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# Sex differences in the prevalence and clinical correlates of autistic features in patients with chronic schizophrenia: a large scale cross-sectional study

Qihui Guo<sup>a,b</sup>, Rongrong Zhu<sup>a,b</sup>, Zheng Ma<sup>a,b</sup>, Ying He<sup>a,b</sup>, Dongmei Wang<sup>a,b</sup> and Xiangyang Zhang<sup>a,b</sup>

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#### **ABSTRACT**

**Objective:** Sex differences have been suggested in both schizophrenia (SCZ) and autism spectrum disorder (ASD). This study aims to assess the prevalence and clinical correlates of autistic features in male and female patients with chronic SCZ.

**Methods:** A total of 1690 chronic SCZ patients (M/F: 1122/568) were recruited from ten psychiatric hospitals in China. The Positive and Negative Syndrome Scale Autism Severity Score and the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) were utilised to assess the presence of autistic features and measure cognitive function, respectively.

**Results:** Female SCZ patients had a higher prevalence of autistic features than male SCZ patients. In male patients, those with autistic features exhibited higher illness duration and RBANS scores, but lower years of education. Whereas in female patients, those with autistic features had higher RBANS scores, but lower years of education. Binary logistic regression analysis revealed that years of education, illness duration, visuospatial/constructional abilities, and language were correlated with autistic features in male patients. In female patients, years of education, language, and delayed memory were correlated with the presence of autistic features.

**Conclusions:** Our findings suggest that sex differences exist in the prevalence and clinical correlates of autistic features in chronic SCZ patients.

#### **KEY POINTS**

- Sex differences exist in the prevalence and clinical correlates of autistic features in patients with chronic SC7
- Years of education, illness duration, visuospatial/constructional abilities, and language were correlated with autistic features in male chronic SCZ patients.
- Years of education, language, and delayed memory were correlated with autistic features in female chronic SCZ patients.

#### **ARTICLE HISTORY**

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#### **KEYWORDS**

Sex differences; schizophrenia; autistic features

#### Introduction

Schizophrenia (SCZ) is one of the most severe psychiatric disorders (Jauhar et al., 2022), with a global lifetime prevalence of about 1% (Saha et al., 2005). SCZ is marked by impaired perception, thinking, emotions, behaviour, cognitive function and mental activities (Saha et al., 2005) and imposes significant healthcare burdens on patients (Cloutier et al., 2016). SCZ patients have a higher lifetime risk of suicide, and the mean life expectancy of SCZ patients was about 15 years shorter than healthy people (Hjorthøj et al., 2017).

Autism spectrum disorder (ASD) is a neurodevelopmental condition marked by abnormality in social interaction, communication, and sensory perception and repetitive, stereotyped behaviour (American Psychiatric Association, 2013). In fact, prior to the 1970s, the term 'autism' and 'schizophrenia' were often used synonymously (Chisholm et al., 2015). As research and understanding in the field continued to grow, a clearer distinction between the two conditions emerged. ASD is now considered a developmental disorder separate from SCZ. ASD and SCZ are distinct diagnoses, but share some common features (Jutla et al., 2022). They both fall under the umbrella of neurodevelopmental disorders (Goldstein

et al., 2002). Individuals with ASD may exhibit psychotic symptoms, whereas those diagnosed with early-onset SCZ may exhibit features commonly associated with ASD (Chisholm et al., 2015). Previous studies have demonstrated that ASD develops SCZ later in life (de Lacy & King, 2013; Larson et al., 2017), and that childhood-onset SCZ has a higher likelihood of co-occurring with ASD (Rapoport et al., 2009). According to a review, the prevalence of ASD in patients diagnosed with SCZ ranges from 3.4% to 52% (Zheng et al., 2018).

There are many clinical, aetiological, and pathophysiological similarities between SCZ and ASD (Barlati et al., 2019; Chisholm et al., 2015; de Lacy & King, 2013; Wilson et al., 2014). For example, affective retardation in SCZ patients is similar to emotional reciprocity in ASD patients. The parallels alogia (poverty of speech) in SCZ patients is similar to the delayed or absent speech development in ASD patients. Social communication deficits and catatonic features are observed in both SCZ and ASD (Chisholm et al., 2015). Social cognition deficits, particularly social information processing deficits, are prevalent in individuals with both SCZ and ASD (Eack et al., 2013; Sugranyes et al., 2011). SCZ patients with autistic features perform poorer in social cognition (Deste et al.,

2020; Vita et al. 2020). Also, genetic evidences support an association between the two diagnoses, as children of parents with SCZ face a higher risk of developing ASD (Sullivan et al., 2012). Additionally, there are some similarities in neuroimaging findings, such as smaller grey matter volume in limbic-striato-thalamic circuitry of both SCZ and ASD patients (Cheung et al., 2010). Notably, Nakata et al. (2020) found that treatment-resistant SCZ patient were close to ASD patients, suggesting SCZ patients with autistic features may not respond well to treatment. Thus, SCZ patients with autistic features appear to exhibit some specific features that warrant study as a separate subgroup.

There are also many differences between SCZ and ASD (Tarasi et al., 2022). Psychometric analysis has revealed that autistic features predominantly overlap with negative symptoms of SCZ, but display differences when compared to positive symptoms (Nenadić et al., 2021; Zhou et al., 2019). According to Trevisan et al. (2020), SCZ and ASD can be more effectively differentiated by their positive symptoms than by their negative symptoms. Additionally, previous reviews indicate that SCZ and ASD exhibit notable distinctions in areas such as neurocognition, social cognition, decision-making processes, and neural oscillations (Ozbek et al., 2023; Tarasi et al., 2022). Autistic features have also been found to exert significant impacts on non-ASD populations. For instance, Liu et al. (2023) demonstrated a correlation between autistic features and empathy. In SCZ patients, Deste et al. (2020) discovered that autistic features were associated with social cognitive performance, with higher autistic features being linked to poorer social cognitive performance.

Sex differences have been reported in various aspects of SCZ, including prevalence, onset age, clinical symptoms, and social functioning. For example, studies have indicated that male SCZ patients have a higher prevalence and younger onset age of SCZ compared to female SCZ patients (Loranger, 1984; McGrath et al., 2008). Moreover, male SCZ patients tend to have fewer affective symptoms than female SCZ patients (Ochoa et al., 2012). It has been observed that male SCZ patients tend to exhibit more pronounced social isolation, unemployment, and withdrawal compared to female SCZ patients (Vila-Rodriguez et al., 2011; Zhang et al., 2012). Additionally, studies have indicated sex differences in the structure of brain regions and DNA methylation in patients with SCZ (Adanty et al., 2022; Kovalev et al., 2003). Similarly, sex differences exist in multiple aspects of ASD patients (Hull et al., 2017). For example, the prevalence of ASD has been consistently reported to be higher in males than females (Fombonne, 2009; Goldblum et al., 2024). Female ASD patients exhibit poorer reciprocal behaviour than male ASD (Backer van Ommeren et al., 2017). In younger higher functioning ASD patients, males exhibit more repetitive and stereotyped behaviours (Knutsen et al., 2019). A recent review suggested there were sex differences in social behaviours and social communication in young ASD patients (de la Roche & Kelley, 2024).

In conclusion, sex differences have been suggested in both SCZ and ASD patients. This study aimed to explore sex differences in the prevalence and clinical correlates of autistic features in patients with chronic SCZ, as this may contribute to a better understanding of autistic features in SCZ patients.

#### **Methods**

#### Study design and study population

This study was a large scale cross-sectional multi-centre study. A total of 1690 chronic SCZ patients from ten psychiatric hospitals in China were recruited. The study was approved by the

Institutional Review Board of the Institute of Psychology, Chinese Academy of Sciences (H18031).

The inclusion criteria were as follows: (1) aged between 16 to 75 years; (2) diagnosis of SCZ by two experienced psychiatrists using the Structured Clinical Interview for DSM-IV (SCID); (3) illness duration of at least 1 year; (4) stable dose of antipsychotics for at least six months. The exclusion criteria were: (1) history of substance or alcohol abuse, except for nicotine; (2) pregnant or lactating; and (3) organic brain diseases or severe physical illnesses.

#### Data collection and assessment

A questionnaire was designed in this study to collect the demographic information (age, sex, marital status, BMI) and clinical information (onset age, illness duration, family history of SCZ, antipsychotic dosages, suicidal attempts) from all participants. All participants were required to state a male or female gender according to their biological features. The Insomnia Severity Index (ISI) was used to assess the severity of insomnia (Bastien et al., 2001). The higher the ISI scores, the more severe insomnia.

The Positive and Negative Syndrome Scale (PANSS) was used to assess the psychiatric symptoms and the severity of clinical symptoms in SCZ patients (Kay et al., 1987). Mohr's five-factor model (negative, positive, cognitive, mood, hostility) was utilised as the subscales of PANSS (Jiang et al., 2013). The higher PANSS scores indicate more severe the psychotic symptoms.

The PANSS Autism Severity Score (PAUSS) was used to assess the presence of autistic features in SCZ patients (Kästner et al., 2015). The items of PAUSS were extracted from PANSS. PAUSS contains three subscales: social activities (N1, N3, N4), communication (N5, N6), and stereotypic behaviour (N7, G5, G15). The higher the PAUSS score, the more pronounced the autistic features, and a PAUSS score above 30 is defined as the presence of autistic features (Kästner et al., 2015).

The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) was used to assess the cognitive function, including immediate memory, visuospatial/constructional ability, language, attention, and delayed memory (Randolph et al., 1998). RBANS assessment was conducted by several psychiatrists through structured interviews, all psychiatrists had received standardised training. The higher RBANS scores indicate better cognitive functioning.

#### Statistical analysis

Normality was examined using Skewness and Kurtosis test, with 'skewness < 2 and kurtosis < 7' indicating that the data distribution was normal (Kim, 2013). In order to compare the differences in demographic and clinical variables between patients with autistic and without autistic features, Student's t-tests, Mann-Whitney nonparametric and  $x^2$  test were utilised for categorical variables, continuous, non-normally distributed continuous, respectively. The calculated Cohen's d values represented effect sizes. Bonferroni corrections were utilised to correct multiple tests.

Binary logistic regression analyses were performed separately for male and female patients to determine independent associations between autistic features and other variables. Regression analyses were performed using backward methods. The area under the receiver operating characteristic (AUC-ROC) was calculated to determine the ability of the significant variables in regression model to discriminate autistic features in male or female SCZ patient.

All statistical analyses were performed using SPSS version 25.0 and R version 4.3.1. p Values <.05 (two-tailed) were considered statistically significant.

#### **Results**

#### Sex differences in the prevalence of autistic features in SCZ patients

Of the 1690 SCZ patients, 66.39% (n=1122) patients were male and 33.61% (n = 568) patients were female. There were significant sex differences in the following characteristics: age, marital status, body mass index (BMI), illness duration, family history (all p < .05). Please see Table 1 for details.

Autistic features were present in 18.54% (n = 208) of the male patients and 25.70% (n = 146) of the female patients. The sex difference in prevalence of autistic features was statistically significant ( $\chi^2 = 11.694$ , p = .001).

#### Sex differences in clinical characteristics of SCZ patients with and without autistic features

Table 2 indicates that among male SCZ patients, individuals with autistic features had lower years of education and BMI, along with longer illness duration (all p < .05), compared to those without autistic features. Additionally, individuals with autistic features showed higher PANSS total score, PANSS negative factor score, PANSS cognitive factor score, PANSS hostility factor score, PANSS mood factor score, and lower RBANS total score and all of its subscale scores (all p < .01, all Bonferroni corrected p < .05).

Table 2 shows that among female SCZ patients, individuals with autistic features had lower years of education (p < .001), compared to those without autistic features. Additionally, individuals with autistic features showed higher PANSS total and all of its subscale scores, as well as lower RBANS total and all its subscale scores (all p < .001, Bonferroni corrected p < .01).

#### Sex differences in clinical correlates of autistic features in SCZ patients

In male SCZ patients, a binary logistic regression was performed with several variables including years of education, BMI, illness duration and all subscale scores of RBANS as independent variables, and the presence of autistic feature as a dependent variable. The results showed that years of education (B = -0.069, p = .037,odds ratio [OR] = 0.934, 95% confidence interval [CI] = 0.875-0.995), RBANS visuospatial/constructional subscale (B = -0.025, p < .001, OR = 0.976, 95%CI = 0.964-0.987), and RBANS language subscale (B = -0.056, p < .001, OR = 0.946, 95%CI = 0.933 - 0.958) were negatively correlated with the presence of autistic features, while illness duration (B = 0.015, p = .024, OR = 1.015, 95%CI = 1.002–1.029) was positively correlated with autistic features (Table 3). The predictive performance of the regression model and individual variables were assessed using ROC curves. The AUC for years of education was 0.624, for illness duration was 0.547, for RBANS visuospatial/ constructional subscale was 0.680, for RBANS language subscale was 0.719 (Figure 1(a)). Combined these variables, the AUC for regression model was 0.654.

In female SCZ patients, a binary logistic regression was performed with several variables including years of education, and all subscale scores of RBANS as independent variables, and autistic feature as a dependent variable. The results showed that years

Table 1. Characteristics of patients with chronic schizophrenia grouped by sex.

	Male (n=1122)	Female ( <i>n</i> = 568)	$t/Z/x^2$	p Value	Cohen's d	
Age	45.68 ± 13.28	44.38 ± 12.65	1.97	.049	0.100	
Years of education	$9.33 \pm 2.94$	$9.10 \pm 3.44$	1.39	.166	0.075	
Marital status			158.90	<.001		
Single	797	235				
Married	168	208				
Divorced	149	107				
Widowed	8	18				
BMI	$24.23 \pm 4.67$	$24.92 \pm 4.93$	-2.55	.011	-0.145	
Onset age	25.07 ± 7.95	$25.32 \pm 8.43$	-0.59	.559	-0.031	
Illness duration	$20.62 \pm 12.33$	19.06 ± 11.99	2.82	.005	0.049	
Family history			7.15	.008		
Yes	168	115				
No	954	453				
Antipsychotic dosages	$409.03 \pm 511.53$	$384.26 \pm 500.06$	0.95	.340	0.049	
Suicidal attempts			3.08	.079		
Yes	120	78				
No	1002	490				
ISI	$3.00 \pm 3.95$	$3.43 \pm 4.23$	-1.61	.108	-0.105	
PANSS	$76.71 \pm 18.94$	$83.95 \pm 20.31$	-7.08	<.001	-0.373	
Negative factor	$21.53 \pm 7.64$	$22.23 \pm 7.80$	-1.75	.080	-0.091	
Positive factor	$11.99 \pm 5.46$	$13.91 \pm 5.60$	-6.72	<.001	-0.349	
Cognitive factor	$25.05 \pm 7.29$	$27.32 \pm 8.10$	-5.64	<.001	-0.300	
Hostility factor	$7.59 \pm 3.37$	$8.68 \pm 3.46$	-6.17	<.001	-0.320	
Mood factor	$10.58 \pm 3.85$	$11.81 \pm 4.10$	-5.97	<.001	-0.313	
PAUSS	$23.22 \pm 7.35$	$24.79 \pm 7.50$	-4.10	< 0.001	-0.212	
Difficulty in social	$9.67 \pm 3.66$	$10.00 \pm 3.59$	-1.74	.082	-0.089	
Difficulty in communication	$7.03 \pm 2.63$	$7.27 \pm 2.68$	-1.73	.085	-0.089	
Stereotypic behaviour	$6.52 \pm 2.68$	$7.53 \pm 2.93$	-6.90	<.001	-0.366	
RBANS	$360.13 \pm 63.76$	$347.69 \pm 60.79$	3.70	<.001	0.198	
Immediate memory	$58.67 \pm 21.81$	57.65 ± 16.01	0.94	.350	0.051	
Visuospatial/constructional	$77.67 \pm 17.22$	$72.17 \pm 15.76$	6.57	<.001	0.328	
Language	$80.17 \pm 13.29$	$75.12 \pm 16.62$	6.30	<.001	0.349	
Attention	$78.20 \pm 16.20$	$78.19 \pm 17.92$	0.02	.985	0.001	
Delayed memory	$64.57 \pm 18.36$	$64.05 \pm 18.42$	0.55	.586	0.028	
PANSS minus PAUSS	$53.49 \pm 13.66$	59.16 ± 14.82	-7.63	<.001	-0.405	

Note: BMI: body mass index; ISI: Insomnia Severity Index; PANSS: Positive and Negative Syndrome Scale; PAUSS: PANSS Autism Severity Score; RBANS: Repeatable Battery for the Assessment of Neuropsychological Status. Bold font indicates statistical significance.

Table 2. Characteristics of chronic schizophrenia patients with and without autistic features grouped by sex.

	Male			Female						
	Non-autistic	Autistic	$t/Z/x^2$	p Value	Cohen's d	Non-autistic	Autistic	$t/Z/x^2$	p Value	Cohen's d
	(n = 914)	(n = 208)				(n = 422)	(n = 146)			
Age	45.35 ± 13.29	47.17 ± 13.15	-1.80	.073	-0.137	44.26 ± 12.78	44.74 ± 12.3	-0.41	.689	-0.038
Years of education	$9.56 \pm 2.95$	$8.32 \pm 2.68$	5.94	<.001	0.430	$9.69 \pm 3.32$	$7.38 \pm 3.19$	7.45	<.001	0.701
Marital status			1.80	.614				3.31	.508	
Single	645/914	152/208				172/422	63/146			
Married	136/914	32/208				152/422	56/146			
Divorced	127/914	22/208				86/422	21/146			
Widowed	6/914	2/208				12/422	6/146			
BMI	$24.37 \pm 4.77$	$23.61 \pm 4.14$	2.27	.023	0.163	$24.92 \pm 4.91$	$24.93 \pm 5.0$	-0.08	.938	-0.002
Onset age	$25.13 \pm 7.86$	$24.78 \pm 8.34$	0.55	.583	0.044	$25.59 \pm 8.01$	$24.54 \pm 9.54$	1.19	.237	0.124
Illness duration	$20.22 \pm 12.27$	$22.38 \pm 12.49$	-2.27	.024	-0.176	$18.67 \pm 12.24$	$20.2 \pm 11.19$	-1.39	.166	-0.128
Family history			2.71	.100				0.06	.800	
Yes	145/914	23/208				87/422	28/146			
No	769/914	185/208				355/422	118/146			
Antipsychotic	395.45 ± 497.18	$468.69 \pm 567.76$	-1.79	.073	-0.143	$402.03 \pm 557.94$	$332.89 \pm 265.34$	1.64	.100	0.138
dosages										
Suicidal attempts			0.00	1.000				0.51	.477	
Yes	98/914	22/208				61/422	17/146			
No	816/914	186/208				361/422	129/146			
ISI	$2.94 \pm 3.94$	$3.28 \pm 3.98$	-1.03	.301	-0.086	$3.28 \pm 4.06$	$3.85 \pm 4.68$	-1.50	.133	-0.135
PANSS	$71.84 \pm 16.36$	$98.1 \pm 14.1$	-23.49	<.001	-1.644	$77.01 \pm 17.23$	$104.03 \pm 14.33$	-18.60	<.001	-1.634
Negative factor	$19.22 \pm 6.21$	$31.66 \pm 4.4$	-33.81	<.001	-2.100	$19.37 \pm 6.45$	$30.49 \pm 4.97$	-21.50	<.001	-1.821
Positive factor	$11.86 \pm 5.44$	$12.53 \pm 5.53$	-1.59	.115	-0.123	$13.45 \pm 5.57$	$15.23 \pm 5.48$	-3.36	<.001	-0.320
Cognitive factor	$23.03 \pm 6.01$	$33.93 \pm 5.58$	-25.06	<.001	-1.838	$24.57 \pm 6.65$	$35.29 \pm 6.47$	-17.13	<.001	-1.623
Hostility factor	$7.36 \pm 3.24$	$8.59 \pm 3.75$	-4.35	<.001	-0.366	$8.21 \pm 3.25$	$10.03 \pm 3.69$	-5.30	<.001	-0.542
Mood factor	$10.39 \pm 3.72$	$11.38 \pm 4.31$	-3.07	.002	-0.258	11.41 ± 3.96	$12.97 \pm 4.29$	-3.87	<.001	-0.386
PAUSS	$20.7 \pm 5.32$	$34.33 \pm 3.95$	8.38	<.001	-0.667	$21.56 \pm 5.36$	$34.14 \pm 4.25$	-17.90	<.001	-2.467
Difficulty in social	$8.56 \pm 2.93$	$14.59 \pm 2.24$	-32.89	<.001	-2.140	$8.69 \pm 2.96$	$13.77 \pm 2.43$	-14.80	<.001	-1.792
Difficulty in	$6.26 \pm 2.17$	$10.39 \pm 1.64$	-30.65	<.001	-1.981	$6.28 \pm 2.19$	$10.12 \pm 1.76$	-15.00	<.001	-1.838
communication	F 00 + 2 24	0.25 + 2.61	-17.77	<.001	-1.499	C FO + 2 41	10.26 + 2.54	-12.90	<.001	1 502
Stereotypic behaviour	$5.88 \pm 2.24$	$9.35 \pm 2.61$	-17.//	<.001	-1.499	$6.59 \pm 2.41$	$10.26 \pm 2.54$	-12.90	<.001	-1.502
RBANS	367.77 ± 61.07	326.56 ± 64.64	9.54	<.001	0.667	359.18 ± 58.07	314.45 ± 56.26	7.83	<.001	0.776
Immediate			9.5 <del>4</del> 4.72	<.001	0.867			7.63 5.12	<.001	0.776
	$59.74 \pm 22.96$	$53.98 \pm 14.97$	4./2	<.001	0.266	$59.52 \pm 16.31$	$52.25 \pm 13.82$	5.12	<.001	0.463
memory	70.62 : 17.41	60 11 + 12 24	0.14	. 001	0.630	7415 : 162	66 42 + 12 01	F 00	. 001	0.501
Visuospatial/	$79.62 \pm 17.41$	$69.11 \pm 13.34$	8.14	<.001	0.628	$74.15 \pm 16.2$	$66.43 \pm 12.81$	5.09	<.001	0.501
constructional							4= 44 . 44 =			
Language	82.33 ± 11.76	$70.7 \pm 15.36$	9.89	<.001	0.930	$77.68 \pm 15.82$	$67.69 \pm 16.7$	6.40	<.001	0.623
Attention	$79.59 \pm 15.53$	$72.11 \pm 17.64$	6.12	<.001	0.469	$81.05 \pm 16.63$	$69.92 \pm 18.97$	6.73	<.001	0.645
Delayed memory	$66.33 \pm 18.39$	$56.81 \pm 16.08$	6.85	<.001	0.529	$66.43 \pm 18.33$	$57.16 \pm 16.93$	5.62	<.001	0.516
PANSS minus PAUSS	$51.15 \pm 12.84$	$63.77 \pm 12.36$	-12.10	<.001	-0.990	$55.45 \pm 13.64$	$69.88 \pm 12.78$	-10.2	<.001	-1.075

Note: BMI: body mass index; ISI: Insomnia Severity Index; PANSS: Positive and Negative Syndrome Scale; PAUSS: PANSS Autism Severity Score; RBANS: Repeatable Battery for the Assessment of Neuropsychological Status. Bold font indicates statistical significance.

Table 3. Binary logistic regression model to predict the presence of autistic features.

	Male				Female			
	В	Wald x <sup>2</sup>	р	OR (95% CI)	В	Wald $x^2$	р	OR (95% CI)
Years of education	-0.069	-4.347	.037	0.934(0.875,0.995)	-0.156	-19.844	<.001	0.856(0.798,0.915)
Illness duration RBANS	0.015	5.072	.024	1.015(1.002,1.029)				
Visuospatial/ constructional	-0.025	-15.817	<.001	0.976(0.964,0.987)				
Language Attention Delayed memory	-0.056	-70.939	<.001	0.946(0.933,0.958)	-0.021 -0.013 -0.014	-8.532 -3.057 -4.055	.003 .080 .044	0.979(0.965,0.993) 0.987(0.973,1.001) 0.986(0.973,1.000)

Note: RBANS: Repeatable Battery for the Assessment of Neuropsychological Status. Bold font indicates statistical significance.

of education (B = -0.156, p < .001, OR = 0.856, 95%CI = 0.798-0.915), RBANS language subscale (B = -0.021, p = .003, OR = 0.979, 95%CI=0.965-0.993), RBANS delayed memory subscale (B=-0.014, p = .044, OR = 0.986, 95%CI = 0.973-1.000) were negatively associated with the presence of autistic features (Table 3). The AUC for years of education was 0.692, for RBANS language subscale was 0.677, for RBANS delayed memory subscale was 0.680 (Figure 1(b)). Combined these variables, the AUC for regression model was 0.766.

#### Discussion

### Sex differences in prevalence of autistic features in SCZ patients

Our study revealed that the prevalence of autistic features was higher in female SCZ patients than male SCZ patients (25.70% vs 18.54%). A systematic review by Zeidan et al. (2022) demonstrated a significant sex difference in the prevalence of ASD (Zeidan et al.,

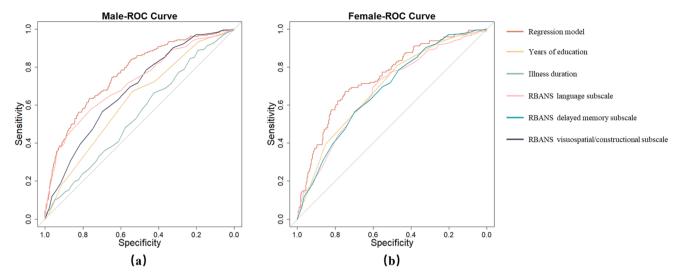


Figure 1. (a) ROC curve in male patients with chronic schizophrenia; and (b) ROC curve in female patients with chronic schizophrenia. Note: AUC in male-ROC curves (regression model = 0.766; years of education = 0.624; illness duration = 0.547; RBANS visuospatial/constructional subscale = 0.680; RBANS language subscale = 0.719). AUC in female-ROC curves (regression model = 0.747; years of education = 0.692; RBANS language subscale = 0.677; RBANS delayed memory subscale = 0.680).

2022). In China, the sex ratio (M:F) of ASD was reported as 4.3 (Zhou et al., 2020). It is also worth noting that the prevalence of SCZ is usually higher in males than females (McGrath et al., 2008). However, in this study, the prevalence of autistic features was higher in female patients than male patients with SCZ.

One possible explanation for the higher prevalence of autistic features in female SCZ patients is that their clinical symptoms were more severe in this study. We observed that PANSS scores and its subscale scores (except for the negative factor) were higher in female patients compared to male patients with SCZ. Additionally, female SCZ patients had lower RBANS scores than male SCZ patients, implying that female SCZ patients have more severe cognitive impairment. When assessing the subscales of the PAUSS, significant differences between female and male SCZ patients were found only in the stereotypic behaviour subscale, with female SCZ patients exhibiting more severe stereotypic behaviour than male SCZ patients. Stereotypic behaviour is one of the core autistic features. However, stereotypic behaviour has been reported to be milder in female ASD patients than male ASD patients (Horwitz et al., 2023). Based on these evidences, female SCZ patients had more severe clinical symptoms than male SCZ patients, specifically in stereotypic behaviour, and female SCZ patients have higher prevalence of autistic features than male SCZ patients.

#### Common correlates associated with autistic features in both male and female SCZ patients

A previous study reported a strong association between years of education and the risk of developing SCZ (Luo et al., 2020). In the present study, years of education was found to be associated with autistic features in both male and female patients with SCZ. It was observed that SCZ patients with autistic features had fewer years of education than those without autistic features. Individuals with autistic features tend to struggle with education, and students with ASD face numerous challenges, especially in social and academic skills (Anderson et al., 2017; Gelbar et al., 2014).

Also, we found that language was associated with autistic features in both males and females with SCZ. Additionally, we found that SCZ patients with autistic features had lower language

skills than those without autistic features. Language and communication impairments are a core feature of ASD patients (Georgiou & Spanoudis, 2021; Riches et al., 2011). Delayed communication, impaired language initiation, or poor language skills compared to peers are the primary reasons why parents seek professional ASD evaluation and diagnosis for their children (Kozlowski et al., 2011). In addition, language impairment is also common in SCZ patients (Hartopo & Kalalo, 2022). Therefore, the severity of language impairment may serve as a potential marker in distinguishing the presence of autistic features in SCZ patients.

#### Sex differences in correlates associated with autistic features in SCZ patients

In this study, illness duration and RBANS visuospatial/constructional subscale was associated with autistic features in male SCZ patients while not in female SCZ patients. In male SCZ patients, those with autistic features had longer illness duration and weaker visuospatial/constructional abilities compared to those without autistic features. Studies indicated that male psychiatric patients with longer illness duration have higher levels of social and global disability (Hanlon et al., 2017). Therefore, male SCZ patients with longer illness duration may exhibit more autistic features, whereas this effect is not significant in female SCZ patients.

Visuospatial ability is an important cognitive function that facilitates our interaction with the environment (Cardillo et al., 2020; Jansen et al., 2010). Abnormal processing of visuospatial material has been reported in both patients with ASD (Cardillo et al., 2022; Caron et al., 2006) and patients with SCZ (Daniell et al., 2021; Ribolsi et al., 2015). Furthermore, previous studies found that there are sex differences in visuospatial ability, with males typically performing better than females (Herlitz & Rehnman, 2008; Voyer et al., 1995). There are also sex differences in visuospatial ability in ASD patients (Beacher et al., 2012). Based on these findings, we speculate that visuospatial impairment has significant impact on the presence of autistic features in male SCZ patients while not in female SCZ patients.

The RBANS delayed memory subscale was associated with autistic features in female SCZ patients while not in male SCZ patients. Impairment in delayed memory is a common feature of

ASD patients. Previous studies indicated that episodic memory retrieval abilities of children with ASD would deteriorate over time (Almeida et al., 2019; Southwick et al., 2011). Similarly, SCZ patients also had poor performance on delayed memory tasks (Garcia et al., 2012; Robles et al., 2008). In ASD patients, females exhibited better memory performance than males (Demetriou et al., 2021). Interestingly, this study revealed that SCZ patients did not exhibit a sex-based memory difference. A previous study found that oestrogen hormone plays an important role in learning and memory, suggesting that high oestrogen can improve the impairments in learning and memory (Igbal et al., 2024). Our study identified a significant association between delayed memory and the presence of autistic features, but only in female SCZ patients. This intriguing observation may be linked to the influence of oestrogen; however, further studies are needed to clarify this complex phenomenon.

#### Limitations

This study has several limitations that are worth considering. Firstly, the cross-sectional design conducted in this study limits our ability to infer causality. In order to prospectively understand sex differences in SCZ patients with autistic features, a longitudinal study is needed in the future. Second, it is worth noting that the present study included only hospitalised patients with chronic SCZ, who typically exhibit more severe symptoms and cognitive deficits. Thus, there may be a selection bias which could account for our results. Thirdly, there were sex differences in the PANSS scores in patients with SCZ. Since the PAUSS is extracted from the PANSS, there may be a potential bias in detecting sex differences in the prevalence and clinical correlates of autistic features in patients with SCZ. Forth, it should be noted that autistic features did not equate to a diagnosis of autism, so SCZ patients with autistic features cannot represent SCZ patients comorbid with ASD.

#### **Conclusions**

In conclusion, this study provides valuable insights into understanding autistic features in chronic SCZ patients. The findings suggest that autistic features are more prevalent in female SCZ patients and that there are significant sex differences in the clinical correlates associated with autistic features. Therefore, it is necessary to consider sex differences in the study and clinical treatment of autistic features in SCZ patients. Future studies are warranted to deeply explore the sex differences of autistic features in SCZ patients, which will provide a prospective view to deepen our understanding of autistic features in SCZ patients.

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#### **Ethics statement**

The authors declare that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

#### **Disclosure statement**

No potential conflict of interest was reported by the author(s).

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#### Data availability statement

The data that support the findings of this study are publicly available. The corresponding author can be contacted upon reasonable request.

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