

# Anxiety and Mood Disorder in Children With Autism Spectrum Disorder and ADHD

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abstract

**OBJECTIVES:** Autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD) frequently co-occur. Understanding the endophenotype of children with both ASD and ADHD may impact clinical management. In this study, we compare the comorbidity of anxiety and mood disorders in children with ASD, with and without ADHD.

**METHODS:** We performed a cross-sectional study of children with ASD who were enrolled in the Interactive Autism Network, an Internet-mediated, parent-report, autism research registry. Children ages 6 to 17 years with a parent-reported, professional, and questionnaire-verified diagnosis of ASD were included. Data were extracted regarding parent-reported diagnosis and/or treatment of ADHD, anxiety disorder, and mood disorder. ASD severity was measured by using Social Responsiveness Scale total raw scores.

**RESULTS:** There were 3319 children who met inclusion criteria. Of these, 1503 (45.3%) had ADHD. Comorbid ADHD increased with age ( $P < .001$ ) and was associated with increased ASD severity ( $P < .001$ ). A generalized linear model revealed that children with ASD and ADHD had an increased risk of anxiety disorder (adjusted relative risk 2.20; 95% confidence interval 1.97–2.46) and mood disorder (adjusted relative risk 2.72; 95% confidence interval 2.28–3.24) compared with children with ASD alone. Increasing age was the most significant contributor to the presence of anxiety disorder and mood disorder.

**CONCLUSIONS:** Co-occurrence of ADHD is common in children with ASD. Children with both ASD and ADHD have an increased risk of anxiety and mood disorders. Physicians who care for children with ASD should be aware of the coexistence of these treatable conditions.

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**WHAT'S KNOWN ON THIS SUBJECT:** Autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD) frequently co-occur. Recently, researchers have explored the endophenotype of individuals with both ASD and ADHD. Whether these individuals are more prone to other psychiatric comorbidities than those with ASD alone is unknown.

**WHAT THIS STUDY ADDS:** We report that children with both ASD and ADHD have higher ASD severity scores and have an increased risk for anxiety and mood disorders when compared with children with ASD alone.

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Autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD) are neurodevelopmental disorders that begin during childhood with long-term clinical and social implications for affected individuals, their families, and the community. According to the most recent data, ASD affects ~1 in 68 children,<sup>1</sup> and ADHD affects ~1 in 10 children in the United States.<sup>2</sup> It has long been recognized that these disorders may have overlapping features and often occur together.<sup>3</sup> Before 2013, research on these 2 disorders was primarily focused on the comparison of the behavioral and psychological profiles of the 2 disorders individually.<sup>3</sup> However, with the new *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*, ASD and ADHD can be diagnosed as co-occurring disorders. There has subsequently been increased interest in understanding the etiology and clinical implications of their co-occurrence.<sup>4,5</sup>

There is evidence that together, ASD and ADHD may negatively impact behavioral development,<sup>6–8</sup> attentional performance,<sup>9</sup> adaptive behavior, and sleep.<sup>10,11</sup> Psychiatric comorbidities, including anxiety and mood disorders, are also common in both ASD and ADHD independently.<sup>5,12–15</sup> Up to 70% of children with ASD may be affected by other psychiatric disorders.<sup>14,15</sup> Of those with ASD who have 1 comorbidity, 45% had > 2. Similarly, 1 study of ADHD revealed that 52% of individuals had at least 1 comorbid psychiatric disorder, and 26% had 2 or more.<sup>13</sup> Given that both ASD and ADHD each have an increased risk of comorbidities (and that the co-occurrence of these disorders has negative developmental, cognitive, behavioral, and functional implications), it follows that ASD and ADHD co-occurrence may compound the risk of further comorbidity. However, to our knowledge, whether individuals with both ASD and ADHD

are more prone to other psychiatric comorbidities than those with ASD alone has not yet been studied. The identification of treatable psychiatric comorbidities in this population is important because they may impact therapeutic interventions,<sup>16</sup> short- and long-term outcomes, and quality of life.<sup>17</sup> Our objective in this study was to compare children with ASD with and without ADHD by the prevalence of comorbidity and clinical characteristics. We hypothesized that children with both ASD and ADHD have an increased prevalence of other psychiatric comorbidities. The primary outcome measures were professional diagnoses or treatment of anxiety disorder and mood disorder by parental report. Secondary outcome measures were population demographics, report of intellectual disability (ID), and ASD severity score by standardized questionnaire.

## METHODS

This study was approved by the Johns Hopkins University Institutional Review Board.

### Participants

We performed a cross-sectional, network-based study of children with ASD who were enrolled in the Interactive Autism Network, referred to as IAN, between 2006 and 2013. IAN is a family-centered, online registry and research database that was created to accelerate ASD research by linking participants with studies and by sharing deidentified data for analysis.<sup>18</sup> Children and adults with ASD may register for IAN along with parents and siblings. To register with IAN, participant probands must have a professional diagnosis of ASD. Approximately 60 000 people have consented to participate, including >18 500 children and 7500 adults with ASD. Children with ASD are 80% boys with an ethnic and racial profile of

~80% white, 4% African American, 2% Asian American, and 10% Hispanic. Parents are primarily college educated (85%). IAN content is in English only. Every state in the United States is represented. IAN has provided recruitment and data services for >500 studies. The IAN registry has been clinically validated for children with a Social Communication Questionnaire-Lifetime (SCQ-Lifetime) total score cutoff of 12,<sup>19–21</sup> and it has been verified by a review of parent- and professional-provided medical records.<sup>22</sup>

We included individuals in the IAN registry ages 6 to 17 years who had completed the IAN Child with Autism Spectrum Disorder Questionnaire (CAQ) (a baseline questionnaire with demographic and core clinical information), had a total score  $\geq 12$  on the SCQ-Lifetime,<sup>20</sup> and had a total T-score  $\geq 60$  on the Social Responsiveness Scale (SRS)-Parent Report<sup>23</sup> with no more than 6 missing responses. Children outside of the age range and/or with incomplete questionnaires and/or with reported diagnosis of schizophrenia were excluded.

### Measures

#### IAN CAQ

The CAQ is a baseline questionnaire for children with ASD that asks parents questions about their children's birth, ASD diagnosis, development, and additional medical history.

Parent report of additional diagnoses was obtained from the following questions on the CAQ: "Has [child name] ever been diagnosed with or received treatment for \_\_\_?" Options included depression, bipolar disorder, ADHD, and anxiety disorder. In this study, parent-reported mood disorder was defined as a positive response to the above question for depression and/or a positive response to the above question for bipolar disorder.

ID was defined as a positive response to the question, “Has [child name] ever been diagnosed with intellectual disability (also known as mental retardation)?” and/or an IQ score <70 on the question, “What was [child name]’s most recent IQ test score?”

For the purposes of this study, children with autism spectrum disorder with parent-reported attention-deficit/hyperactivity disorder are referred to as ASD (+) ADHD, and children with autism spectrum disorder without parent-reported attention-deficit/hyperactivity disorder are referred to as ASD (–) ADHD.

Age was calculated by using the date of birth and the date on which the CAQ was completed.

### The SCQ-Lifetime

The SCQ-Lifetime is a 40-item, parent-report questionnaire that is designed as a screening test for ASD.<sup>20</sup> It is validated for ages 4 years and older. Scores range from 0 to 39 with a cutoff of 15 for ASD in a general population, and a cutoff as low as 11 is recommended for a high-risk population to optimize the area under the curve.<sup>24</sup> In this study, we used a cutoff of 12 as 1 of several inclusion criteria in the IAN registry per the manual’s recommendation to use a lower threshold if there are additional risk factors<sup>20</sup> because registrants of the IAN are considered high risk for ASD given that they have received a professional diagnosis of ASD per parent report. In the IAN registry, the SCQ-Lifetime total score cutoff of 12 has been validated against the Autism Diagnostic Interview with 99% accuracy.<sup>19</sup>

### The SRS-Parent Report

The SRS-Parent Report consists of 65 items and is designed to identify the presence and severity of social impairment in ASD.<sup>23</sup> The questionnaire is validated in ages 4 to 18 years. Scores range from 0 to

**TABLE 1** Subject Characteristics and Differences by the Presence or Absence of Comorbid ADHD

Variable	Total ASD (n = 3319)	ASD (–) ADHD (n = 1816; 54.7%)	ASD (+) ADHD (n = 1503; 45.3%)	P	Effect Size
Demographic data					
Age, y, mean (SD)	10.3 (3.08)	9.9 (3.06)	10.8 (3.0)	<.001	0.30 <sup>a</sup>
Boys, No. (%)	2753 (83.0)	1481 (81.6)	1272 (84.6)	.019	0.04 <sup>b</sup>
White race, No. (%)	2894 (87.2)	1574 (86.7)	1320 (87.8)	.348	NA
Hispanic race and/or ethnicity, No. (%)	254 (7.7)	150 (8.3)	104 (6.9)	.150	NA
Phenotypic data					
ID, No. (%)	649 (19.6)	381 (21.0)	268 (17.8)	.023	0.04 <sup>b</sup>
SRS total raw score, mean (SD)	112.60 (26.10)	110.04 (26.22)	115.70 (25.63)	<.001	0.22 <sup>a</sup>
Psychiatric comorbidities, No. (%)					
Anxiety disorder	1025 (30.9)	345 (19.0)	680 (45.2)	<.001	0.28 <sup>b</sup>
Mood disorder	532 (16.0)	146 (8.0)	386 (25.7)	<.001	0.24 <sup>b</sup>

NA, not applicable.

<sup>a</sup> Cohen’s *d*.

<sup>b</sup> Phi.

145, and T-scores are standardized for sex. A T-score on the SRS-Parent Report  $\geq 60$  is considered abnormal and associated with ASD. The SRS has strong psychometric properties, including an interrater reliability of 0.9 between parents, an internal consistency of >0.9, and discriminant validity between other developmental behavioral disorders, including ADHD, mood disorders, conduct disorder, and psychosis.<sup>23,25</sup> It has been validated against clinical evaluation and the Autism Diagnostic Interview with a sensitivity of 0.75 and a specificity of 0.96.<sup>24,26</sup>

### Data Management and Analysis

Detailed methodology regarding data management and data analysis may be found in the Supplemental Information.

### RESULTS

There were 3319 children who met inclusion criteria for this study, of whom 1503 (45.3%) reported a diagnosis of or treatment for ADHD. Demographics, the prevalence of parent-reported ID, mean SRS-Parent Report total raw scores, and the presence of comorbid parent-reported anxiety disorder

and mood disorder for the entire cohort are presented in Table 1 in addition to a comparison between the ASD (+) ADHD and ASD (–) ADHD groups. Survey completion was near contemporaneous, with 92.2% completing both the CAQ and the SRS within 1 calendar year and 96.5% within 2 calendar years. The cohort was primarily male (82.9%), white (87.2%), and non-Hispanic (92.4%), with a mean age of 10.3 years. Of the children, 649 (19.6%) were reported to have ID, 1025 (30.8%) were reported to have a diagnosis of or treatment for an anxiety disorder, and 532 (16.0%) were reported to have a diagnosis of or treatment for a mood disorder. A statistically significant difference in the sex proportion and prevalence of parent-reported ID was found when comparing the ASD (+) ADHD and ASD (–) ADHD groups. The ASD (+) ADHD group was older than the ASD (–) ADHD group and had higher ASD severity per the SRS-Parent Report total raw score. We found no significant difference in either race or ethnicity between the groups.

In Table 2, we provide the results of generalized linear model (GLM)<sup>27</sup> analyses in which we compare

**TABLE 2** Rates and Relative Risks of Psychiatric Conditions in Children With ASD: A Comparison of Those With to Those Without ADHD

	Age 6–11 y			Age 12–17 y			All		
	ASD (–) ADHD, Reference ( <i>n</i> = 1381), <i>n</i> (%)	ASD (+) ADHD ( <i>n</i> = 973), <i>n</i> (%)	Adjusted Risk Ratio <sup>a</sup> <i>n</i> (95% CI)	ASD (–) ADHD, Reference ( <i>n</i> = 435), <i>n</i> (%)	ASD (+) ADHD ( <i>n</i> = 530), <i>n</i> (%)	Adjusted Risk Ratio <sup>a</sup> <i>n</i> (95% CI)	ASD (–) ADHD, Reference ( <i>n</i> = 1816), <i>n</i> (%)	ASD (+) ADHD ( <i>n</i> = 1503), <i>n</i> (%)	Adjusted Risk Ratio <sup>a</sup> <i>n</i> (95% CI)
Anxiety disorder	205 (14.8)	400 (41.1)	2.65 (2.26–3.05)	140 (32.2)	280 (52.8)	1.65 (1.41–1.94)	345 (19.0)	680 (45.2)	2.20 (1.97–2.46)
Mood disorder	64 (4.6)	184 (18.9)	3.59 (2.73–4.73)	82 (18.9)	202 (38.1)	2.00 (1.60–2.49)	146 (8.0)	386 (25.7)	2.72 (2.28–3.24)

<sup>a</sup> GLM analysis by using ASD without ADHD as reference and adjusted for sex (male or female), ethnicity (Hispanic or non-Hispanic), race (white or people of color), age (continuous), and the presence of ID (yes or no).

the presence of anxiety or mood disorders with the presence or absence of ADHD. The ASD (+) ADHD group had an increased risk of reported anxiety disorder (adjusted relative risk 2.20; 95% confidence interval [CI] 1.97–2.46) and mood disorder (adjusted relative risk 2.72; 95% CI 2.28–3.24) compared with the ASD (–) ADHD group. Increasing age was the most significant contributor for both anxiety disorder and mood disorder (both  $P < .001$ ), and the absence of report of ID was a significant contributor for mood disorder only ( $P < .001$ ). Given the association between increasing age and parent-reported ADHD, we also analyzed relative risks by age subgroups (school-aged and adolescent) to better appreciate a clinical practice perspective. As expected, we found an increased prevalence of both anxiety disorder and mood disorder in the adolescent group compared with the school-aged group for both the ASD (+) ADHD and ASD (–) ADHD groups; however, there were higher relative risk ratios for the school-aged group compared with the adolescent group for both anxiety disorder and mood disorder. Within the age subgroups, we also found the same pattern as in the full data set that increasing age was the most significant contributor to the presence of both anxiety and mood disorders (for both age groups and both conditions:  $P < .001$ ), and absence of report of ID was a significant contributor for mood

disorder only (school-aged:  $P = .041$ ; adolescent:  $P = .001$ ). Neither sex, nor race, nor ethnicity were significant in any of the GLM analyses.

## DISCUSSION

To our knowledge, this is the largest study in which researchers compare comorbidities in individuals with ASD alone and ASD with ADHD. It is also 1 of the largest in which researchers compare the clinical phenotypes of these populations. We found an extremely high prevalence of parent-reported ADHD among children with ASD, with ADHD affecting 45.2% of the children, which is commensurate with previous studies that reveal a 31% to 95% co-occurrence.<sup>28–31</sup> Previous studies reveal that there may be a genetic or symptom overlap of these disorders.<sup>3,32</sup> Nonetheless, this should not invalidate either diagnosis, especially when diagnosis-specific treatments are available.

Our primary study findings were that children with both ASD and ADHD are at an increased risk for being diagnosed with or treated for anxiety and mood disorders when compared with those with ASD alone. These are supported by a 2011 study of adolescents in special education that revealed increased rates of antidepressant and/or anti-anxiety medication use among children with ASD and ADHD in comparison with ASD only.<sup>33</sup> Furthermore, the prevalence of reported anxiety and mood disorders increases with age,

independent of ADHD, which is unsurprising given that the CAQ asks if a child has ever been diagnosed with these conditions, leading to an inevitable cumulative diagnosis with time. Additionally, both groups follow the same trajectory as typically developing peers in that the onset of symptoms consistent with mood and anxiety disorders is most often seen in adolescence, which may explain the higher prevalence of these disorders in the older cohort. In contrast, the relative risks of anxiety and mood disorders are greater in the younger, school-aged children than in the older adolescents for those with ADHD compared with those without ADHD. This suggests that ADHD may make children with ASD more vulnerable to an earlier onset of the symptoms of anxiety or mood disorders or more likely to exhibit detectable symptoms at an earlier age.

The specific etiology behind the relationships among these conditions is unclear at this time. It is possible that there is a genetic basis for an increased risk of multiple psychiatric disorders, as has been found with ASD and ADHD.<sup>32</sup> Alternatively, it is possible that 1 syndrome is an early manifestation of the other, or the development of 1 syndrome increases the risk for the other. One may also consider that children with ADHD and ASD are at an increased risk for behavioral problems,<sup>8,10</sup> and these behaviors may contribute to anxiety or mood symptoms. This may

also contribute to the differences in SRS scores between the groups, which is discussed below.

Referral bias may explain an increased risk for reported anxiety and mood disorders in children with ASD and ADHD in comparison with ASD alone because practitioners who diagnose ADHD may be more likely to also diagnose anxiety or mood disorders. However, this question was addressed in a previous study of the IAN registry,<sup>12</sup> in which children with both ASD and ADHD were less likely to have a third diagnosis than to not (odds ratio 0.1, 95% CI 0.1–0.2), implying that referral bias is unlikely in this sample. Registration bias may also influence the findings if parents of children with multiple comorbidities are more likely to participate in IAN.

Evolving diagnostic criteria may also influence population-based studies. The *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*, has broadened the construct of autism toward a spectrum and narrowed the diagnostic criteria for ASD, although the definitions of ADHD and mood disorders are similar to those outlined in the previous edition. The evolution of definitions and allowing the coexistence of multiple psychiatric diagnoses acknowledges and may affect medical recognition and treatment. The high rates of comorbidity in this study may thus reflect changing practice with the evolution of the *Diagnostic and Statistical Manual of Mental Disorders*.

Pharmacotherapy may also contribute to our findings because ADHD, anxiety, and mood disorders all have treatments that are widely available and increasingly used in practice.<sup>34</sup> Notably, IAN asks whether a child has ever been diagnosed with or treated for these comorbidities, acknowledging that with the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, many children with ASD

were not assigned a diagnosis because symptoms may overlap but were prescribed medication for hyperactivity, anxiety, or mood symptoms in the absence of a formal diagnosis. With this in mind, our rates of ADHD, anxiety, and mood disorders may reflect the rate of symptoms that are consistent with these disorders rather than formal diagnosis. Frequently still, diagnoses are not used until intervention is needed, which suggests that our sample may be underidentifying these comorbidities if the children are not being medically treated.

Recognizing the increased risk for psychiatric disorders in this population has implications for clinical practice. This may be challenging in ASD because symptoms of anxiety and mood disorders may present differently in these children than in typically developing children. Unfortunately, information regarding how anxiety and mood disorders were diagnosed and/or treated was not available for this study. Further research is needed to better understand how mood and anxiety disorders present in both ASD and ADHD populations to optimally assess and diagnose these disorders. Importantly, both anxiety and mood disorder symptoms are treatable medical conditions through psychotherapy<sup>35</sup> and medication.<sup>36</sup> Recognizing and treating the symptoms can impact quality of life<sup>37</sup> and improve other short- and long-term outcomes, with further knowledge also being needed about effective, evidence-based treatments for these comorbidities in ASD.

We found that the presence of ADHD has a small association with greater ASD symptom severity, as reflected in the SRS score, suggesting that children with increased ASD severity are either more likely to be diagnosed with ADHD, or a dual diagnosis of ASD and ADHD impacts ASD symptoms. Researchers in another study found similarly that

children with ASD and ADHD have SRS scores ~3 points higher than children with ASD who do not have ADHD.<sup>38</sup> There is also evidence suggesting that children with ADHD alone may have higher SRS scores than the normative population,<sup>39</sup> suggesting that a behavioral overlap between ASD and other psychiatric disorders exists. The clinical implication of a small increase in ASD symptom severity in children with both ASD and ADHD is unclear. Six points on the SRS may not translate to appreciable differences in an individual child's outcome, but such a difference may have a broader social or economic impact among this population. It is possible that the SRS is not an adequately sensitive or specific tool to assess ASD function in this setting, and additional studies of ASD symptomatology in the context of ADHD are needed.

We also found a difference in the rates of ID among those children with ASD with and without ADHD. In our cohort, those with ADHD had slightly lower rates of ID. It may be that ADHD symptoms are more easily or frequently detected in children with normal intellect or that the genetic phenotype associated with ASD and ADHD is also associated with normal intellect. Differential rates of ID among those children with ASD with and without ADHD may also be a function of diagnostic overshadowing (eg, ascribing inattention and/or impulsivity to ID rather than ADHD). Researchers in future studies examining this question may help clarify whether this association is replicable and what its clinical implications may be.

The diagnosis of ASD has been validated in the IAN database with 98% accuracy,<sup>19,21</sup> but similar data are not available for the other diagnoses in this study. Although performing standardized, comprehensive psychiatric assessment is the gold standard for diagnosis, participant report

is efficient in sampling a large population, with data for other diagnoses supporting that such report is valid with equal accuracy (S. Terry, MA, personal communication, 2017).<sup>40</sup> Furthermore, the parent-reported diagnoses in this study are supported by similar rates of comorbidity with ASD in large epidemiologic studies.<sup>28,30,31,33,41–43</sup> However, we do acknowledge that participant-reported data may be susceptible to recall or reporting bias. Self- and parent-report data have also demonstrated statistical validity in the social sciences<sup>44</sup> and is frequently relied on for the diagnosis of ADHD<sup>45</sup> and anxiety disorders.<sup>46</sup> Furthermore, there is similar precedent for the use of parent-reported diagnoses in other large epidemiologic studies of children, such as the National Health Interview Survey,<sup>47–49</sup> in which the language is identical to that used in the IAN questionnaire. Incorporating psychiatric diagnostic questionnaires may help validate this report in the future.

Both ADHD and ID may be underreported in this cohort, as is seen with chronic health conditions.<sup>48</sup> For ID specifically, parents may be underinformed or misinformed of their children's intellectual skills. We further acknowledge that our definition of ID (parent report or IQ <70) does not conform to the current *Diagnostic and Statistical Manual of Mental Disorders* definition because it does not incorporate adaptive functioning.

This study represents a cross-sectional sample of lifetime

information, and we did not assess individuals longitudinally. Therefore, our trends in age groups are based on prevalence rather than incidence. Longitudinal data may help clarify the relationships between these conditions and age.

Because computer and Internet access are required to complete the IAN questionnaires, there is bias toward participants of higher socioeconomic status.<sup>50</sup> We have assumed that this bias is constant throughout the sample, although this sample is not precisely representative of the general population.

### CONCLUSIONS

ADHD affects nearly half of the children with ASD. This subgroup of individuals with ASD may represent a distinct clinical phenotype, with different diagnostic and therapeutic implications. Better understanding the differences between children with ASD with and without ADHD is crucial to designing effective interventions.

Our study supports that anxiety and mood disorders, although highly prevalent in those with ASD alone, are even more prevalent in individuals who have ADHD. They are also more prevalent with increasing age. The identification of psychiatric conditions in children with ASD is important because these disorders are treatable and affect quality of life. Physicians who treat children with ASD should be vigilant about screening for anxiety and mood

symptoms, particularly in those with ADHD.

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### ABBREVIATIONS

ADHD:	attention-deficit/hyperactivity disorder
ASD:	autism spectrum disorder
ASD (–) ADHD:	children with autism spectrum disorder without parent-reported attention-deficit/hyperactivity disorder
ASD (+) ADHD:	children with autism spectrum disorder with parent-reported attention-deficit/hyperactivity disorder
CAQ:	Child with Autism Spectrum Disorder Questionnaire
CI:	confidence interval
GLM:	generalized linear model
IAN:	Interactive Autism Network
ID:	intellectual disability
SCQ-Lifetime:	Social Communication Questionnaire-Lifetime
SRS:	Social Responsiveness Scale

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