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RESEARCH ARTICLE

Risk of psychosis in autism spectrum disorder individuals exposed to psychosocial stressors: A 9-year chart review study

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Abstract

Psychosocial stressors have been suggested to precipitate psychotic episodes in patients with pre-existing psychosis and otherwise healthy subjects. However, such a risk has never been formally investigated in individuals with autism spectrum disorder (ASD). Sixty-nine autistic adolescents hospitalized for psychotic/manic symptoms (PSY) and other mental health issues (NPSY) over a 9-year period were compared with reference to their previous exposure to psychosocial stressors. ASD diagnoses satisfied the International Classification of Diseases (ICD)-10 criteria. Psychotic/manic symptom assessment followed the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS). Psychosocial stressor exposure was collected separately at each admission. Preliminarily, univariate between-group comparisons were conducted. Then, a binomial model was adopted to investigate associations with previous exposure to psychosocial stressors. Results were reported with a change in AIC (ΔAIC). PSY patients presented with higher previous exposure to adverse life events (30.43% vs. 6.52%, OR = 6.079 [1.209, 40.926], $p = 0.013$) and school/work difficulties (30.43% vs. 8.70%, OR = 4.478 [0.984, 23.846], $p = 0.034$) than NPSY ones. Admissions for psychotic/manic symptoms occurred more likely in the context of family disturbances (OR = 2.275 [1.045, 5.045], $p = 0.030$) and adverse life events (OR = 3.489 [1.194, 11.161], $p = 0.014$). The fitted binomial model was found to be significant compared to the random effects model (ΔAIC = −1.962; $\chi^2_{10} = 21.96$, $p = 0.015$), with the risk of presenting psychotic/manic symptoms being increased by family disturbances ($z = +4.118$) and school/work difficulties ($z = +2.455$). The results suggest a potential psychosis-inducing effect of psychosocial stressors in ASD, which has clinical and policy implications.

Lay Summary

Although autistic individuals were found to face more stressful life events and to perceive them more severely than neurotypical peers, the psychosis-inducing effect of psychosocial stressors in autism spectrum disorder (ASD) has never been assessed so far. We conducted a retrospective observational study in adolescents with ASD in-patiently hospitalized for mental health issues over a 9-year period, recording exposure to psychosocial stressors at each admission. We found that family disturbances and conflicts with peers are associated with the occurrence of

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psychotic symptoms in autistic individuals, which has important clinical and policy implications for mental health professionals.

KEYWORDS
Asperger's syndrome, bipolar disorder, childhood adversities, neurodevelopment, schizophrenia, youth mental health

INTRODUCTION

Non-affective (e.g., schizophrenia) and affective psychoses (e.g., bipolar disorder with psychotic features) may be regarded as part of a developmental trajectory also embracing autism spectrum disorder (ASD) and other neurodevelopmental conditions arising earlier in life (Owen & O'Donovan, 2017). The significant clinical comorbidity between these conditions (Hossain et al., 2020; Varcin et al., 2022), the emerging evidence of shared genetic background between psychoses and ASD (Craddock & Owen, 2010; Owen & O'Donovan, 2017), and the presence of common environmental risk factors impacting early brain development (Bortoletto & Colizzi, 2022; Colizzi et al., 2022; Howes & Murray, 2014; Owen et al., 2016; Owen & O'Donovan, 2017) strengthen the paradigm of an etiological and neurodevelopmental continuum model. Importantly, increasing psychosis rates and clinical high risk for psychosis (CHR-P) states have been reported among autistic individuals (Foss-Feig et al., 2019; Gadow, 2012; Selten et al., 2015). Accumulating evidence highlights how exposure to psychosocial stressors may promote the developmental cascade to psychosis at all stages (Kraan et al., 2015; Sideli et al., 2020), playing a crucial precipitating role in up to one-third of psychosis patients (Varese et al., 2012). To this extent, associations between childhood adversities (CAs; e.g., diverse forms of child maltreatment, peer victimization, witnessed or experienced threatening events) or stressful life-events (SLEs) on one hand, and psychotic symptoms occurrence (Comacchio et al., 2019; Lu et al., 2017; Murphy et al., 2013; Newman-Taylor et al., 2020), first-episode psychosis (FEP) (Mansueto et al., 2022; Veru et al., 2022), or psychosis progression (Baudin et al., 2016) on the other, were extensively investigated among general population cohorts (Konings et al., 2012; Murphy et al., 2013), healthy subjects (DeRosse et al., 2014), and individuals with specific biological risk for schizophrenia (Alemany et al., 2014; Newman-Taylor et al., 2021; Vinkers et al., 2013), as well as CHR-P (Lu et al., 2017) or schizophrenia (Baudin et al., 2016; Colizzi, Cullen et al., 2023; Lemvigh et al., 2021; Newman-Taylor et al., 2020) patients. A role for psychological mechanisms was questioned, including insecure attachment styles, dysfunctional cognitive schemas, thinking errors, and non-psychotic symptoms (Appiah-Kusi et al., 2017; Bebbington, 2015; Rafiq et al., 2018). Moreover, a growing body of research has explored several potential biological underpinnings (Davies et al., 2022; Di Nicola et al., 2013; Egerton et al., 2016; Howes & Murray, 2014; Pruessner et al., 2017; Selten et al., 2013), accounting for the association between psychosocial stressors and psychosis, as well as the interacting or mediating role of other risk factors (e.g., cannabis use) (Arranz et al., 2018; Colizzi, Bortoletto et al., 2023). Interestingly, individuals with ASD were found to experience more psychosocial stressors over the course of their lives (e.g., family poverty, sexual abuse, parental illness, parental alcoholism, and parental divorce) compared with neurotypical individuals (Berg et al., 2016; Berg et al., 2018; Hoover & Kaufman, 2018; Schneider et al., 2019). Also, due to intrinsically reduced cognitive flexibility, the impact of such stressors on physical and mental health may be perceived as more severe by autistic individuals than neurotypical peers (Howes & Murray, 2014; Kerns et al., 2015). In fact, available resources and coping skills represent a critical factor in stress perception, often found to be poor in autistic subjects (Hirvikoski & Blomqvist, 2015; Howes & Murray, 2014). In addition, as interpersonal factors also influence perception of stressors and their effect on health, subjects with ASD are likely to be disadvantaged due to social isolation and low social support, causing even greater negative effects on their mental state (Howes & Murray, 2014; Moseley et al., 2021; Selten et al., 2013). Noteworthy, recent robust evidence emphasizes that, in the context of interpersonal childhood trauma, autistic traits and social communication difficulties may result in distressing and frequent psychotic experiences until young adulthood, independent of genetic liability to psychosis (e.g., schizophrenia Polygenic Risk Scores [PRS]) (Dardani et al., 2022). Nevertheless, the role of psychosocial stressors in the risk of psychotic symptoms among autistic patients has not been investigated so far, and real-world studies examining this association are still scarce.

Objectives

A retrospective observational study aimed at describing the sociodemographic and clinical characteristics

of adolescents with ASD in-patiently admitted to a tertiary hospital's Child and Adolescent Psychiatry ward for positive psychotic and/or manic symptoms, as compared to those admitted for any other mental health issue in the same time window. Autistic patients presenting with positive psychotic and/or manic symptoms were combined together based on converging evidence for a single-dimensional structure of such psychopathological constructs (Quattrone et al., 2019; Reininghaus et al., 2016; Reininghaus et al., 2019; Smith et al., 2018). Further, exploratory analyses investigated whether any specific psychosocial stressor was associated with the occurrence of psychotic and/or manic symptoms among autistic patients.

METHODS

Study setting and participants

The study was conducted at the Child and Adolescent Psychiatry and Psychotherapy Department (CAPPD) of Merano Hospital, Italy, a local tertiary referral inpatient facility for all subjects coming from the South Tyrol region presenting with severe mental health issues in their developmental age. Of all inpatient admissions over the observation period, only those of autistic patients aged 10–19 (Sawyer et al., 2018) were considered for the purpose of this study. ASD diagnoses (F84-F84.9) were already defined by clinicians prior to admission according to the International Classification of Diseases (ICD)-10 criteria (Volkmar et al., 1992). Included referrals were either scheduled (e.g., upon referral from liaison neuropsychiatrists for diagnostic or therapeutic purposes) or urgent (e.g., after initial Emergency Department (ED) assessment or transfer from other inpatient wards/peripheral hospitals). The occurrence of positive psychotic symptoms (e.g., delusions, hallucinations) and/or manic symptoms (e.g., grandiosity, flight of ideas, and increased goal-directed activities) at the time of admission had to be clearly established by a senior clinician, following the child-administered Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS)—Psychosis and Mania screening, based on the Diagnostic and Statistical Manual of Mental Disorders 5th Edition (DSM-5) criteria (Tsuji et al., 2019). Information about personal medical history, family history, and psychosocial context was collected from each patient's parents or caregivers by two experienced interviewers (e.g., physician and a psychologist) independently of each other. In the occasional instances of conflicting attribution, a consensus was reached through discussion with a third senior clinician.

Source of clinical data

The following data were retrospectively retrieved from electronic and paper clinical records of all consecutive autistic patients admitted to the CAPPD throughout the period May 2013 to May 2022: (1) age; (2) sex; (3) population density; (4) intelligence quotient [IQ, as measured with the Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV) for verbal participants (Wechsler, 2003) and with the Leiter-R scale for non-verbal participants (Bradley-Johnson, 1998)]; (5) intellectual disability (no/yes); (6) physical comorbidity (no/yes); (7) impairment in daily-life activities (no/yes); (8) delayed speech or language development (no/yes); (9) predating Child and Adolescent Mental Health Service (CAMHS) support (no/yes); (10) predating social services support (no/yes); (11) predating limited parental authority (no/yes); (12) genetic aberrancies (e.g., monogenic mutation, polygenic mutation, chromosomal abnormality) (no/yes); (13) any family history of psychopathology (no/yes); (14) ASD family history (no/yes); (15) psychosis/affective disorder family history (no/yes); (16) substance misuse family history (no/yes); (17) other neuropsychiatric disorder family history (no/yes); (18) level of support needs (level 1/level 2/level 3); (19) number of hospitalizations; (20) year of first hospitalization; (21) length of inpatient stay; (22) urgent access (no/yes); (23) aggressiveness during the stay (no/yes); (24) need for oral sedation during the stay (no/yes); (25) need for intramuscular sedation during the stay (no/yes); (26) number of psychotropic medications at admission; (27) number of psychotropic medications at discharge; (28) psychotropic medication-free hospitalization (no/yes); (29) hospitalization with stable psychotropic medication (no/yes); (30) psychotropic medication dosage modulation during hospitalization (no/yes); (31) psychotropic medication change during hospitalization (no/yes); (32) reason for referral (no/yes): (i) positive psychotic symptoms, (ii) manic symptoms, (iii) disruptive behavior, (iv) anxiety symptoms, (v) withdrawal symptoms, (vi) repetitive behavior, (vii) depressive symptoms, (viii) attention-deficit/hyperactivity disorder (ADHD) symptoms, (ix) sleep disturbances, (x) aberrant eating behavior, (xi) substance abuse, (xii) suicidal ideation, (xiii) self-harm, (xiv) suicide attempt; (33) family stressors (no/yes): (i) altered intra-familial relationships, (ii) family disturbances, (iii) distorted communication, (iv) abnormal parenting conditions; (34) environmental stressors (no/yes): (i) abnormal living conditions, (ii) adverse life events, (iii) migration, (iv) school/work difficulties, and (v) adversities due to disability; (35) global psychosocial functioning at discharge. Data concerning the variables 33–35 were coded according to the multi-axial ICD-10 system for psychopathological diagnoses (Janca et al., 1996) and collected from axis V and VI of each discharge report.

Statistical analysis

The collected data were reported as the mean and standard deviation (SD) and range of variation for continuous variables. Counts and percentages were used to describe categorical measures. Preliminarily, differences between the two groups were analyzed with Fisher's exact test for categorical variables (also reporting Odds Ratios, ORs, and 95% confidence interval, CI). With regards to continuous variables, between-group comparisons were analyzed with the median-centered Levene's test, using Welch's corrected t-test for homoscedastic measures and Mann-Whitney's test for variables with a skewed distribution. A binomial model for the occurrence of psychotic/manic symptoms (yes = 1) was fitted as a generalized linear mixed model by maximum likelihood using Laplace's approximation. The analysis was performed on hospitalizations, including participant and year of hospitalization as random factors. Given the sample size, only those measures showing statistically significant association ($p < 0.05$) in preliminary analyses were included as fixed factors, further reducing the number of covariates with summary measures of these results. Also, a psychosocial stressor (i.e., V9) was excluded from the model because it was not represented in the group with psychotic/manic symptoms. To obtain comparable estimates, participants' ages were standardized in the sample as z-scores, and the natural logarithm (ln) of population density was used. Results were reported with Akaike's Information Criterion (AIC), change in AIC (ΔAIC), and χ^2-test. Fixed effects were reported as ln of ORs with their standard error (SE) corresponding z-score and statistical significance. Potential overdispersion was tested considering deviance/mean ratio. Collinearity was tested by calculating Variance Inflation Factor (VIF) of the included predictors. VIF values were considered acceptable if lower than 10 and discussed if greater than 5. To manage missing data, case-wise selection was preferred in univariate analyses. In multivariable analyses, imputation of missing data was carried out with the Random Forest algorithm (maximum number: 100; trees in each forest: 1000), a non-parametric method suitable for both continuous and categorical variables (Stekhoven & Buhlmann, 2012). Normalized Root Mean Squared Error (NRMSE) and Proportion of Falsely Classified (PFC) were estimated after imputation. Also, the multivariable analysis was replicated without imputation of missing data, and after excluding those patients presenting manic symptoms but not psychotic ones, that were the main outcome of interest. List-wise selection was preferred to evaluate the effects of moderators. Statistical significance was conventionally set at $\alpha = 0.050$. All analyses were performed with R in version 4.2.2 (https://www.R-project.org). All retrieved information is commonly collected in clinical practice following the completion of informed consent by patients and their parents/caregivers. Since this study was part of a clinical audit, ethical approval was not required.

RESULTS

Preliminary analyses

The study counted 69 participants with ASD. Comparisons between subjects without (NPSY, $n_1 = 46$) and with psychotic/manic symptoms (PSY, $n_2 = 23$) are reported in Table 1. The groups did not significantly differ as per the majority of sociodemographic and clinical characteristics. A higher need for urgent admissions to CAPPD among PSY compared to NPSY (OR = 3.488, 95% CI: [1.095, 12.173], $p = 0.022$) was observed. Concerning psychosocial stressors, PSY subjects experienced more "Adverse life-events" (V6; 30.43% vs. 6.52%, OR = 6.079 [1.209, 40.926], $p = 0.013$) and "School/Work difficulties" (V8; 30.43% vs. 8.70%, OR = 4.478 [0.984, 23.846], $p = 0.034$) than NPSY.

One hundred and thirty-six hospitalizations of subjects with ASD were recorded throughout the observation period. Hospitalizations with psychotic/manic symptoms (PSY-h, 54 observations) were evenly distributed per year, except for 2021 (with more cases: 24.07% vs. 8.54%, $p = 0.024$). As compared to hospitalizations without psychotic/manic symptoms (NPSY-h), PSY-h occurred more frequently among older patients (PSY-h vs. NPSY-h; 16.10 ± 1.609 years vs. 14.89 ± 1.906 years, $t_{125.9} = 3.98$, $p < 0.001$), and those coming from smaller (29206.89 ± 40729.285 inhabitants vs. 51873.05 ± 46384.142 inhabitants, $U = 2750.0$, $p = 0.008$) and less densely populated centers (533.90 ± 752.347 inhabitants/Km^2 vs. 1133.88 ± 875.765 inhabitants/Km^2, $U = 3012.5$, $p < 0.001$). Also, as compared to NPSY-h, PSY-h occurred more frequently among individuals without medical/physical comorbidities (PSY-h vs. NPSY-h, 56.10% vs. 74.07%, $p = 0.045$), less impaired in daily-life activities (35.37% vs. 61.11%, OR = 0.351 [0.161, 0.751], $p = 0.005$), less commonly presenting with delayed speech or language development (65.85% vs. 83.33%, OR = 0.388 [0.146, 0.955], $p = 0.030$), and with lower support needs (level-2/−3: 1.85% vs. 25.61%, OR = 0.056 [0.001, 0.369], $p < 0.001$). Furthermore, PSY-h occurred significantly more often among patients with family history of ASD (≥2 relatives: 7.84% vs. 0.00%, $p = 0.024$), psychotic/affective disorders (≥2 relatives: 11.76% vs. 0.00%, $p = 0.003$), substance misuse (one relative: 25.49% vs. 10.53%, $p = 0.031$), and other neuropsychiatric disorders (≥2 relatives: 70.59% vs. 35.53%, $p < 0.001$).

Finally, PSY-h were more frequent in the context of "Family disturbances" (V2; OR = 2.275 [1.045, 5.045], $p = 0.030$) and "Adverse life-events" (V6; OR = 3.489 [1.194, 11.161], $p = 0.014$), and less frequent in the

TABLE 1 Sample description with comparison between participants without (NPSY) and with (PSY) psychotic/manic symptoms.

Measure (unit)	NPSY mean ± SD (range)/*N* (%)	PSY mean ± SD (range)/*N* (%)	
	46 (66.7%)	23 (33.3%)	-
General description			
Sex (male = 1)	37 (80.4%)	19 (82.6%)	
Population density (inhabitants/Km^2)	999.7 ± 882.51 (10.8, 2043.4)	754.8 ± 865.35 (10.8, 2043.4)	
Minimum age (years)	14.7 ± 2.10 (10.3, 18.6)	15.4 ± 1.86 (12.0, 18.3)	
Maximum age (years)	15.3 ± 2.09 (10.3, 18.6)	16.0 ± 1.90 (12.0, 19.0)	
IQ (standard score)	87.9 ± 24.71 (34.0, 128.0)	90.9 ± 19.88 (49.0, 129.0)	
Has intellectual disability (yes = 1)	13 (28.3%)	4 (17.4%)	
Has physical comorbidity (yes = 1)	22 (47.8%)	6 (26.1%)	
Has impairments in daily-life activities (yes = 1)	31 (67.4%)	11 (47.8%)	
Has delayed speech or language development (yes = 1)	14 (30.4%)	5 (21.7%)	
Predating CAMHS support (yes = 1)	44 (95.7%)	20 (87.0%)	
Predating social services support (yes = 1)	12 (26.1%)	7 (30.4%)	
Predating limited parental responsibility (yes = 1)	6 (13.0%)	3 (13.0%)	
Genetic aberrancies (yes = 1)	2 (4.4%)	2 (8.7%)	
Any family history of psychopathology (yes = 1)	31 (67.4%)	17 (73.9%)	
ASD family history (yes = 1)	5 (10.9%)	4 (17.4%)	
Psychosis/Affective disorder family history (yes = 1)	9 (19.6%)	9 (39.1%)	
Substance misuse family history (yes = 1)	10 (21.7%)	7 (30.4%)	
Other neuropsychiatric disorder family history (yes = 1)	23 (50.0%)	14 (60.9%)	
ASD with Level-1 support needs (yes = 1), versus Level-2/-3 support needs	36 (78.3%)	22 (95.7%)	
Hospitalizations			
Number of hospitalizations (count)	1.7 ± 1.12 (1.0, 6.0)	2.6 ± 2.78 (1.0, 13.0)	
Year of first hospitalization by participant	2013: 3 (6.5%), 2014: 7 (15.2%), 2015: 5 (10.9%), 2016: 4 (8.7%), 2017: 2 (4.4%), 2018: 5 (10.9%), 2019: 10 (21.7%), 2020: 3 (6.5%), 2021: 5 (10.9%), 2022: 2 (4.4%)	2013: 2 (7.3%), 2014: 4 (15.9%), 2015: 0 (5.8%), 2016: 0 (5.8%), 2017: 3 (8.7%), 2018: 1 (7.3%), 2019: 5 (21.7%), 2020: 2 (7.3%), 2021: 4 (13.0%), 2022: 2 (7.3%)	-
Any urgent access (yes = 1)	18 (39.13%)	16 (69.6%)	*
Mean length of hospitalization (days)	15.8 ± 9.97 (2.0, 45.5)	19.8 ± 14.05 (2.0, 58.0)	
Maximum length of hospitalization (days)	20.4 ± 17.90 (2.0, 94.0)	29.1 ± 30.71 (2.0, 150.0)	
Aggressiveness/Need-for-sedation during the stay, any (yes = 1)	4 (8.7%)	5 (21.7%)	
Aggressiveness during the stay, any (yes = 1)	3 (6.5%)	4 (17.4%)	
Oral sedation during the stay, any (yes = 1)	3 (6.5%)	5 (21.7%)	
Intramuscular sedation during the stay, any (yes = 1)	1 (2.2%)	2 (8.7%)	
Mean number of psychotropic medications, on admission (count)	0.6 ± 0.73 (0.0, 2.7)	0.9 ± 1.13 (0.0, 4.0)	
Mean number of psychotropic medications, at discharge (count)	1.0 ± 0.88 (0.0, 3.0)	1.3 ± 1.00 (0.0, 3.3)	
Medication-free hospitalizations, any (yes = 1)	18 (39.1%)	7 (30.4%)	
	12 (26.1%)	6 (26.1%)	

(Continues)

TABLE 1 (Continued)

Measure (unit)	NPSY mean ± SD (range)/*N* (%)	PSY mean ± SD (range)/*N* (%)	
Hospitalizations with stable psychotropic medication, any (yes = 1)			
Psychotropic medication dosage modulation during hospitalization, any (yes = 1)	8 (17.4%)	7 (30.4%)	
Psychotropic medication change during hospitalization, any (yes = 1)	25 (54.4%)	17 (73.9%)	
Psychotic symptoms, any (yes = 1)	0 (0.0%)	20 (87.0%)	-
Manic symptoms, any (yes = 1)	0 (0.0%)	8 (34.8%)	-
Disruptive behavior, any (yes = 1)	23 (50.0%)	11 (47.8%)	
Anxiety symptoms, any (yes = 1)	17 (37.0%)	13 (56.5%)	
Withdrawal symptoms, any (yes = 1)	20 (43.5%)	8 (34.8%)	
Repetitive behavior, any (yes = 1)	15 (32.6%)	8 (34.8%)	
Depressive symptoms, any (yes = 1)	13 (28.3%)	8 (34.8%)	
ADHD symptoms, any (yes = 1)	14 (30.4%)	6 (26.1%)	
Sleep disturbance, any (yes = 1)	7 (15.2%)	3 (13.0%)	
Aberrant eating behavior, any (yes = 1)	7 (15.2%)	3 (13.0%)	
Substance abuse, any (yes = 1)	0 (0.0%)	1 (4.4%)	
Suicidal ideation, any (yes = 1)	7 (15.2%)	7 (30.4%)	
Self-harm, any (yes = 1)	3 (6.5%)	4 (17.4%)	
Suicidal attempt, any (yes = 1)	1 (2.2%)	2 (8.7%)	

Abbreviations: ADHD, Attention-Deficit/Hyperactivity Disorder; ASD, Autism Spectrum Disorders; CAMHS, Child and Adolescent Mental Health Services; IQ, Intelligence Quotient; Level-1, Low support needs; Level-2/−3, Moderate/High support needs; NPSY, Group without psychotic/manic symptoms; PSY, Group with psychotic/manic symptoms.
*Statistically significant ($p < 0.05$).

TABLE 2 Psychosocial conditions by hospitalization (136 observations) with comparison between hospitalizations without (NPSY-h) and with (PSY-h) psychotic/manic symptoms.

Measure	NPSY-h	PSY-h	
With psychotic/manic symptoms	82 (60.3%)	54 (39.7%)	-
Family stressor			
Altered intra-familial relationships (V1)	15 (20.3%)	18 (35.3%)	
Family disturbances (V2)	29 (39.2%)	31 (59.6%)	*
Distorted communication (V3)	16 (21.6%)	11 (21.6%)	
Abnormal parenting conditions (V4)	23 (31.1%)	3 (5.9%)	*
Environmental stressor			
Abnormal living conditions (V5)	27 (36.5%)	17 (33.3%)	
Adverse life-events (V6)	7 (9.5%)	14 (26.9%)	*
Migration (V7.1)	6 (8.1%)	5 (9.8%)	
School/Work difficulty (V8)	7 (9.5%)	8 (15.4%)	
Adversities due to disability (V9)	12 (16.2%)	0 (0.0%)	*
Global psychosocial functioning (0, 9)	3.9 ± 1.30 (0.0, 8.0)	3.8 ± 0.71 (3.0, 6.0)	

Abbreviations: NPSY-h, Hospitalizations without psychotic/manic symptoms; PSY-h, Hospitalizations with psychotic/manic symptoms; V-, 5th chapter of the International Classification of Diseases, version 10.
*Statistically significant ($p < 0.05$).

presence of "Abnormal parenting conditions" (V4; OR = 0.140 [0.025, 0.510], $p < 0.001$) and "Adversities due to disability" (V9; OR = <0.001 [<0.001, 0.468], $p = 0.001$; Table 2).

Mixed-effects model (multivariable)

Eleven measures were included in the model as fixed factors: Age at hospitalization (years, in sample *z*-score),

TABLE 3 Fixed effects from binomial mixed model for the occurrence of psychotic/manic symptoms at hospitalization.

Predictor	Ln(OR) ± SE	*p*	
Intercept	−18.047 ± 6.085	0.003	*
Covariates			
Age (sample *z*-score)	+0.724 ± 2.508	0.773	
Natural logarithm of the population density (ln [inhabitants/Km^2])	−1.686 ± 4.439	0.704	
Family history of any psychopathology in more than two relatives (any = 1)	+7.076 ± 5.737	0.217	
Medical/Physical comorbidity (any = 1)	−17.351 ± 6.433	0.007	*
Impaired daily-life activities or in speech/ language (impairment = 1)	−7.030 ± 10.941	0.521	
Access route to the service (urgent = 1)	+0.150 ± 4.914	0.976	
Psychosocial stressors			
Family disturbances (V2) (any = 1)	+27.903 ± 6.776	<0.001	*
Abnormal parenting conditions (V4) (any = 1)	−10.447 ± 7.712	0.176	
Adverse life-events (V6) (any = 1)	+12.191 ± 8.775	0.165	
School/Work difficulties (V8) (any = 1)	+19.915 ± 8.112	0.014	*
Autism spectrum disorders symptoms			
Level of support needs moderate/high (yes = 1)	−48.658 ± 17.498	0.005	*

Abbreviations: ln, Natural logarithm; OR, Odd Ratio; SE, Standard error; V-, 5th chapter of the International Classification of Diseases, version 10.
*Statistically significant ($p < 0.05$).

Population density (ln(inhabitants/Km^2)), Family history of any neuropsychiatric disorder in more than two relatives (any = 1; intended to summarize the significance of psychopathology in the family), Medical/physical comorbidities (any = 1), "Impaired daily-life activities" or "Delayed speech or language development" (yes = 1), Admission route (urgent = 1), level of support needs (Level-2/−3 = 1). The following psychosocial stressors were selected: "Family disturbances" (V2; any = 1), "Abnormal parenting conditions" (V4; any = 1), "Adverse life-events" (V6; any = 1), and "School/Work difficulties" (V8; any = 1).

The imputation of missing data (3.19% of the selected) resulted acceptable (NRMSE = 0.08%, PFC = 7.46%). The model did not show overdispersion (ratio: 0.046, $\chi^2_{122} = 5.57$, $p > 0.999$). No excessive collinearity was noticed, even though low tolerance was observed for Population density (VIF = 5.700), V6 (VIF = 5.268), and V8 (VIF = 5.418). The inclusion of Participant as a random factor ($\Delta AIC = -41.249$; $\chi^2_1 = 43.25$, $p < 0.001$) and year of hospitalization ($\Delta AIC = -5.161$; $\chi^2_1 = 7.16$, $p = 0.007$) improved the model at a statistically significant level. Then, fixed effects were found as to be significant when compared to the model with random effects only (AIC = +101.178; $\Delta AIC = -1.962$; $\chi^2_{10} = 21.96$, $p = 0.015$). Overall, the model had a high accuracy (98.53%, 95% CI: [94.79%, 99.82%]) in classifying hospitalizations with psychotic/manic symptoms. The model's coefficients for fixed factors are reported in Table 3. Intercepts for the two random factors ranged from −51.13 to +15.56 for the participant, and from −6.54 to +10.45 for the year of hospitalization. Once adjusted for other confounders, for the effects of repeated observation (Participant) and for prolonged sampling (year of hospitalization), the risk of presenting with psychotic/manic symptoms was significantly increased by psychosocial stressors "Family disturbances" (V2; $z = +4.118$) and "School/Work difficulties" (V8; $z = +2.455$), while being reduced by having moderate/high level of support needs (level-2/−3; $z = -2.781$) and having medical/physical comorbidities ($z = -2.697$). When the analysis was performed after excluding those patients presenting with manic symptoms only (see Supplementary Results), results were unchanged in indicating an increased risk of presenting with psychotic/manic symptoms as a function of the psychosocial stressors "Family disturbances" (V2) and "School/Work difficulties" (V8). Also, overlapping results were obtained when the analysis was conducted without the imputation of missing data.

DISCUSSION

To the best of our knowledge, this is the first study addressing the impact of psychosocial stressors on the risk of psychotic and/or manic symptoms in an autistic adolescent sample, focusing on subsequent inpatient admissions for mental health issues in a tertiary hospital throughout a 9-year observation period. Taken together, results indicate that individuals with ASD who are inpatiently admitted with (PSY) and without (NPSY)

psychotic and/or manic symptoms do not significantly differ in their sociodemographic characteristics. Instead, a higher rate of urgent referrals was observed among PSY patients compared to NPSY ones, with PSY patients more likely to have been exposed to adverse life events (i.e., mourning, risky situations due to extra-familial placement, risky situations due to family members, reduced self-esteem, extra-familial sexual abuse, and terrifying personal experiences) (Janca et al., 1996) and school/work difficulties (i.e., peer victimization, adult victimization, and restlessness at school/work) (Janca et al., 1996). Further, admissions due to psychotic and/or manic symptoms (PSY-h) were more likely to happen to patients exposed to family disturbances (i.e., parental psychiatric/behavioral disturbances, parental disabilities, and sibling disabilities) (Janca et al., 1996) and adverse life events (Janca et al., 1996). Such evidence was confirmed in multivariable analysis, with family disturbances and school difficulties increasing the risk of presenting with psychotic/manic symptoms among autistic patients, even after controlling for potential confounders such as age, population density, and family history of psychopathology, as well as for other types of psychosocial stressors.

The high prevalence of stressful events and trauma in this study sample is in line with previous evidence for a higher probability of experiencing adverse childhood experiences in autistic individuals compared to neurotypical peers (Berg et al., 2016; Fuld, 2018), especially stress and trauma experienced within the family, such as parental divorce, traumatic loss, low socioeconomic status, and neighborhood violence (Berg et al., 2016; Hoover & Kaufman, 2018). The experience of stress and trauma would then put individuals with ASD at an increased risk of incurring severe mental health comorbidities (Berg et al., 2016; Kerns et al., 2015). Growing evidence points to the frequent occurrence of mental disorders in close relatives of autistic patients, highlighting cross-generational associations between parental psychiatric illness and ASD in offspring (Birmaher et al., 2010; Chien et al., 2022; Liang et al., 2021), as well as common neurodevelopmental abnormalities (e.g., cognitive, learning, coordination, social, or emotional disturbances) among the siblings of individuals with ASD (Lauritsen et al., 2005; Lin et al., 2022; Pisula & Ziegart-Sadowska, 2015). Also, recent findings suggest worsened parental well-being measures to be consistently associated with the severity of the autistic child's clinical picture (Lanyi et al., 2022; Lohiya et al., 2023; Valicenti-McDermott et al., 2015). Moreover, mainly due to their socio-communicative difficulties and atypical interests and/or behaviors, adolescents with ASD are often exposed to aggressive peer victimization and bullying (Hoover & Kaufman, 2018), which are commonly recognized as risk factors for exacerbated ASD core symptoms and comorbid psychopathologies (Cappadocia et al., 2012; Fuld, 2018; Taylor & Gotham, 2016). Evidence from the present study corroborates and extends such findings, supporting the importance of family disturbances/disabilities and conflicts with peers as potential risk factors for the occurrence of psychotic and/or manic symptoms among autistic adolescents. To this extent, implications from this research warrant the need for mental health professionals and social workers to always address the exposure to such psychosocial stressors when dealing with ASD in daily practice and to modify the pathway to psychotic and/or manic symptoms through trauma prevention, assessment, and treatment.

An increased risk was also observed among less impaired autistic adolescents. Evidence from the present study can be considered somewhat consistent with the neurodevelopmental continuum paradigm, as it highlights the plausible underlying neurobiological proximity between ASDs with lower support needs (e.g., level 1 ASD) and psychoses (Owen & O'Donovan, 2017). Future research will be needed to understand whether autistic individuals with low support needs exhibit a genetic makeup predisposing them more to stress-determined epigenetic variations that would facilitate their evolution toward psychoses as compared to more disabling forms of ASD. Besides, autistic patients with low support needs may have deeper insight about feelings of distrust, isolation, and defeat due to their communication difficulties, possibly making them more prone to develop and be able to verbalize psychotic and manic symptoms (Ghaziuddin & Ghaziuddin, 2021; Howes & Murray, 2014).

Some strengths from this study deserve to be underlined. The previous very limited evidence about the potential role of psychosocial stressors in conferring a risk of psychotic symptoms among autistic patients makes this specific study population worth noting. In addition, although retrospective, information about psychosocial stressors was collected separately at each hospitalization, thus accounting for the time period preceding the respective admission event in terms of temporality. Moreover, the sample was characterized by several clinically relevant features, including both current (e.g., symptoms at admission) and early measures (e.g., family history, predating contact with CAMHS). Undeniably, the present study has some limitations. Firstly, it may be challenging to comprehensively account for psychotic and/or manic presentations across all levels of support needs and age groups. Indeed, to what extent different levels of ASD severity represent risk factors for the occurrence of psychotic or manic symptoms remains to be better clarified. Second, given the small sample size, it was not possible to include all single fixed predictors whose effects would have been interesting to control for. In fact, a ratio of predictors to observations of at least 10:1 was deemed appropriate. Predictors were chosen according to the observed differences in admissions and participant characteristics. Besides, sampling was extended over several years of observation; however, this

was accounted for in statistical analyses. Third, the collection of psychosocial stressors was purely anecdotal, unaccompanied by standardized assessment questionnaires or biological measures, and susceptible to recall bias. Fourth, although the sample includes participants with co-occurring specific medical conditions or cognitive impairment at different degrees, it cannot be considered fully representative of the whole autistic service population as it only encompasses individuals with ASD deserving inpatient diagnostic evaluation and medical care. Lastly, as the electronic system is not primarily designed for research purposes and clinical notes may lack standardization, information that is not strictly important to clinical care may have been lost.

Nevertheless, the findings from this study may have important public health implications. Indeed, the assessment of psychotic and manic symptoms among adolescents with ASD deserves further attention. That is particularly relevant when autistic adolescents have experienced family disturbances and conflicts with peers, as such stressful events may potentially precipitate the developmental trajectory of ASD to psychosis.

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CONFLICT OF INTEREST STATEMENT

Marco Colizzi has been a consultant/advisor to GW Pharma Limited, F. Hoffmann-La Roche Limited, and GW Pharma Italy SRL outside of this work. All the other authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study 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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