Identifying Associations Among Co-Occurring Medical Conditions in Children With Autism Spectrum Disorders

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Abstract

Objective: Children with autism spectrum disorder (ASD) have a high prevalence of co-occurring medical conditions, including speech, sleep, and gastrointestinal disorders (constipation and feeding difficulties); developmental delay; attention deficit/hyperactivity disorder; hypotonia; epilepsy; anxiety; disruptive behavior; pica; and eczema. Less is known about whether these commonly coexist in the same children. We sought to determine clinically meaningful, statistically significant associations among co-occurring medical conditions in children with ASD that could lead to better understanding, identification, and treatment of these disorders.

Methods: We studied 2114 children with ASD aged 17 months to 5 years and 1221 children aged 6 to 17 years at 15 Autism Speaks Autism Treatment Network Registry sites. Clinician-reported diagnoses and problems were grouped into 12 core conditions. We determined the observed prevalence (O) of co-occurring conditions and the estimated expected prevalence (E) across the network, adjusting for site variability in the prevalence of individual conditions. *P* values were calculated using a Cochran–Mantel–Haenszel test stratified by site. We identified pairs of conditions co-occurring more frequently than expected (O/E >1) and less frequently than expected (O/E <1) and highlighted statistically significant differences.

Results: Among the 66 condition pairs for each age group, we confirmed previously identified associations, such as sleep disorders and anxiety symptoms, in older children. We found some associations not previously described, including feeding with sleep disorders (younger children only), constipation with sleep disorders, feeding with speech disorders, and constipation with speech disorders.

Conclusions: We have identified new associations among co-occurring medical conditions in children with ASD, offering the potential to examine common pathways.

Keywords: autism spectrum disorder; children; medical conditions

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What's New

Children with autism spectrum disorder have a high prevalence of co-occurring medical conditions. This study shows some new associations, including feeding and constipation with speech disorders, and feeding (younger children) and constipation (all ages) with sleep disorders.

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by impairments in social interaction and communication and atypical, restricted, and repetitive patterns of behavior. The prevalence of ASD is now reported to be 1 in 68 children in the United States.[1] Compared with their neurotypical peers, children with ASD have higher prevalences of a variety of co-occurring medical conditions, including seizures,[2] sleep disturbances,[3,4] gastrointestinal (GI) conditions,[5] and behavioral/psychiatric conditions.[6] Previous studies have demonstrated varied associations between co-occurring conditions and developmental status, including language/communication abilities.[7,8] In children with ASD, lower scores on cognitive (verbal and nonverbal intelligence quotient) and expressive language measures

have been correlated with increased disruptive behaviors, such as aggression.[9] This finding is consistent with research in general pediatric populations indicating that lower language levels predict later disruptive behavior conditions.[10] In children with ASD, both food selectivity and sleep conditions have been associated with lower adaptive skills in multiple domains (communication, daily living skills, socialization, and motor skills), but not with lower developmental/intelligence quotient scores.[11]

Previous studies have shown associations of a number of these co-occurring conditions with each other.[12–14] Sleep disorders, common in children with ASD, are associated with increased anxiety and sensory overresponsivity,[15] aggression,[6] self-injury,[16] and difficulties with regulation and behavior.[17] Constipation, another common co-occurring condition, has been associated with an increased prevalence of maladaptive behaviors, including elevated scores on 4 of 5 subscales of the Aberrant Behavior Checklist: irritability, social withdrawal, stereotypy, and hyperactivity.[18] Similarly, chronic abdominal pain, which occurs in one quarter of children with ASD, has been positively associated with anxiety and sensory overresponsivity, with the presence of sensory overresponsivity, predicting the new onset of abdominal pain in a cohort of children with ASD.[19]

Despite the known associations of co-occurring conditions in children with ASD, the etiology of their associations remains obscure in most cases. Ascertainment of additional associations could provide some insight into common mechanisms or etiology. Based on our review of the literature of prevalent co-occurring conditions that have the potential to negatively impact the day-to-day functioning and quality of life of children with ASD and the concerns of the families involved with our clinical sites, we focused our analysis on sleep conditions, GI and feeding/eating concerns, and behavioral symptoms, such as anxiety and repetitive behaviors. Given that some of these associations have previously been described in the literature,[12–14] we sought to both confirm previous findings and to identify potential associations among other conditions, such as neurologic conditions (eg, epilepsy, hypotonia) and developmental disorders (eg, speech disorders, language delay, intellectual disability). Whereas neurologic conditions, such as epilepsy, are common in ASD (epilepsy frequency ranging from 6%–27%), many unanswered questions remain about the biological basis for this relationship and its association with intellectual disability.[20] We took advantage of the very large numbers of children in the Autism Treatment Network (ATN) data registry, with extensive clinician data, to use statistical strategies in a novel application to seek unexpected relationships that might not be apparent from previous studies that could lead to clinically relevant information and go beyond the current understanding of physical health conditions in this population. We sought to address the following main research question: are there clinically meaningful and statistically significant associations between co-occurring medical conditions in children with ASD?

METHODS

SUBJECTS

All subjects came from the Autism Speaks ATN Registry, a multisite database including diagnostic, medical, behavioral, and quality of life data in children with ASD.[21] The ATN sites represent a network of academic-affiliated children's hospitals with autism centers of excellence, committed to a comprehensive evaluation and care program for children and youth with ASD. Thus, participants represent children who receive care in high-quality care programs and might not be representative of all children with ASD. The ATN Registry has been described in detail previously[21,22] and is briefly summarized here. The registry includes cross-sectional and longitudinal data for a subset of patients with ASD receiving care at a network clinical center. Site patients who were age <17.5 years and met diagnostic cutoffs for ASD as determined by the Autism Diagnostic Observation Schedule (ADOS/ADOS-2) and *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria were eligible for enrollment. Exclusion criteria included a medical condition precluding valid testing (eg, blindness). Parents or guardians had to be fluent in English or Spanish and speak English or Spanish ≥75% of the time with the child at home. Data were collected by clinical assessment and parent report at the initial visit and annually as part of routine clinical care visits. This study received Institutional Review Board approval. For this cross-sectional study, we included only data collected at the initial visit from children for whom the clinician-reported child diagnoses and problems form was included in the registry in its current form (instituted 2011), leaving 3335 (48%) of the >7000 subjects in the registry. For each analysis, subjects were split into 2 age groups (<6 years and ≥6 years).

VARIABLES

Disorders were defined by the clinicians at the initial visit for the ATN registry. Clinicians were asked to "[check] any additional diagnoses or conditions observed today whether or not they are being managed by an ATN [Autism Treatment Network] clinician." There were 18 specific diagnoses or conditions that could be reported by clinicians. We reduced this to 12 conditions by combining several related sleep diagnoses, several related speech diagnoses, and the 2 attention deficit/hyperactivity disorder (ADHD) diagnostic categories. Table 1 presents these disorders, listing the specific conditions, groups of conditions, and overall prevalence of each condition across the network by age group.

STATISTICAL ANALYSIS

We determined the prevalence of each condition by age and site and the prevalence of each possible pair

Table 1. Prevalence of Clinician-Identified Diagnoses

Diagnosis	Age <6 Years (N = 2114), % (n)	Age ≥6 Years (N = 1221), % (n)
Speech*	50.1 (1059)	27.4 (335)
Delay in development, unspecified	23.7 (500)	11.5 (141)
ADHD†	6.4 (135)	34.5 (421)
Hypotonia	14.5 (306)	11.0 (134)
Seizure disorder	2.5 (53)	3.4 (42)
Sleep‡	26.8 (567)	24.3 (297)
Anxiety NOS	2.8 (59)	19.7 (241)
Disruptive behavior disorder NOS	2.4 (50)	6.1 (74)
Constipation	12.8 (270)	15.2 (186)
Feeding difficulty	14.9 (316)	8.8 (108)
Pica	3.0 (64)	2.4 (29)
Eczema	5.2 (109)	5.2 (63)

ADHD indicates attention deficit/hyperactivity disorder; NOS, not otherwise specified.

*Speech includes expressive language disorder, mixed receptive-expressive language disorder, and speech delay.

†ADHD includes ADHD NOS and attention deficit disorder with hyperactivity.

‡Sleep includes sleep disturbance NOS, insomnia (organic unspecified), inadequate sleep hygiene, and behavioral insomnia of childhood.

of conditions. A pair of interest is a pair of conditions for which the occurrence of the 2 together is either greater than or less than what would be expected from the individual prevalence of each condition. We found substantial site-to-site variability in the prevalences of the conditions. As shown in the hypothetical example in the Supplementary Material, it is important to take this variability into account, so the expected prevalence (E) of the pair of conditions is calculated based on the prevalence at each site. We then estimated the degree to which the observed prevalence (O) deviated from the expected prevalence (E) and used the O/E ratio to summarize the relationship between conditions. The O/E ratio is similar to a standardized morbidity ratio in the epidemiologic literature.

We used an O/E ratio rather than relative risk for 2 reasons. First, it reduces the number of outcomes needing to be examined, because the relative risk of condition 2 given the presence of condition 1 is not the same as the relative risk of condition 1 given the presence of condition 2. Second, it avoids the need to determine which of the 2 populations is of primary interest when describing the association.

We used a Cochran-Mantel-Haenszel chi-square test stratified by site to determine the statistical significance of the O/E ratio. In this test, the expected number at each site is calculated based on the prevalence of the 2 conditions at that site, and then these numbers are summed over all sites to obtain the overall expected number of children with the co-occurring conditions. Similarly, the variability of the expected number is calculated separately for each site, and the numbers are pooled for an overall measure of variability. The Cochran-Mantel-Haenszel chi-square test is used when the crude prevalence can be misleading owing to differences across a third variable (in this case, site) (Supplementary Material). In summary, our main approach was to determine when co-existing conditions occurred at statistically significantly higher or lower prevalence than expected in the network.

RESULTS

Our study population included 3335 children with ASD with a mean age of 5.9 ± 3.3 years. Sixty-three percent of the sample (n = 2114) was age <6 years, and 37% (n=1221) was age ≥6 years. The majority of participants were male (83%), Caucasian (79%), and met diagnostic criteria for autism (77%) relative to the other *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* ASD categories of Asperger's and pervasive developmental disorder not otherwise specified (Table 2).

Each of the figures contains 66 pairs of results, with Figure 1 for the younger sample (<6 years) and Figure 2 for the older sample (≥6 years). To illustrate how the data are presented in Figure 1, the shaded cell in the upper left (first row, second column) shows a positive association of speech and developmental delay, which are found together more often than expected. The association of development delay with other conditions is shown to the right of the diagonal in the second row, which demonstrates a positive association with sleep, a negative association with anxiety, and positive associations with disruptive behavior, constipation, feeding difficulties, and pica. There are no significant associations with ADHD, hypotonia, seizure disorders, or eczema.

To prioritize the large number of results, we focused on the consistency of patterns rather than on single pairs. For example, speech shows consistent results with each of the other variables, with strong associations with developmental delay, hypotonia, sleep, disruptive behavior, constipation, and feeding difficulty. As with all these pairs, speech and feeding difficulty have a higher joint prevalence than would be expected from their individual prevalence. In contrast, many variables have a strong relationship to anxiety, but the direction of the relationship changes. In younger children, anxiety and ADHD occur together more than twice as often as expected (O/E = 2.37; $P < .001$), whereas anxiety and developmental delay or anxiety and speech conditions both occur substantially less often than expected (anxiety and

Table 2. Demographic Data and Diagnostic Categories by Age Group

Parameter	Age <6 Years		Age ≥6 Years	
	N	Value	N	Value
Age at baseline, y, mean ± SD	2114	3.8 ± 1.08	1221	9.6 ± 2.63
Male sex, % (n)	2103	82.0 (1724)	1220	83.6 (1020)
Hispanic or Latino, % (n)	1941	10.8 (209)	1143	11.9 (136)
Race, % (n)				
Caucasian	1931	77.5 (1496)	1112	80.6 (896)
African American or Black Canadian	1931	8.2 (159)	1112	7.1 (79)
Multiracial	1931	8.4 (163)	1112	6.8 (76)
Asian	1931	5.3 (103)	1112	4.7 (52)
Native American or Aboriginal Canadian	1931	0.3 (6)	1112	0.8 (9)
Hawaiian or Pacific Islander	1931	0.2 (4)	1112	0.0 (0)
ASD diagnosis, % (n)				
Autism	2108	83.0 (1749)	1217	65.3 (795)
Asperger	2108	14.6 (308)	1217	19.1 (233)
PDD-NOS	2108	2.4 (51)	1217	15.5 (189)

SD indicates standard deviation; ASD, autism spectrum disorder; and PDD-NOS, pervasive developmental disorder not otherwise specified.

developmental delay, O/E = 0.36; $P = .002$; anxiety and speech, O/E = 0.70; $P = 0.023$).

Among the 66 condition pairs for each age group, we confirmed previously identified associations such as sleep disorders and anxiety symptoms (observed prevalence of the pair, 5.65%; O/E = 1.29; $P = .030$) and ADHD symptoms (11.22%; O/E = 1.30; $P < .001$) in older children (Fig. 2) and disruptive behavior with speech conditions in both age groups (1.89%; O/E = 1.25; $P < .001$ and 3.11%; O/E = 1.41; $P < .001$) (Figs. 1 and 2).[15,23,24] We found heretofore unreported associations with sleep disorders, including feeding (younger children only, 7.00%; O/E = 1.47; $P < .001$) and constipation (younger children, 6.24%; O/E = 1.62; $P < .001$; older children, 6.06%;

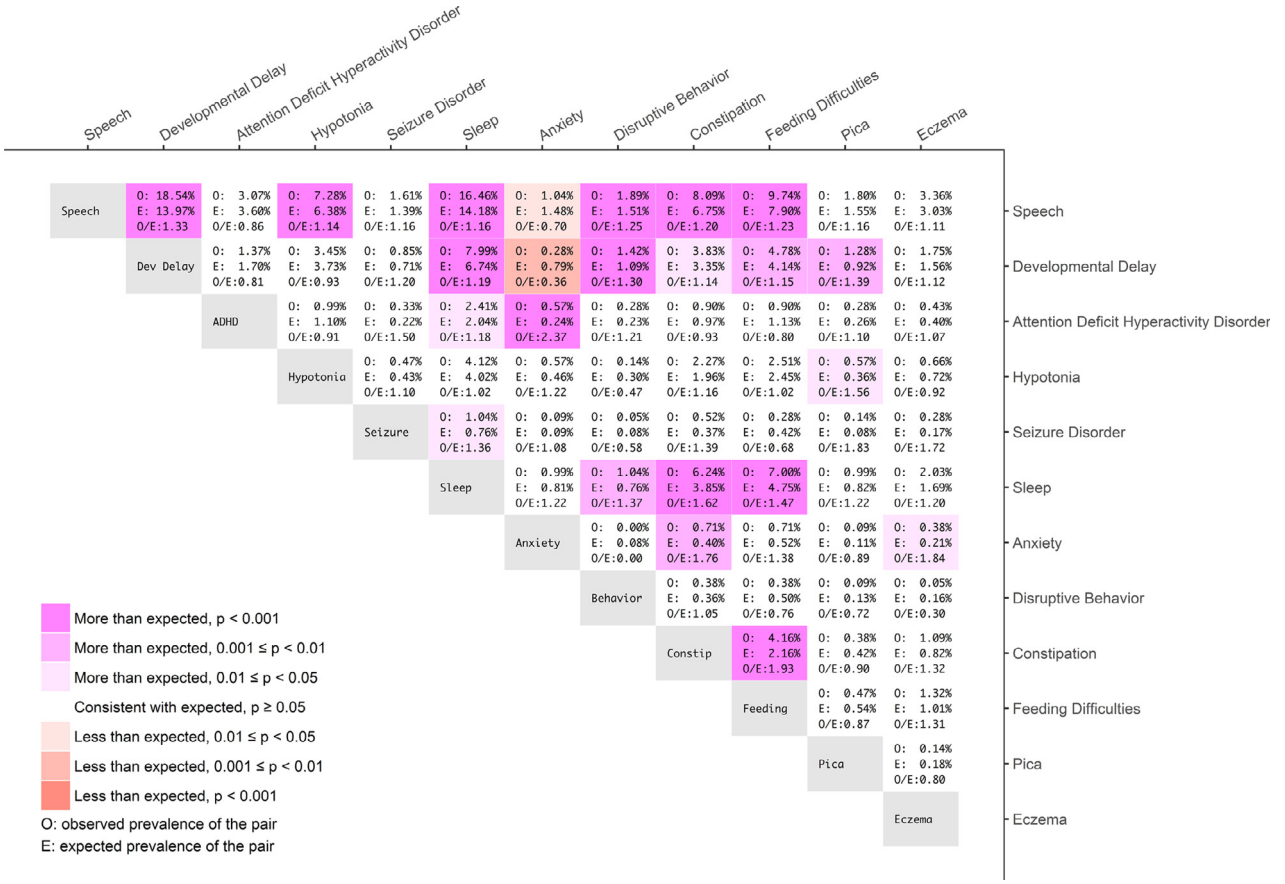

Figure 1. *Co-occurrence of clinician-identified comorbid medical conditions in children age <6 years. Each box shows the results for a pair of conditions, indicating the observed prevalence (O) for the 2 conditions occurring together across the network, the expected prevalence (E) for the 2 conditions together, and the ratio (O/E) of the 2 conditions.*

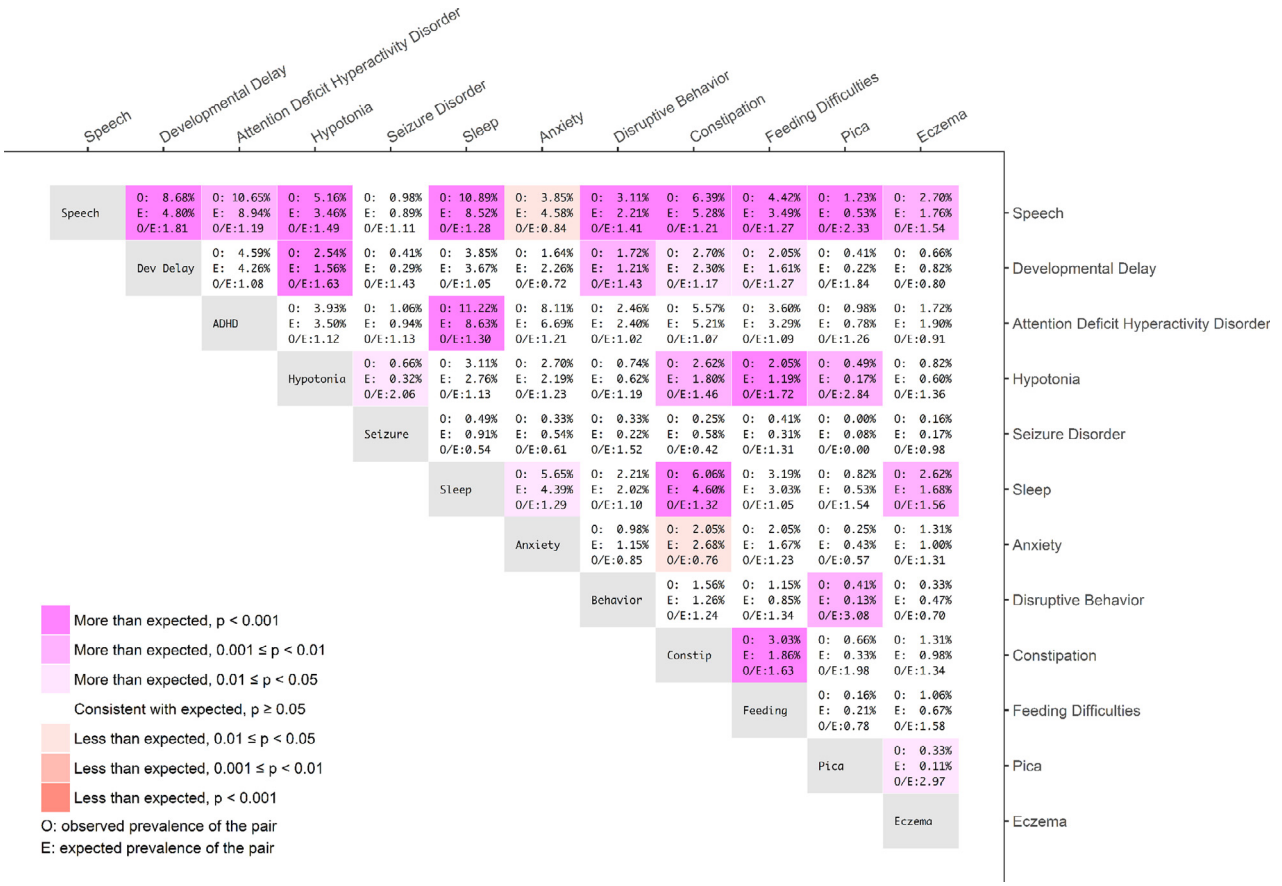

Figure 2. *Co-occurrence of clinician-identified comorbid medical conditions for children age ≥6 years. Each box shows the results for a pair of conditions, indicating the observed prevalence (O) for the 2 conditions occurring together across the network, the expected prevalence (E) for the 2 conditions together, and the ratio (O/E) of the 2 conditions.*

O/E = 1.32; $P < .001$) (Figs. 1 and 2). We found novel associations with speech disorders in both age groups, including feeding (younger children, 9.74%; O/E = 1.23; $P < .001$; older children, 4.42%; O/E = 1.27; $P < .001$), constipation (younger children, 8.09%; O/E = 1.20; $P < .001$; older children, 6.39%; O/E = 1.21; $P < .001$), and hypotonia (younger children, 7.28%; O/E = 1.14; $P < .001$; older children, 5.16%; O/E = 1.49; $P < .001$) (Figs. 1 and 2).

Discussion

This study is the first reported occurring prevalence analysis on such a large dataset examining associations of medical and behavioral conditions in children and youth with ASD. Using this strategy, we found several significant relationships. Although some of the findings in this study are consistent with clinical expectations (eg, speech conditions related to developmental delay greater than expected), other relationships may contribute new clinically relevant considerations.

Specifically, the increased associations between sleep and constipation (age 0−5 years) and between sleep and feeding conditions (age 0−5 years and 6−17 years) have been less clearly described in other studies with large samples of individuals with ASD. Aldinger et al[14] reported a twofold odds ratio for GI disorders and sleep disorders reported in patient medical histories from 2 large datasets of individuals with ASD (N = 3351). Likewise, Krakowiak et al[4] reported a frequency of GI conditions as high as 30% in a cohort of 2- to 5-year-olds with ASD, a higher prevalence than seen in developmentally delayed children or typically developing controls, and GI conditions were associated with greater sleep onset difficulties in multivariable linear regression analysis (N = 529). In 2013, using a portion of the ATN registry dataset (N = 1583), Hollway et al[25] found an increased association between GI conditions and sleep disturbances when comparing results of parent ratings on the Child Behavior Checklist and Sleep Habits Questionnaire. Although there was some overlap of subjects in that study and our present series, in the present study we used clinician-assigned diagnoses rather than parent ratings. A clinician diagnosis may suggest that the subject's symptoms were of sufficient severity to warrant this documentation, as opposed to a parent report of subclinical symptoms.

Feeding issues have been less directly associated with sleep disturbances in other studies. In 2016, Zachor and Ben-Itzchak[11] reported increased parent-reported ASD symptoms in 1224 children with ASD who also had impaired sleep and increased food selectivity. Similarly, Allen et al[26] identified correlations between parent-reported sleep problems and feeding behaviors in 347 children with ASD, and feeding problems again were

associated with worse ASD symptoms. A high prevalence of constipation in children with ASD could be related to selective eating habits, including low levels of dietary fiber,[27] and could be a factor that further reinforces feeding difficulties owing to loss of appetite.[28] It is logical that constipation that causes abdominal pain and discomfort would be associated with greater levels of maladaptive, challenging behaviors and possibly of sleep conditions, particularly in children with ASD, who often struggle with communication, and may express their feelings through their behavior. The association of feeding conditions with speech disorders has been noted in neurologic disorders such as cerebral palsy but is less well described in ASD.[29] There has been a longstanding belief that deficits in acquisition of speech in ASD are at least partly causally associated with conditions with gross, fine, and oral motor control.[30] The relationship of feeding conditions with speech disorders could suggest a possible common underlying neuromuscular problem, or may reflect difficulty communicating food preferences. The relationship of constipation with speech is more difficult to explain directly. Additional investigation of these cases may detect causative genetic variants such as 22q13 deletion (Phelan-McDermid syndrome) which has features of hypotonia, speech delay and autistic traits.[31] Regardless, understanding the relationship of constipation with speech deserves further research investigation.

This study has several limitations. The ATN dataset, while large and comprehensive, includes patients/families who were receiving care at one of the 15 participating ATN sites during the enrollment period and consented to participate in a research registry, and may not represent the broader population of children with ASD in the United States. The sample is predominantly Caucasian, well educated, and of higher socioeconomic status, which could also affect the generalizability of our results. Patients entered by a site are a convenience sample of all the children seen at the site during the recruitment period. Physician diagnosis relies in part on subjective information from parents, although physicians use all available data to make as consistent a diagnosis as possible. The analysis also did not incorporate measures of ASD severity or other cognitive or adaptive measures, and did not assess the impact of medication treatment. Given that some previous studies have linked the severity of comorbid medical symptoms with parent report of ASD severity, it is possible that the associations identified in this analysis are proxy measures of ASD severity rather than independent relationships. Although a number of statistical tests of associations between co-occurring conditions have been published, we did not make formal adjustments for multiple testing; however, many of the results reported herein were statistically significant at $P < .001$, making this less of a concern. Moreover, the purpose of the present study was to highlight potential areas for enhanced screening in this population, regardless of core symptom severity or degree of cognitive impairment. Genetic evaluation of children with these co-occurring conditions also might provide new information that would help explain their association. Further investigation of associations between sleep conditions and feeding and/or other GI conditions may help define common neurobiological pathways, as well as strengthen potential screening or treatment strategies.

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SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at https://doi.org/10.1016/j.acap.2018.06.014.

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