Journal of Affective Disorders 331 (2023) 245–250

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

Longitudinal follow-up of subsequent psychiatric comorbidities among children and adolescents with autism spectrum disorder

Ta-Chuan Yeh [a], Mu-Hong Chen [b,c,*], Ya-Mei Bai [b,c], Shih-Jen Tsai [b,c], Ju-Wei Hsu [b,c], Kai-Lin Huang [b,c], Tung-Ping Su [b,c,d], Tzeng-Ji Chen [e,f,g], Chih-Sung Liang [h,**]

[a] Department of Psychiatry, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan
[b] Department of Psychiatry, Taipei Veterans General Hospital, Taipei, Taiwan
[c] Department of Psychiatry, College of Medicine, National Yang-Ming Chiao Tung University, Taipei, Taiwan
[d] Department of Psychiatry, General Cheng Hsin Hospital, Taipei, Taiwan
[e] Department of Family Medicine, Taipei Veterans General Hospital, Taipei, Taiwan
[f] Institute of Hospital and Health Care Administration, National Yang Ming Chiao Tung University, Taipei, Taiwan
[g] Department of Family Medicine, Taipei Veterans General Hospital, Hsinchu Branch, Hsinchu, Taiwan
[h] Department of Psychiatry, Beitou Branch, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan

ARTICLE INFO

Keywords:
Autism
Time course
Schizophrenia
Bipolar disorder
Depressive disorder
Anxiety disorder

ABSTRACT

Background: The mental health of children and adolescents with autism spectrum disorder (ASD) is a concern of recent years. However, a large-scale longitudinal study investigating the risk and the time course of subsequent psychiatric comorbidities is still lacking.

Methods: Using the Taiwan National Health Insurance Research Database, 13,382 children and adolescents with ASD, and 53,528 age- and sex-matched non-ASD controls were enrolled between 2001 and 2009, and followed to the end of 2011. The adjusted hazard ratio (HR) with a corresponding 95 % confidence interval for psychiatric comorbidities among children and adolescents with ASD vs matched controls was estimated. The subjects who developed schizophrenia, bipolar disorder, depressive disorder, anxiety disorder, and obsessive-compulsive disorder (OCD) were identified during the follow-up.

Results: Children and adolescents with ASD compared with controls were more likely to be diagnosed with schizophrenia (19.21; 13.74, 26.88), bipolar disorder (17.59; 12.66, 24.44), depressive disorder (5.56; 4.72, 6.56), anxiety disorder (5.01; 4.49, 5.59), and OCD (16.12; 11.66, 22.30) later in life. The time course of subsequent psychiatric comorbidity showed that anxiety disorder occurred first, usually in late childhood, with psychotic and affective disorders proceeding in adolescence. Those with ASD and anxiety disorder had an additionally increased likelihood of developing subsequent psychiatric comorbidity compared with those with ASD only.

Limitation: In claims data analysis, clinical parameters or possible confounders may not be fully captured.

Conclusion: Patients with ASD are predisposed to the development of anxiety disorder in late childhood, as well as schizophrenia, bipolar disorder, depressive disorder, and OCD in adolescence.

1. Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by impaired social communication and restricted repetitive behaviors or interests. It is estimated to affect almost 1 % of the population (Baird et al., 2006), with a lifelong persistence of core symptoms due to the early-onset nature and lack of effective treatment. Individuals with ASD often require additional educational, social, and medical services to manage their symptoms. However, the comorbidity of psychiatric disorders with ASD can further impair the individual's social, occupational, and other important areas of life (Berkovits et al., 2017; Rosen et al., 2018). Therefore, understanding the interrelatedness and coexistence of psychiatric comorbidity with ASD is vital. Research has shown that individuals with ASD are more likely to develop

* Correspondence to: Mu-Hong Chen, Department of Psychiatry, No. 201, Sec. 2, Shihpai Road, Beitou District, Taipei 11217, Taiwan.
** Correspondence to: Chih-Sung Liang, Department of Psychiatry, No. 60, Xinmin Road, Beitou District, Taipei 11243, Taiwan.
E-mail addresses: kremer7119@gmail.com (M.-H. Chen), lcsyfw@gmail.com (C.-S. Liang).

https://doi.org/10.1016/j.jad.2023.03.042
Received 8 November 2022; Received in revised form 4 March 2023; Accepted 16 March 2023
Available online 23 March 2023

comorbid psychiatric disorders than the general population (Lai et al., 2019; Selten et al., 2015; Zheng et al., 2018).

A meta-analysis by Lai et al. estimated that the prevalence of co-occurring psychiatric disorders in individuals with ASD ranged from 4 % to 28 %, with anxiety disorder being the most common diagnosis (Lai et al., 2019). Anxiety disorders affect approximately 27–40 % of school-age children with ASD, which is twice that of neurotypical children (Beesdo et al., 2009; Costello et al., 2005; Simonoff et al., 2008; Gadow et al., 2005; van Steensel et al., 2013). Furthermore, certain psychiatric disorders, such as psychotic disorders and bipolar disorder (BD), are highly associated with the diagnosis of ASD (Selten et al., 2015). Simonoff et al. reported that over 70 % of children with ASD met the criteria for at least one additional psychiatric disorder, and 41 % had two or more additional disorders as early as aged 12 (Simonoff et al., 2008). These studies suggest that ASD and certain psychiatric disorders may share several risk factors.

Understanding the risks of psychiatric disorders in individuals with ASD is critical for evaluating mental health and providing appropriate services, especially in children and adolescents when the likelihood of developing these conditions increases. Lai et al.'s meta-analysis also emphasized the importance of timeframe and the moderator effect of age on the prevalence of psychiatric comorbidities (Lai et al., 2019). Thus, the current study aims to examine the risks of psychiatric disorders in a representative sample of children and adolescents with ASD and determine whether the early development of anxiety disorder in ASD can influence the risks of subsequent psychiatric comorbidity.

2. Methods and materials

2.1. Data source

Taiwan's National Health Insurance—a mandatory universal health insurance program—was implemented in 1995 and covers up to 99 % of the country's 23 million residents. The National Health Research Institute audits and releases the National Health Insurance Research Database (NHIRD) for scientific and study purposes (Huang et al., 2021; Liang et al., 2020). Individual medical records included in the NHIRD are anonymous to protect personal privacy. Comprehensive information on insured individuals is included in the database, including demographic data, dates of clinical visits, and disease diagnoses. The diagnostic codes used are based on the *International Statistical Classification of Diseases and Related Health Problems* (9th ed.; *ICD-9*). The NHIRD has been used extensively in many epidemiologic studies in Taiwan (Chen et al., 2015; Chen et al., 2016; Li et al., 2012; Shen et al., 2013). The Institutional Review Board of Taipei Veterans General Hospital approved this study (2018–07-016 AC).

2.2. Inclusion criteria for children and adolescents with ASD and the control group

Children aged ≤12 years and adolescents aged 13–17 years with a diagnosis of ASD (ICD-9-CM code: 299) given by board-certificated psychiatrists based on clinical judgment and a psychiatric interview between January 1, 2002, and December 31, 2009, were utilized for this study. All had no history of schizophrenia, BD, depressive disorder, obsessive-compulsive disorder (OCD), and anxiety disorder before enrollment as an ASD cohort; the time of ASD diagnosis was defined as the time of enrollment. The age-, sex-, and time of enrollment-matched (1:4) control cohorts were randomly selected after eliminating those who had been given a diagnosis of ASD at any time, and those with schizophrenia (ICD-9-CM code: 295.X), BD (ICD-9-CM codes: 296.0×, 296.1×, 296.4×, 296.5×, 296.6×, 296.7×, 296.80, 296.81, 296.89), depressive disorder (ICD-9-CM code: 296.2×, 296.3×, 300.4, 311), OCD (ICD-9-CM code: 300.3), and anxiety disorder (ICD-9-CM code: 300.X except 300.3 and 300.4) prior to enrollment. Individuals who developed schizophrenia, BD, depressive disorder, OCD, and anxiety disorder during the follow-up period from enrollment to December 31, 2011 (or the date of death) were identified. The level of urbanization (level 1 to level 5; level 1 = most urbanized; level 5 = least urbanized) was also assessed (Liu et al., 2006).

2.3. Statistical analysis

For between-group comparisons, the F-test was utilized for continuous variables, and Pearson's X^2 test for nominal variables, where appropriate. Kaplan–Meier survival curves with log-rank tests were performed to compare the survival curves of the two groups. The Cox regression model was used to investigate the hazard ratios (HRs), with 95 % CIs of developing schizophrenia, BD, depressive disorder, OCD, and anxiety disorder after adjusting for demographic data (age, sex, level of urbanization). Subanalyses stratified by ASD age were also performed to clarify the risks of subsequent psychiatric comorbidities at different ages of ASD patients. In addition, the relationship between the diagnosis of anxiety disorder with ASD and the risks of subsequent psychiatric comorbidities was further investigated. All data processing and statistical analyses were performed using the Statistical Package for Social Science (SPSS, V.17) software (SPSS Inc.) and Statistical Analysis Software (SAS, V.9.1) (SAS Institute, Cary, NC).

3. Results

In all, 13,382 children and adolescents, and 53,528 matched controls were included, with a male predominance (83.1 % vs. 16.9 %). The ASD cohort had higher incidences of subsequent comorbidities, including schizophrenia (1.5 % vs. 0.1 %, $p < 0.001$), BD (1.6 % vs. 0.1 %, $p < 0.001$), depressive disorder (2.8 % vs. 0.5 %, $p < 0.001$), OCD (1.5 % vs. 0.1 %, $p < 0.001$), and anxiety disorder (5.8 % vs. 1.3 %, $p < 0.001$) than

Table 1
Demographic data and incidence of subsequent psychiatric disorders among patients with ASD and controls.

	Patients with ASD (n = 13,382)	Controls (n = 53,528)	P
Age (years, SD)	6.96 (4.20)	6.96 (4.24)	0.937
Sex (n, %)			1.000
Male	11,118 (83.1)	44,472 (83.1)	
Female	2264 (16.9)	9056 (16.9)	
Incidence of subsequent psychiatric disorders			
Anxiety disorder (n, %)	772 (5.8)	673 (1.3)	<0.001
Age onset (years, SD)	10.80 (4.46)	11.03 (5.00)	0.360
OCD (n, %)	200 (1.5)	49 (0.1)	<0.001
Age onset (years, SD)	13.84 (3.80)	14.38 (4.13)	0.381
Schizophrenia (n, %)	203 (1.5)	45 (0.1)	<0.001
Age onset (years, SD)	15.24 (4.19)	16.42 (4.22)	0.087
Bipolar disorder (n, %)	213 (1.6)	47 (0.1)	<0.001
Age onset (years, SD)	13.76 (4.24)	15.67 (5.26)	0.008
Depressive disorder (n, %)	373 (2.8)	279 (0.5)	<0.001
Age onset (years, SD)	14.50 (3.63)	16.43 (4.04)	<0.001
Level of urbanization (n, %)			<0.001
1 (most urbanized)	2420 (18.1)	15,251 (28.5)	
2	4112 (30.7)	16,338 (30.5)	
3	941 (7.0)	9701 (18.1)	
4	900 (6.7)	7412 (13.8)	
5 (most rural)	5009 (37.4)	4826 (9.0)	

ASD: autism spectrum disorder; SD: standard deviation; OCD: Obsessive-compulsive disorder.

the controls (Table 1). Compared with the controls, patients with ASD had an earlier age of developing BD (13.76 ± 4.24 vs. 15.67 ± 5.26 years, $p = 0.008$), and depressive disorder (14.50 ± 3.63 vs. 16.43 ± 4.04 years, $p < 0.001$) (Table 1), while the ages of developing anxiety disorder (10.80 ± 4.46 vs. 11.03 ± 5.00 years, $p = 0.360$), OCD (13.84 ± 3.80 vs. 14.38 ± 4.13 years, $p = 0.381$), and schizophrenia (15.24 ± 4.19 vs. 16.42 ± 4.22 years, $p = 0.087$) did not differ between these two groups (Table 1). Fig. 1 demonstrated the time course of subsequent psychiatric comorbidities among patients with ASD.

Children and adolescents with ASD were prone to developing schizophrenia (HR: 19.21, 95 % CI: 13.74–26.88), BD (HR: 17.59, 95 % CI: 12.66–24.44), depressive disorder (HR: 5.56, 95 % CI: 4.72–6.56), OCD (HR: 16.12, 95 % CI: 11.66–22.30), and anxiety disorder (HR: 5.01, 95 % CI: 4.49–5.59) later in life compared with the controls (Table 2). Subanalyses stratified by ASD age indicated consistent findings.

Comorbidity of anxiety disorder with ASD was associated with additionally elevated risks of subsequent comorbidities, including developing schizophrenia (HR: 3.39, 95 % CI: 2.40–4.78), BD (HR: 2.49, 95 % CI: 1.72–3.59), depressive disorder (HR: 3.89, 95 % CI: 3.05–4.96), and OCD (HR: 4.59, 95 % CI: 3.34–6.30) (Table 3).

Table 2
Cox regression models of developing subsequent psychiatric disorders among patients with ASD and controls.

	Children (HR, 95 % CI)	Adolescents (HR, 95 % CI)	All (HR, 95 % CI)
Anxiety disorder	**4.98 (4.41–5.62)**	**5.27 (4.02–6.91)**	**5.01 (4.49–5.59)**
OCD	**13.84 (9.30–20.58)**	**20.68 (11.72–36.49)**	**16.12 (11.66–22.30)**
Schizophrenia	**14.27 (9.08–22.43)**	**25.25 (15.23–42.15)**	**19.21 (13.74–26.88)**
Bipolar disorder	**21.28 (13.74–32.94)**	**12.95 (7.83–21.44)**	**17.59 (12.66–24.44)**
Depressive disorder	**5.33 (4.25–6.69)**	**5.88 (4.60–7.52)**	**5.56 (4.72–6.56)**

ASD: autism spectrum disorder; HR: hazard ratio; CI: confidence interval; Obsessive-compulsive disorder. **Bold** indicates statistical significance ($p < 0.05$).

Table 3
Cox regression models of developing subsequent psychiatric disorders among ASD patients with/without anxiety disorder.

	OCD (HR, 95 % CI)	Schizophrenia (HR, 95 % CI)	Bipolar disorder (HR, 95 % CI)	Depressive disorder (HR, 95 % CI)
Anxiety disorder				
Absence	1	1	1	1
Presence	**4.59 (3.34–6.30)**	**3.39 (2.40–4.78)**	**2.49 (1.72–3.59)**	**3.89 (3.05–4.96)**

ASD: autism spectrum disorder; HR: hazard ratio; CI: confidence interval; OCD: obsessive compulsive disorder. **Bold** indicates statistical significance ($p < 0.05$).

4. Discussion

Children and adolescents with ASD were found to be at greater risk of developing schizophrenia, BD, depressive disorder, and OCD than the control group. In terms of the time course of psychiatric disorders, individuals with ASD are more likely to develop BD and depressive disorder at an earlier age, although no similar trend is observed for other co-occurring psychiatric disorders. Among psychiatric comorbidities, anxiety disorders tend to occur first in childhood, with other psychiatric disorders following in adolescence. Compared to people with ASD alone, the diagnosis of anxiety disorder solely increased the likelihood of subsequent psychiatric comorbidities during subanalysis. These findings are consistent with previous studies that have suggested anxiety disorder may be an important prognostic factor in children with ASD (Montazeri et al., 2019; Pearcey et al., 2021) or as a specific phenotype (Wood and Gadow, 2010). To our knowledge, this is the first large longitudinal cohort study to use a nationwide database to reveal the risks and time course of psychiatric comorbidity in an Asian sample, as well as to illustrate the influences of anxiety disorder in ASD.

The results presented in this manuscript support previous research indicating that individuals with autism spectrum disorder (ASD) are at a greater risk of comorbid psychiatric disorders. Zheng et al.'s meta-analyses found that the odds ratio for schizophrenia was 3.55 in individuals with ASD, with a prevalence ranging from 3.4 % to 52 % (Zheng et al., 2018). Mouridsen et al.'s study followed 89 children with ASD for 36.9 years and found that 31 were diagnosed with spectrum disorders of schizophrenia and 10 with affective disorders (Mouridsen et al., 2008). Selten et al.'s case-control study demonstrated a 10-fold higher risk for nonaffective psychotic disorder and a six-fold higher risk for BD in adolescents with ASD compared to controls (Selten et al., 2015). Previous whole-genome studies have provided evidence of overlapping genetic etiology between ASD, BD, and schizophrenia, with heritability estimated at least 80 % for these disorders (Carroll and Owen, 2009). However, Vorstman et al.'s study revealed only a low genetic correlation between ASD and schizophrenia and a non-

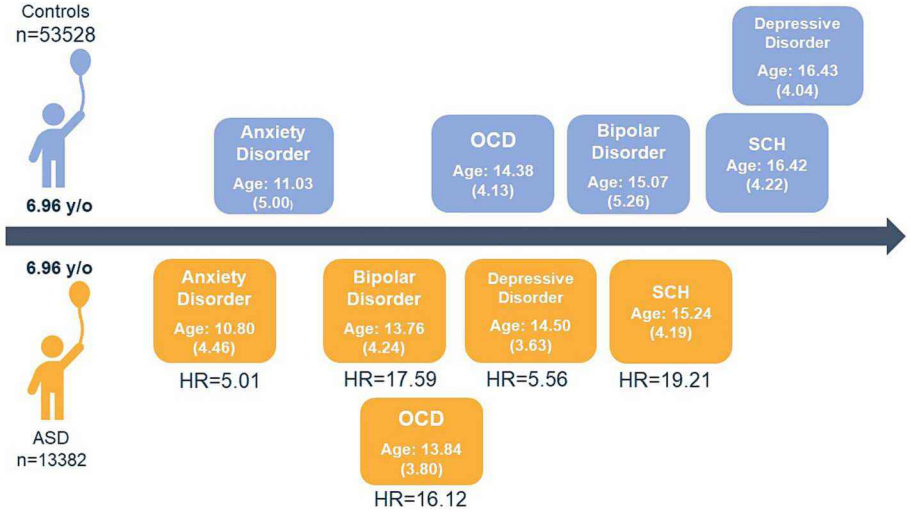

Fig. 1. Illustration of study design and time course of subsequent psychiatric comorbidities among patients with ASD.
ASD: autism spectrum disorder; OCD: obsessive compulsive disorder; HR: hazard ratio.

significant correlation between ASD and BD using polygenic risk scores (Vorstman et al., 2013).

Our current study found increased hazards for schizophrenia (HR: 19.21) and BD (HR: 17.59) in children (<12 years old) and adolescents (13–17 years old) with ASD, which is consistent with Selten et al.'s findings (Selten et al., 2015). Furthermore, our study identified increased hazards for depressive disorder (HR: 5.56), OCD (HR: 16.12), and anxiety disorder (HR: 5.01) in the ASD population, which is in line with Lai et al.'s previous study (Lai et al., 2019). However, diagnosing major mental disorders, such as schizophrenia and BD, in children or young adolescents with ASD may be challenging due to diagnostic overshadowing, which is a diagnostic bias attributing feature symptoms of other psychiatric disorders to pre-existing ASD (Rosenberg et al., 2011). Moreover, the misdiagnosed rate of ASD is 0.6 % in Taiwan, which is much lower than previously reported (Chang et al., 2003; Davidson et al., 2014). In brief, our findings highlight the importance of carefully assessing the core symptoms of psychopathological phenomena while considering the mental comorbidity in children with ASD. Psychiatrists should be aware of the increased risk of comorbid psychiatric disorders in this population and tailor their diagnostic approach accordingly (Fusar-Poli et al., 2022).

The early onset of anxiety disorders in ASD is a clinically important finding of this study. Our results suggest that anxiety disorders tend to emerge in late childhood, preceding the onset of psychotic and affective disorders in adolescence. Similar findings were also reported in the siblings or broader autism phenotype of individuals with ASD (Jokiranta-Olkoniemi et al., 2016). Age has been shown to moderate the prevalence of comorbid psychiatric disorders in ASD (Lai et al., 2019; Stewart et al., 2022). In contrast to Lai et al.'s findings, our results show that the age of onset of affective disorders is substantially earlier than in controls. The variation in results might be attributed to the heterogeneity and wide-ranging age samples of Lai et al.'s enrolled studies (Lai et al., 2019). The present findings also suggest that impaired emotion regulation skills, including self-regulation and mutual regulation, may be identified earlier in individuals with ASD (Laurent and Rubin, 2004). As early as preschool and early school years, emotion dysregulation in ASD may significantly impact social and behavioral symptoms (Berkovits et al., 2017; Vasa et al., 2013). Reduced flexibility may interfere with the engagement of adaptive emotional regulation strategies during development (Berkovits et al., 2017). Patients with ASD who use more maladaptive emotion regulation strategies from early childhood to school-age years may be more likely to develop internalized disorders later, such as anxiety and depression (Cai et al., 2018).

Previous reviews proposed that anxiety may play three roles for adolescents with ASD: (1) a downstream consequence of ASD symptoms (e.g., via stress generation through social rejection); (2) a moderator of ASD symptom severity, such that certain core autism symptoms like social skill deficits and repetitive behaviors may be exacerbated by anxiety; and (3) a proxy of core ASD symptoms (Cachia, 2017; Wood and Gadow, 2010). The results reported here are in accordance with the theory that anxiety may be a load for other psychopathology (Schutters et al., 2012; Woodward and Fergusson, 2001), and the risks for subsequent psychiatric disorders are proved to be significant in the younger population. Several reports indicate that anxiety symptoms are largely related to aggressive behavior in ASD from toddler age (Cervantes and Matson, 2015; Mazurek et al., 2019), whilst another by Vasa et al. showed affective problems are strongly associated with clinical anxiety through preschool to adolescence (Vasa et al., 2013). As for psychotic symptoms, Weisbrot et al. showed that ASD children with more intense anxiety were observed to have more delusions, hallucinations, and disorganized behaviors, and the results remained significant after controlling ASD symptoms (Weisbrot et al., 2005). In line with the previous evidence, the findings found here suggest the presence of a co-occurring anxiety disorder—whether it is a manifestation of the ASD diathesis or not (Montazeri et al., 2019)—may phenotypically result in high risks of psychiatric comorbidity (Wood and Gadow, 2010).

Leader et al. found that challenging behavior and sensory issues were positively associated with comorbid anxiety symptoms in children and adolescents with ASD (Leader et al., 2021). These findings highlight the importance of early identification and intervention for anxiety disorders in individuals with ASD. A multimodal approach that includes both pharmacological and non-pharmacological interventions, such as cognitive-behavioral therapy, social skills training, and mindfulness-based interventions, should be considered for the early treatment of anxiety in this population. It is essential to individualize the treatment approach based on the patient's specific needs and abilities, with a focus on increasing flexibility and enhancing particular social skills (Reaven et al., 2018; Sharma et al., 2018). Involving caregivers and family members in the treatment process is also crucial. Regular monitoring and assessment of treatment effectiveness should be conducted to ensure optimal outcomes. Overall, these findings contribute to a better understanding of the pathogenesis of psychiatric comorbidities in ASD and emphasize the need for targeted interventions to improve outcomes for individuals with this condition.

The current study has several strengths. First, psychiatric disorders were confirmed after a diagnostic interview by a psychiatrist. Compared to the previous study that utilized using parent-reported scales, misattributing psychiatric symptoms to ASD or 'diagnostic overshadowing' may be less likely (Rosenberg et al., 2011). Second, the study used a large population-based sample that provides the solid statistical power needed to examine rare psychiatric disorders in children and adolescents. The NHIRD data have almost complete national coverage, with the link between registers leading to almost no loss of individuals. Third, the diagnoses were coded by psychiatrists prospectively, which limited the possibility of detection bias. Additionally, the study design and matched procedure practically eliminated the risk of recall and selection bias. Third, this is the first study to reveal the risks and time course of psychiatric comorbidity in an Asian ASD sample.

5. Limitations

The findings from the present study should be interpreted in light of several limitations. First, the follow-up period of the current study may only reflect the risks before early adulthood, which may limit the generalization of the results to the at-risk period for adulthood disorders. The patient with baseline Second, psychopathology in the pre-existing ASD might be more likely recognized as having other psychiatric symptoms, which may partially explain the earlier detection age of affective disorder in the current study. However, the healthcare system in Taiwan is based on public services, meaning virtually all children were registered in the database before school age. Therefore, the rate of underestimating mental symptoms in neurotypical control can be reduced. Third, intellectual disability affects approximately one-third of ASD patients (Christensen et al., 2016), which may hinder accurate assessment of overlapping symptoms of co-occurring psychiatric disorders (Rosen et al., 2018; Selten et al., 2015). On the other hand, more cognitive function can be attributed to a greater awareness of their disability. The diagnostic bias and interaction with the level of intelligence warrants further investigation. Fourth, the possibility of residual confounding must be taken into account. This study could not include other important covariates, such as exposure to substances, self-perception, and parenting style. Fifth, using NHIRD only captures the well-defined categorical diagnoses. For instance, there are subclinical or atypical anxiety symptoms manifesting in ASD at an early age (Kerns et al., 2014; Vasa et al., 2013), which may also mediate the risks of co-occurring psychiatric disorders. Sixth, the prevalence of ASD and psychiatric comorbidities may have been underestimated because only individuals who sought medical help were enrolled. Additionally, the NHIRD did not include some essential information, such as family history, personal lifestyle, and environmental factors, which could have potentially influenced the development of psychiatric comorbidities in individuals with ASD. Therefore, further studies that consider these

factors are warranted to gain a more comprehensive understanding of the comorbidities associated with ASD. Lastly, although the findings indicate an increase in the risk of subsequent psychiatric disorders in ASD with anxiety disorder compared to ASD alone, they do not confirm the causality.

6. Conclusions

Our findings indicated that children and adolescents with ASD are at risk for psychiatric comorbidities. Among them, the diagnosis of anxiety disorder independently increases the risks of other comorbidities. These findings contribute to our understanding of the dynamic pathology of these disorders and have implications for the management of ASD.

Financial disclosure

All authors have no financial relationships relevant to this article to disclose.

Role of funding source

The study was supported by grant from Taipei Veterans General Hospital (V106B-020, V107B-010, V107C-181, V108B-012, V110C-025, V110B-002), Yen Tjing Ling Medical Foundation (CI-109-21, CI-109-22, CI-110-30) and Ministry of Science and Technology, Taiwan (107–2314-B-075-063-MY3, 108-2314-B-075 -037). The funding source had no role in any process of our study.

Contributors

Drs Yeh and Liang conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript. Drs Hsu, Huang, and T.-J. Chen collected data, carried out the initial analyses and interpreted the data. Prof Bai, Su, Tsai and Dr. M.-H.Chen conceptualized and designed the study, coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Conflict of interest

The authors have no relevant financial or non-financial interests to disclose.

Acknowledgements

None.

References

Baird, G., Simonoff, E., Pickles, A., Chandler, S., Loucas, T., Meldrum, D., Charman, T., 2006. Prevalence of disorders of the autism spectrum in a population cohort of children in South Thames: the special needs and autism project (SNAP). Lancet 368, 210–215.

Beesdo, K., Knappe, S., Pine, D.S., 2009. Anxiety and anxiety disorders in children and adolescents: developmental issues and implications for DSM-V. Psychiatr. Clin. North Am. 32, 483–524.

Berkovits, L., Eisenhower, A., Blacher, J., 2017. Emotion regulation in young children with autism Spectrum disorders. J. Autism Dev. Disord. 47, 68–79.

Cachia, R.L., 2017. Mindfulness and autism spectrum disorder. In: Fitzgerald, M., Yip, J. (Eds.), Autism—Paradigms Recent Research and Clinical Applications. IntechOpen, London, pp. 253–368.

Cai, R.Y., Richdale, A.L., Uljarevic, M., Dissanayake, C., Samson, A.C., 2018. Emotion regulation in autism spectrum disorder: where we are and where we need to go. Autism Res. 11, 962–978.

Carroll, L.S., Owen, M.J., 2009. Genetic overlap between autism, schizophrenia and bipolar disorder. Genome Med. 1, 102.

Cervantes, P.E., Matson, J.L., 2015. The relationship between comorbid psychopathologies, autism, and social skill deficits in young children. Res. Autism Spectr. Disord. 10, 101–108.

Chang, H.-L., Juang, Y.-Y., Wang, W.-T., Huang, C.-I., Chen, C.-Y., Hwang, Y.-S., 2003. Screening for autism spectrum disorder in adult psychiatric outpatients in a clinic in Taiwan. Gen. Hosp. Psychiatry 25, 284–288.

Chen, M.-H., Pan, T.-L., Li, C.-T., Lin, W.-C., Chen, Y.-S., Lee, Y.-C., Tsai, S.-J., Hsu, J.-W., Huang, K.-L., Tsai, C.-F., 2015. Risk of stroke among patients with post-traumatic stress disorder: nationwide longitudinal study. Br. J. Psychiatry 206, 302–307.

Chen, M.-H., Lan, W.-H., Hsu, J.-W., Huang, K.-L., Su, T.-P., Li, C.-T., Lin, W.-C., Tsai, C.-F., Tsai, S.-J., Lee, Y.-C., 2016. Risk of developing type 2 diabetes in adolescents and young adults with autism Spectrum disorder: a Nationwide longitudinal study. Diabetes Care 39, 788–793.

Christensen, D.L., Baio, J., Van Naarden Braun, K., Bilder, D., Charles, J., Constantino, J. N., Daniels, J., Durkin, M.S., Fitzgerald, R.T., Kurzius-Spencer, M., Lee, L.-C., Pettygrove, S., Robinson, C., Schulz, E., Wells, C., Wingate, M.S., Zahorodny, W., Yeargin-Allsopp, M., Centers for Disease, C., Prevention, 2016. Prevalence and characteristics of autism spectrum disorder among children aged 8 years–autism and developmental disabilities monitoring network, 11 sites, United States, 2012. MMWR Surveill. Summ. 65, 1–23.

Costello, E.J., Egger, H.L., Angold, A., 2005. The developmental epidemiology of anxiety disorders: phenomenology, prevalence, and comorbidity. Child Adolesc. Psychiatr. Clin. N. Am. 14, 631–648.

Davidson, C., Greenwood, N., Stansfield, A., Wright, S., 2014. Prevalence of a Sperger syndrome among patients of an early intervention in psychosis team. Early Interv. Psychiatry 8, 138–146.

Fusar-Poli, L., Brondino, N., Politi, P., Aguglia, E., 2022. Missed diagnoses and misdiagnoses of adults with autism spectrum disorder. Eur. Arch. Psychiatry Clin. Neurosci. 272, 187–198.

Gadow, K.D., Devincent, C.J., Pomeroy, J., Azizian, A., 2005. Comparison of DSM-IV symptoms in elementary school-age children with PDD versus clinic and community samples. Autism 9, 392–415.

Huang, J.S., Yang, F.C., Chien, W.C., Yeh, T.C., Chung, C.H., Tsai, C.K., Tsai, S.J., Yang, S.S., Tzeng, N.S., Chen, M.H., Liang, C.S., 2021. Risk of substance use disorder and its associations with comorbidities and psychotropic agents in patients with autism. JAMA Pediatr. 175, e205371.

Jokiranta-Olkoniemi, E., Cheslack-Postava, K., Sucksdorff, D., Suominen, A., Gyllenberg, D., Chudal, R., Leivonen, S., Gissler, M., Brown, A.S., Sourander, A., 2016. Risk of psychiatric and neurodevelopmental disorders among siblings of probands with autism Spectrum disorders. JAMA Psychiatry 73, 622–629.

Kerns, C.M., Kendall, P.C., Berry, L., Souders, M.C., Franklin, M.E., Schultz, R.T., Miller, J., Herrington, J., 2014. Traditional and atypical presentations of anxiety in youth with autism spectrum disorder. J. Autism Dev. Disord. 44, 2851–2861.

Lai, M.-C., Kassee, C., Besney, R., Bonato, S., Hull, L., Mandy, W., Szatmari, P., Ameis, S. H., 2019. Prevalence of co-occurring mental health diagnoses in the autism population: a systematic review and meta-analysis. Lancet Psychiatry 6, 819–829.

Laurent, A.C., Rubin, E., 2004. Challenges in emotional regulation in asperger syndrome and high-functioning autism. Top. Lang. Disord. 24, 286–297.

Leader, G., Flynn, C., O'Rourke, N., Coyne, R., Caher, A., Mannion, A., 2021. Comorbid psychopathology, challenging behavior, sensory issues, adaptive behavior and quality of life in children and adolescents with autism Spectrum disorder. Dev. Neurorehabil. 24, 397–407.

Li, C.-T., Bai, Y.-M., Huang, Y.-L., Chen, Y.-S., Chen, T.-J., Cheng, J.-Y., Su, T.-P., 2012. Association between antidepressant resistance in unipolar depression and subsequent bipolar disorder: cohort study. Br. J. Psychiatry 200, 45–51.

Liang, C.S., Bai, Y.M., Hsu, J.W., Huang, K.L., Ko, N.Y., Chu, H.T., Yeh, T.C., Tsai, S.J., Chen, T.J., Chen, M.H., 2020. The risk of sexually transmitted infections following first-episode schizophrenia among adolescents and young adults: a cohort study of 220 545 subjects. Schizophr. Bull. 46, 795–803.

Liu, C.-Y., Hung, Y., Chuang, Y., Chen, Y., Weng, W., Liu, J., Liang, K., 2006. Incorporating development stratification of Taiwan townships into sampling design of large scale health interview survey. J. Health Manag. 4, 1–22.

Mazurek, M.O., Dovgan, K., Neumeyer, A.M., Malow, B.A., 2019. Course and predictors of sleep and co-occurring problems in children with autism Spectrum disorder. J. Autism Dev. Disord. 49, 2101–2115.

Montazeri, F., de Bildt, A., Dekker, V., Anderson, G.M., 2019. Network analysis of anxiety in the autism realm. J. Autism Dev. Disord. 49, 2219–2230.

Mouridsen, S.E., Rich, B., Isager, T., 2008. Psychiatric disorders in adults diagnosed as children with atypical autism. A case control study. J. Neural Transm. 115, 135–138.

Pearcey, S., Gordon, K., Chakrabarti, B., Dodd, H., Halldorsson, B., Creswell, C., 2021. Research review: the relationship between social anxiety and social cognition in children and adolescents: a systematic review and meta-analysis. J. Child Psychol. Psychiatry 62, 805–821.

Reaven, J., Moody, E.J., Grofer Klinger, L., Keefer, A., Duncan, A., O'Kelley, S., Meyer, A., Hepburn, S., Blakeley-Smith, A., 2018. Training clinicians to deliver group CBT to manage anxiety in youth with ASD: results of a multisite trial. J. Consult. Clin. Psychol. 86, 205–217.

Rosen, T.E., Mazefsky, C.A., Vasa, R.A., Lerner, M.D., 2018. Co-occurring psychiatric conditions in autism spectrum disorder. Int. Rev. Psychiatry 30, 40–61.

Rosenberg, R.E., Kaufmann, W.E., Law, J.K., Law, P.A., 2011. Parent report of community psychiatric comorbid diagnoses in autism spectrum disorders. Autism Res. Treat. 2011, 405849.

Schutters, S.I., Dominguez, M.D., Knappe, S., Lieb, R., van Os, J., Schruers, K.R., Wittchen, H.U., 2012. The association between social phobia, social anxiety cognitions and paranoid symptoms. Acta Psychiatr. Scand. 125, 213–227.

Selten, J.P., Lundberg, M., Rai, D., Magnusson, C., 2015. Risks for nonaffective psychotic disorder and bipolar disorder in young people with autism spectrum disorder: a population-based study. JAMA Psychiatry 72, 483–489.

Sharma, S.R., Gonda, X., Tarazi, F.I., 2018. Autism Spectrum disorder: classification, diagnosis and therapy. Pharmacol. Ther. 190, 91–104.
Shen, C.-C., Tsai, S.-J., Perng, C.-L., Kuo, B.I.-T., Yang, A.C., 2013. Risk of parkinson disease after depression a nationwide population-based study. Neurology 81, 1538–1544.
Simonoff, E., Pickles, A., Charman, T., Chandler, S., Loucas, T., Baird, G., 2008. Psychiatric disorders in children with autism Spectrum disorders: prevalence, comorbidity, and associated factors in a population-derived sample. J. Am. Acad. Child Adolesc. Psychiatry 47, 921–929.
van Steensel, F.J., Bogels, S.M., de Bruin, E.I., 2013. Psychiatric comorbidity in children with autism spectrum disorders: a comparison with children with ADHD. J. Child Fam. Stud. 22, 368–376.
Stewart, T.M., Martin, K., Fazi, M., Oldridge, J., Piper, A., Rhodes, S.M., 2022. A systematic review of the rates of depression in autistic children and adolescents without intellectual disability. Psychol. Psychother. 95, 313–344.
Vasa, R.A., Kalb, L., Mazurek, M., Kanne, S., Freedman, B., Keefer, A., Clemons, T., Murray, D., 2013. Age-related differences in the prevalence and correlates of anxiety in youth with autism spectrum disorders. Res. Autism Spectr. Disord. 7, 1358–1369.
Vorstman, J.A., Anney, R.J., Derks, E.M., Gallagher, L., Gill, M., de Jonge, M.V., van Engeland, H., Kahn, R.S., Ophoff, R.A., Autism Genome Project, T.I.S.C., 2013. No evidence that common genetic risk variation is shared between schizophrenia and autism. Am. J. Med. Genet. B Neuropsychiatr. Genet. 162B, 55–60.
Weisbrot, D.M., Gadow, K.D., DeVincent, C.J., Pomeroy, J., 2005. The presentation of anxiety in children with pervasive developmental disorders. J. Child Adolesc. Psychopharmacol. 15, 477–496.
Wood, J.J., Gadow, K.D., 2010. Exploring the nature and function of anxiety in youth with autism Spectrum disorders. Clin. Psychol. Sci. Prac. 17, 281–292.
Woodward, L.J., Fergusson, D.M., 2001. Life course outcomes of young people with anxiety disorders in adolescence. J. Am. Acad. Child Adolesc. Psychiatry 40, 1086–1093.
Zheng, Z., Zheng, P., Zou, X., 2018. Association between schizophrenia and autism spectrum disorder: a systematic review and meta-analysis. Autism Res. 11, 1110–1119.