Sex Differences in Psychiatric Comorbidities in Adolescents With Autism Spectrum Disorder:
A National Inpatient Sample Analysis

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ABSTRACT

Objective: To investigate sex differences in psychiatric comorbidities in adolescents with autism spectrum disorder (ASD).

Methods: The US National Inpatient Sample dataset (January 2016 to December 2018) was used for this retrospective study. The patient population was selected by performing a query on all adolescent patients (aged 12–17 years) having ASD with the *ICD-10-CM* code starting with F84. All missing sex data were excluded. Additional data on mood disorders, anxiety disorders, personality disorders, adjustment disorders, psychotic disorders, attention-deficit/hyperactivity disorder (ADHD)/conduct disorders, sleep-wake disorders, and substance use disorders were collected. Data on psychiatric comorbidities were collected using the *ICD-10-CM* code provided in the Clinical Classifications Software of the dataset.

Results: Mood disorders (37.4% vs 44.1%, $P < .001$) and anxiety disorders (29.4% vs 37.0%, $P < .001$) were more prevalent in females compared to males. The prevalence of ADHD and other conduct disorders was significantly higher in males than females (47.7% vs 36.7%, $P < .001$). Substance use disorders were slightly higher among males compared to females (3.7% vs 3.0%, $P = .04$).

Conclusion: The study findings revealed statistically significant disparities in psychiatric comorbidities among adolescent male and female patients with ASD. These findings could serve as a pilot for larger-scale research with this patient population in the future.

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Autism spectrum disorder (ASD) is a complex neurodevelopmental disorder characterized by chronic difficulties in social interaction and verbal and nonverbal communication with restricted/repetitive activities.[1] Approximately 1 in 54 children in the United States is diagnosed with ASD. Boys are 4 times more likely than girls to be diagnosed with autism.[2]

ASD, though typically diagnosed in childhood, has many of the most visible symptoms between 12 and 18 months of age or earlier.[3,4] However, some children develop autism in toddlerhood when they stop acquiring or lose previously acquired skills.[5] After controlling for child demographics and non–ASD-related illnesses, ASD is associated with higher health care and aggregate non–health care costs, including higher school costs.[6] While the cause of ASD is still unclear, genetics has long been recognized as a risk factor. Twin studies[7,8] found a 76% concordance in monozygotic twins, confirming ASD's significant genetic heritability. Environmental factors also play an essential role.[7,8] ASD typically progresses into adulthood with severe consequences such as difficulties or concerns in finances, jobs, and socialization frequently cited as outcomes.[9]

ASD causes cognitive rigidity, difficulty with emotion regulation, and intolerance of uncertainty, all of which can lead to increased psychiatric disorders in this population.[10] Comorbid psychiatric disorders are more commonly observed in individuals with ASD than in the general population.[10] Major depressive disorder, anxiety, attention-deficit/hyperactivity disorder (ADHD), schizophrenia, and obsessive-compulsive disorder (OCD) are the most common psychiatric comorbidities among individuals with ASD.[11] Research suggests that girls with ASD have more significant sensory profile abnormalities than boys.[12,13] Girls with ASD are more likely to experience anxiety, depression, suicide ideation, and psychiatric hospitalization. In contrast, co-occurring ADHD, OCD, and tics are more common in boys with ASD.[12,13] Compared to males with ASD, girls with ASD have slightly but significantly more trouble with emotion management.[14]

Several factors are associated with an increased risk of comorbid psychiatric disorders. Individuals with ASD are more likely to be bullied and to suffer negative life experiences, which can in turn lead to increased stress and an increased risk of depression and anxiety.[10] As a result of the

Clinical Points

- Autism spectrum disorder (ASD) prevalence discrepancies between males and females are well known but poorly understood.
- There are significant disparities in psychiatric comorbidities such as mood disorders, anxiety disorders, personality disorders, attention-deficit/hyperactivity disorder, sleep-wake disorders, and substance use disorders among adolescent male and female patients with ASD.

cumulative consequences of having more than 1 condition, it has been argued that comorbidity will generally lead to more severe impairments.[15] Clinicians face a significant challenge in identifying psychiatric comorbidity because the nature of ASD makes it difficult to assess thoughts and emotions for reasons such as impaired reciprocity in the conversational process, difficulty identifying emotions, impaired theory of mind, and lack of empathy.[16] It is crucial to investigate comorbidities in ASD, since they might affect the symptoms of the core diagnosis, as well as treatment strategies and outcomes.[17,18] The existence of these comorbidities not only increases the need for further therapy, but can also make it more difficult to learn skills in areas wherein the ASD diagnosis is associated with deficits. More studies are needed on comorbid psychiatric problems in adolescents with ASD, especially regarding sex differences, which are poorly understood. Hence, the objective of this study was to explore sex differences in psychiatric comorbidities in adolescents with ASD through extensive inpatient sample data analysis.

METHODS

Data Source and Patient Population

The US National Inpatient Sample (NIS) dataset (January 2016 to December 2018) was used for this study.[19] The NIS is a part of databases developed by the Healthcare Cost and Utilization Project (HCUP). There are 47 participating states, covering more than 97% of the US population and a 20% stratified sample of discharges from community hospitals. Each record in the dataset contains information on age, sex, race, primary-secondary diagnosis, cost of hospitalization, length of stay, hospital location, primary insurance, admission month, and discharge disposition. The primary and secondary diagnosis data are stored in the dataset based on the *International Classification of Diseases, Tenth Revision, Clinical Modification* (*ICD-10-CM*), *Procedure Coding System*. A detailed description of the dataset is available at https://www.hcup-us.ahrq.gov/.

The patient population was selected by performing a query on all adolescent patients (aged 12–17 years) having ASD with the *ICD-10-CM* code that starts with F84. Patients with missing sex data were excluded. Additional data on mood disorders, anxiety disorders, personality disorders, adjustment disorders, psychotic disorders, ADHD/conduct disorders, sleep-wake disorders, and substance use disorders were collected. Data on psychiatric comorbidities were collected using the *ICD-10-CM* code provided in the Clinical Classifications Software of the dataset.[20]

Table 1. Demographic Characteristics of the Study Population[a]

Characteristic	Males (n = 44,855)	Females (n = 16,265)	*P* Value
Age, mean (SD), y	14.5 (0.02)	14.4 (0.03)	.31
Race			.52
White	67.1	68.8	
Black	12.6	11.4	
Hispanic	13.7	12.8	
Asian or Pacific Islander	2.2	2.3	
Native American	0.4	0.4	
Other	4.0	4.3	
Median household income percentile by patient zip code			.001
0–25th	25.0	22.3	
26th to 50th	26.0	24.9	
51st to 75th	24.9	25.6	
76th to 100th	24.1	27.3	

[a]Data are presented as % unless otherwise specified.

Statistical Analysis

Categorical data were described as counts and percentages and compared using the Rao-Scott adjusted χ^2 test. Continuous data were expressed as mean (standard error) and compared by Student *t* test. Descriptive baseline characteristics are presented in Table 1. Analysis was performed using the SPSS version 26.0 software for Windows (IBM Software Inc, Armonk, New York). All tests were 2-sided, and $P < .05$ was considered statistically significant.

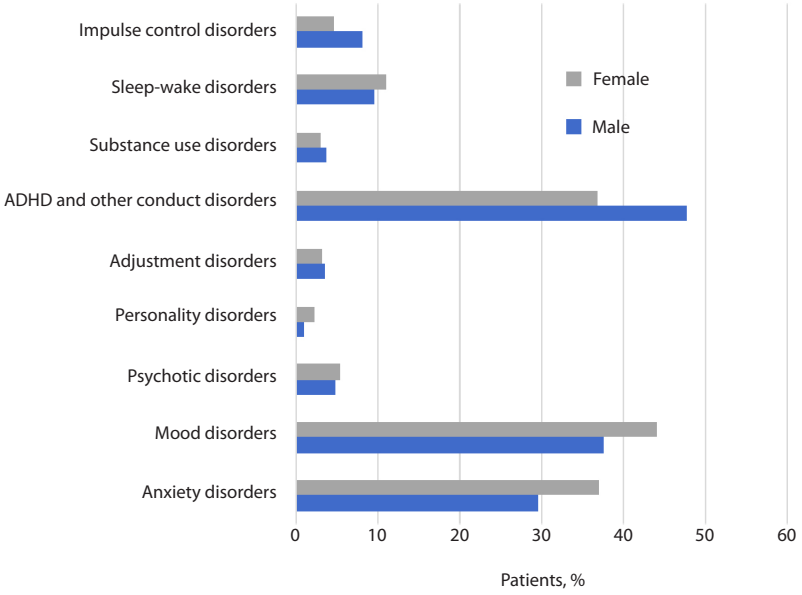
RESULTS

A total of 61,120 patient records with the diagnosis of ASD were included in this study. Baseline characteristics are shown in Table 1. The mean age of the participants in the study population was 14.5 years, and 73.3% of patients were male. Almost two-thirds (67.5%) of patients were White. In the analysis by sex, the mean age was similar between the groups. There was no difference in the racial distribution between males and females ($P = .52$). More female patients were from the area with a median household income in the 51st to 75th percentile (25.6% vs 24.9%) or 76th to 100th percentile (27.3% vs 24.1%) ($P = .001$) compared to males.

Psychiatric Comorbidities

Prevalence of psychiatric comorbidities is provided in Figure 1. Mood disorders (44.1% vs 37.4%, $P < .001$) and anxiety disorders (37.0% vs 29.4%, $P < .001$) were more prevalent in females compared to males. Major depressive disorder prevalence was 18.2% and 27.0% among males and females, respectively. Bipolar depression prevalence was similar between the groups (8.6% vs 10.2%, $P = .22$). Psychotic disorders (4.7% vs 5.2%, $P = .28$) and adjustment disorders (3.4% vs 3.1%, $P = .39$) were similar between the groups. Personality disorders were more prevalent among

Figure 1. Psychiatric Comorbidities Among Patients With Autism Spectrum Disorders



females than males (2.2% vs 0.9%, $P<.001$). Prevalence of ADHD and other conduct disorders was significantly higher in males than females (47.7% vs 36.7%, $P<.001$). More females had sleep-wake disorders compared to males (11.0% vs 9.4%, $P=.01$). Substance use disorders were slightly higher among males compared to females (3.7% vs 3.0%, $P=.04$).

DISCUSSION

This is the first study, to our knowledge, to assess sex differences in psychiatric comorbidities in adolescents with ASD in a national inpatient sample. The results showed significant sex differences in psychiatric comorbidities in adolescents with ASD, supporting the limited existing literature. Female adolescents with ASD had a higher prevalence of mood disorders, anxiety disorders, personality disorders, and sleep-wake disorders compared to their male counterparts. In addition, males had a significantly higher prevalence of ADHD, conduct disorders, and substance use disorders than females. However, the groups were similar in terms of psychotic disorders and adjustment disorders.

ADHD and Conduct Disorders

ADHD and ASD symptoms frequently overlap. In addition, both disorders have an acknowledged hereditary predisposition, with comorbidity within the individual and among family members, and both conditions cause significant behavioral, academic, emotional, and adaptive problems in school, home, and elsewhere.[21] In this study, we found that males had a significantly higher prevalence of ADHD than females. Similarly, Ashraf et al[22] observed that male ASD patients have a higher prevalence of the comorbid diagnosis of ADHD, mainly in Whites.

Sleep Disorders

Sex differences in ASD vary significantly between studies. Sleep disturbances and behavioral dysregulation are common in children with ASD.[23] The present study observed a higher prevalence of sleep-wake disorders in adolescent females than males (11.0% vs 9.4%, $P=.01$) with ASD. Similarly, in a cross-sectional study conducted by Mazurek and Sohl,[24] girls had a higher prevalence of bedtime resistance and parasomnias. Also, Takase et al[25] used a sleep log for 28 days during summer vacation with 89 autistic children (74 boys and 15 girls, aged 3–20 years) and found that only 1 girl, aged 13 years, had a tendency of non–24-hour sleep-wake syndrome. The main reasons for this shift were in how ASD was diagnosed and in which populations were used in different studies to investigate the male to female ratio in ASD.[26]

Anxiety Disorders

Co-occurring anxiety disorder is common in children with ASD, with approximately 40% of children with ASD meeting the criteria for at least 1 anxiety disorder. Anxiety disorders are often much higher than in typically developing peers or those with other neurodevelopmental disabilities.[27] The most pronounced types of anxiety that occur with ASD include specific phobia, OCD, and social anxiety disorder.[28] Also, high-functioning ASD can be associated with anxiety disorders, most commonly social phobia and generalized anxiety disorder.[29]

In our study, anxiety disorders were more prevalent in females than males (37.0% vs 29.4%, $P<.001$). Solomon et al[30] explored sex differences in anxiety in adolescents with ASD aged 12–18 years. They found marginally significant parent-reported sex differences, with females showing higher anxiety levels than males. However, some studies[31,32]

report no sex differences in anxiety, while 1 study[33] reported sex differences. Furthermore, Rynkiewicz et al[12] concluded that females with ASD are more likely to develop anxiety.

Mood Disorders

In this study, mood disorders in adolescents with ASD were more prevalent in females (44.1%) compared to males (37.4%). In line with the findings of our study, Solomon et al[30] concluded that teen girls with ASD had higher affective symptoms, depression, anxiety, and internalizing than boys with ASD. Furthermore, Oswald et al[34] confirmed that adolescents with ASD, compared to controls, had more internalizing problems such as anxiety and depression. In females with ASD, depression peaked during the early teens. In contrast, males with ASD presented with depression later in their adolescent years. In a meta-analysis by Hull et al,[35] females were found to have higher internalizing problems. The mean age of our study population was 14.5 years, which could be why we saw a higher prevalence of mood disorders in females than males. Rynkiewicz et al[12] found that adolescent girls with ASD appear to be at higher risk of developing depression and suicidal ideation than boys with ASD and had more hospitalizations. In a sample of 255 autistic adolescents and adults, female sex and higher ASD severity were associated with more anxiety and depression during adolescence and early adulthood.[36] Unlike depression and anxiety, bipolar disorder prevalence was similar between adolescent females (10.2%) and males (8.6%).

Psychotic Disorders

Our study found no significant difference in the prevalence of psychotic disorders between adolescent males (4.7%) and females (5.2%) with ASD.

Personality Disorders

A study[37] comparing the schizoid phenotype within the Autism Spectrum Quotient (AQ) and Schizotypal Personality Quotient (SPQ) showed no significant sex effects on mean AQ scores. However, there was a substantial difference in SPQ scores. The study[37] covered early adulthood patients and did not expand the search to other personality disorders, unlike our study.

Limitations

Our study has some limitations. The hospital claims data are prone to recognition, reporting, and coding bias. Additionally, because our research uses a de-identified administrative database, it is susceptible to coding errors. Furthermore, because the records in the dataset are discharge records rather than individual patients, the same patients may have been counted more than once. Also, we do not know the severity/medications of ASD in these hospitalized adolescent patients and the reason for their admissions. Finally, almost two-thirds of patients were White, which could also affect the results.

Strengths

This is the first study, to our knowledge, covering a wide range of ASD psychiatric comorbidities, including ADHD, anxiety, mood disorders, psychosis, substance misuse, and personality disorders. In addition, this study is unique in that it explicitly compares sex differences in the occurrence of those comorbidities. This study used US nationwide inpatient sample data and included various socioeconomic backgrounds and adolescent age groups, which gives validity to the findings.

CONCLUSION

Early ASD diagnosis helps clinicians to provide appropriate resources and services. The study findings reveal statistically significant disparities in psychiatric comorbidities such as mood disorders, anxiety disorders, personality disorders, ADHD, sleep-wake disorders, and substance use disorders among adolescent male and female patients with ASD. Our retrospective study could serve as a pilot for larger-scale research in this patient population in the future.

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