#### Review

Sex differences in the prevalence of common comorbidities in autism: a narrative review

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Running title: Sex differences in autism and comorbid conditions

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### **Abstract**

Autism spectrum disorder (ASD) involves challenges in social communication and restricted, repetitive behaviors. Historically, males have received autism diagnoses at comparatively high rates, prompting an underrepresentation of females in research and an incomplete understanding of sex-specific symptom presentations and comorbidities. This review examines sex differences in the prevalence of common comorbidities of autism to inform tailored clinical practices. These conditions include attention deficit hyperactivity disorder (ADHD), anxiety disorders, conduct disorder, depression, epilepsy, intellectual disability, and tic disorders. ADHD is prevalent in both sexes; however, females may more frequently exhibit the inattentive subtype. Anxiety disorders display inconsistent sex differences, while conduct disorder more frequently impacts males. Depression becomes more common with age; some studies indicate more pronounced symptoms in adolescent girls, while others suggest greater severity in males. Epilepsy is more prevalent in females, especially those with intellectual disabilities. Despite displaying a male predominance, intellectual disability may exacerbate the severity of autism to a greater degree in females. No clear sex differences have been found regarding tic disorders. Overall, contributors to sex-based differences include biases stemming from male-centric diagnostic tools, compensatory behaviors like camouflaging in females, genetic and neurobiological differences, and the developmental trajectories of comorbidities. Recognizing these factors is crucial for developing sensitive diagnostics and sex-specific interventions. Inconsistencies in the literature highlight the need for longitudinal studies with large, diverse samples to investigate autism comorbidities across the lifespan. Understanding sex differences could facilitate earlier identification, improved care, and personalized interventions, thus enhancing quality of life for individuals with autism.

**Keywords:** Attention deficit disorder with hyperactivity; Autism spectrum disorder; Intellectual disability; Sex factors; Psychomotor agitation; Comorbidity

### Introduction

## **Background**

Autism is a neurodevelopmental condition that affects an individual's ability to communicate and interact socially, often accompanied by restricted and repetitive behaviors (RRBs). Its presentation varies widely across individuals, leading to the popular saying, "If you've met one person with autism, you've met one person with autism," which emphasizes the distinct strengths and challenges of each individual. Numerous genetic and neurobiological studies have sought to understand the etiology behind the observed sex differences in autism, but the multifactorial nature of the condition has posed challenges. Historically, males with autism have been over-represented compared to females. This disparity is largely reflected in epidemiological research, with an analysis of data from 43 studies indicating a mean male:female prevalence ratio of 4.2:1 [1].

The imbalanced ratio of males to females diagnosed with autism has resulted in an incomplete understanding of core symptom presentations across sexes. Previous studies comparing the social communication skills of males and females with autism have yielded mixed results; some studies have identified distinct challenges faced by each sex [2, 3], while others have found no statistically significant differences [4-6]. Similar inconsistencies have been reported concerning RRBs, with certain studies suggesting greater severity in males [4, 6] and other research not corroborating these results [3, 5].

A variety of factors could explain the observed or unobserved sex differences in autism, ranging from the limitations of measurement tools to participant characteristics such as the developmental stage of the individual, their overall severity of autism, or the presence of comorbid conditions. Comorbidities, which may include neurological, cognitive, psychiatric, and physical conditions, increase the complexity of the person's needs and underscore the critical importance of seeking medical advice and interventions [7, 8]. Moreover, comorbid conditions may influence the manifestation of symptoms [9]. For instance, a study by Gu et al. [10] revealed that boys were more likely than girls to be diagnosed between the ages of 3 and 11, whereas girls were more likely to receive a diagnosis either before age 3 or after age 11. However, after adjusting for comorbid neurodevelopmental and psychiatric conditions, these age-related patterns were no

longer significant. The interaction between the core symptoms of autism and these additional challenges emphasizes the necessity for a more comprehensive understanding of sex differences. This understanding is crucial for the development of tailored intervention strategies and could explain how a subset of the autistic population could be overlooked.

### **Objectives**

This review aims to explore the differences in the prevalence of comorbid conditions between males and females with autism, establishing a necessary foundation to understand the baseline disparities. These insights could guide further investigation into sex-specific clinical presentations and targeted interventions. By examining sex-based discrepancies, we intend to highlight areas in need of additional research and suggest considerations for clinical practice, thus fostering a more inclusive understanding of autism.

# Sex differences in psychiatric and neurologic comorbidities

### Attention deficit hyperactivity disorder

is characterized by challenges in maintaining attention, along with hyperactivity and impulsivity. It represents one of the most common childhood neurodevelopmental disorders, with a weighted prevalence of 10.47% in the United States from 2021 to 2022 [11]. Clinical observations have indicated that a substantial number of children with autism also exhibit symptoms of ADHD, with reported comorbidity rates ranging widely from 30% to 80% [12, 13, 14]. Additionally, the behavioral overlaps between these two conditions suggest they may share a pathophysiological basis [15]. While ADHD has traditionally been recognized to display a male predominance, with a male-to-female prevalence ratio of 2.28 to 1 [16], a study by Margari et al. [17] found no significant sex differences in the prevalence of ADHD as a comorbid condition in adolescents with autism. Notably, female sex was more frequently associated with the predominantly inattentive presentation of ADHD, whereas male participants tended to display the combined presentation.

### Anxiety disorders

Anxiety disorders represent prevalent and chronic mental conditions, with large-scale research suggesting that it may affect around 33.7% of the population at some point in their lives [18]. Up to 40% of individuals with autism may experience at least one comorbid anxiety disorder, most commonly specific phobia [19]. Although anxiety disorders are generally more prevalent among females, research on individuals with autism has yielded mixed results. Some studies have found comparable levels of anxiety between sexes [17, 20], while others have reported higher anxiety scores [21] or more internalizing problems in females with autism [22].

#### Conduct disorder

Conduct disorder is a complex behavioral disorder characterized by aggressive and destructive behavior patterns. The lifetime prevalence of conduct disorder in the general population is approximately 9.5% [23], and it increases to around 13% among individuals with autism [24]. Regarding sex differences, males typically exhibit higher rates of physical aggression [25]. Within the autism community, studies indicate higher rates in males, with a greater manifestation of externalizing problems [24, 26]. Notably, however, this research has generally involved small sample sizes, underscoring the need for further large-scale research to fully understand the extent of conduct disorder comorbidity in autism.

### Depression

The prevalence of depression among individuals with autism, particularly those without intellectual disability, appears to increase with age. DeFilippis [27] noted that adolescents with autism encounter substantial challenges as they navigate their identity and interpersonal relationships. Oswald et al. [28] found that early adolescent girls with autism show more severe depressive symptoms than either their male counterparts or girls without autism. In a statistical analysis by Stacy et al. [29], the rates of mild and moderate/severe depression in girls with autism were estimated at 7.2% and 3.6%, respectively, while boys with autism experience these conditions at rates of 4.5% and 7.8%. These findings not only emphasize the occurrence of depression among individuals with autism but also highlight sex differences in its prevalence, suggesting that males tend to experience more severe forms of depression.

# **Epilepsy**

Epilepsy, a neurological condition characterized by recurrent seizures, affects approximately 1.2% of the general population [30]. A comprehensive meta-analysis conducted by Liu et al. [31] revealed a disparity in the prevalence of epilepsy between children (7%) and adults (19%) with autism. In a pooled analysis of 14 studies, females with autism were found to have a higher prevalence of epilepsy at 34.5%, compared to 18.5% in males [32]. Furthermore, Amiet et al. [32] observed that the incidence of epilepsy is positively correlated with the severity of intellectual disability, suggesting that an increase in cognitive impairment is associated with a heightened risk of epilepsy.

### Intellectual disability

Intellectual disability is a lifelong condition characterized by below-average cognitive functioning. A systematic review conducted in 2016 examined the prevalence and incidence of intellectual disabilities, yielding prevalence estimates ranging from 0.05% to 1.55% [33]. Among six studies that compared sex differences, five reported higher rates of intellectual disability in males [33]. Intellectual disability is also a common comorbid condition in children with autism, with an estimated prevalence of 21.7% [9]. Among individuals with autism, the male-to-female ratio of comorbid intellectual disability was 1.9:1 [34]. In a meta-analysis, Saure et al. [35] found that intellectual disability tends to exacerbate the severity of autism symptoms more in females than in males. These findings indicate that phenotypic differences in autism may be influenced by the level of cognitive functioning.

## Tic disorders

Tic disorders are characterized by sudden, rapid motor movements or vocal outbursts and are estimated to affect between 5 and 6 per 1,000 school-aged children [36]. Among individuals with autism, tic disorders are a common comorbidity, affecting approximately 18% to 22% [37, 38]. Generally, females with tic disorders are diagnosed less frequently than males and typically report a later age of symptom onset [39]. Kim et al. [38] found no significant sex differences between a group of individuals with autism alone and one with both autism and tic disorders, based on parental reports. However, further research is warranted. Studies that

utilize clinician assessments to evaluate the type and severity of tics by sex could provide a deeper understanding of their manifestation in individuals with autism.

### Potential factors contributing to sex differences in prevalence

The exploration of sex-based differences in the prevalence of comorbid conditions among individuals with autism is complex. It involves diagnostic and reporting biases, sex-specific symptom presentations, biological factors, and distinct patterns of comorbidity. In the present exploration of current research, we aim to provide a thorough understanding of these contributing factors.

### Measurement bias

Concerns have arisen regarding the measurement tools used in autism diagnosis, which are often developed with a male-centric bias due to the disproportionate representation of the sexes. This bias toward the male autism phenotype may result in the misclassification of female patients. In an investigation of potential sex biases in widely used diagnostic instruments, Belcher et al. [40] conducted a confirmatory factor analysis on the Autism Spectrum Quotient using data from a large UK adult cohort. Their findings revealed that all but two items showed sex biases, notably indicating that women were more likely than men to endorse items related to social skills and communication. Similarly, Kalb et al. [41] examined the Autism Diagnostic Observation Schedule-2 via differential item functioning (DIF) analysis and identified five items with significant DIF. This suggests that these items function differently for males and females, potentially impacting diagnostic accuracy [42]. Furthermore, there is a clear deficiency in accurate and reliable tools for assessing the wide range of psychiatric comorbid conditions in individuals with autism. Although efforts have been made to validate modified screening tools for psychopathology in children and adolescents with autism, research specifically addressing sex differences remains scarce.

### Compensatory behaviors

The term "camouflaging" refers to the use of compensatory behaviors or coping strategies by individuals

with autism to mask their autistic traits and conform to social norms. These methods often involve mimicking the behaviors and interests of others or deliberately making eye contact. Camouflaging is commonly reported among females and is considered a key reason why this demographic is often overlooked. Such masking strategies contribute to a higher likelihood of misdiagnosis in females with autism compared to their male counterparts [43]. In their research, Cage and Troxell-Whitman [44] underscore the critical need for clinicians to recognize the impact of camouflaging. Acknowledging these behaviors is essential for improving the well-being of individuals with autism, especially when addressing comorbid mental health conditions.

### Different trajectories of comorbid conditions

Considering an individual's age and developmental stage is crucial when examining psychiatric conditions. It is well-established that certain internalizing and externalizing disorders manifest at different times, often influenced by sex-specific developmental trajectories. For example, in the general population, boys are more likely to experience externalizing problems, such as aggression, hyperactivity, and conduct problems, and these patterns tend to remain stable across adolescence [45]. Conversely, males have a lower risk of internalizing problems, such as mood and anxiety issues [46], with the onset of such conditions typically occurring at a later age compared to females. Therefore, the inherent characteristics of these comorbid conditions may meaningfully impact the observed sex differences in individuals with autism.

### **Implications**

In the context of autism, understanding sex-based differences in prevalence is critical, as it can lead to the creation of more sensitive screening and diagnostic tools, as well as the development of therapeutic plans tailored to individual needs.

#### Sensitive measurement tools

Early and accurate identification of autism is crucial for improving outcomes in young children. However, research has shown that girls are consistently diagnosed later than boys, highlighting the need for diagnostic tools that are sensitive to sex differences. Additionally, females with autism often have a higher incidence of

comorbid conditions compared to males [14], including internalizing behaviors that result in anxiety, depression, and social withdrawal [47]. The overlap between these psychiatric comorbidities and the core features of autism can complicate the diagnostic process, potentially leading to delayed diagnoses in female patients.

## Sex-specific intervention planning

Creating a sex-specific intervention strategy for autism requires a nuanced understanding of the ways in which the condition presents in females versus males. Females with autism often demonstrate better communication and social interaction skills and exhibit fewer RRBs than their male counterparts. The use of compensatory mechanisms, such as masking, may further complicate the development of effective intervention strategies, as these behaviors can conceal the true extent of the challenges these individuals face. For females with autism, creating a sex-specific intervention strategy could involve focusing on the management of psychiatric comorbidities through a combination of various therapies and self-advocacy education. By customizing interventions to address both shared characteristics and sex-specific differences in autism, we can improve support for individuals, helping them to realize their full potential.

## Conclusion

This review examines the prevalence of various comorbid conditions among males and females with autism. The current body of research on comorbidities is mixed, with some studies finding no significant differences between sexes and others reporting certain conditions as more common in one sex. These inconsistencies may stem from differences in measurement tools, masking behaviors that complicate diagnosis, and the age of study participants. The recognition of distinct patterns of comorbidity could indicate the presence of subgroups within the autism spectrum. Consequently, longitudinal studies with larger sample sizes are required to explore comorbid conditions from a life-course perspective, considering the developmental trajectories of both sexes. Given our preliminary findings on the differences in the prevalence of common comorbid conditions among individuals with autism, it is imperative that future research expand upon this

work by examining potential sex differences in their manifestation. A deeper understanding of these patterns could support earlier autism diagnosis and improve access to care, enabling the creation of more personalized

intervention plans that improve quality of life for those on the autism spectrum.

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**Conflict of interest** 

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