glorisa Canino, Cristiane S Duarte, Hector Bird, contributed to the conceptualization, data curation, funding acquisition, investigation and revision of the manuscript.

Pablo M De-Salazar worked on the conceptualization of the methodology, statistical analysis plan, writing of the original draft, reviewing and editing of the manuscript. He verified the data and had final responsibility for the decision to submit for publication along with I.F-B, M.C-G and M.A.

Margarita Alegría, PhD., had access to raw data, contributed on conceptualization, data curation, analysis plan, funding acquisition, investigation, revision and editing of the manuscript. She verified the data, shared final responsibility for the decision to submit for publication along with I.F-B, M.C-G and P.M.D.

Data sharing statement

All data and analysis codes can be accessed upon request to the corresponding author.

Declaration of interests

All authors declare no competing interests.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lana.2023.100549.

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