

The Influence of Sex and Age on Prevalence Rates of Comorbid Conditions in Autism

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Individuals with ASD frequently experience one or more comorbid conditions. Here, we investigate the influence of sex and age—two important, yet understudied factors—on ten common comorbid conditions in ASD, using cross-sectional data from 4790 individuals with ASD and 1,842,575 individuals without ASD. Epilepsy, ADHD, and CNS/cranial anomalies showed exceptionally large proportions in both male (>19%) and female (>15%), children/adolescents with ASD. Notably, these prevalence rates decreased drastically with age in both males and females. In contrast, the prevalence of schizophrenia increased with age affecting a disproportionately large number of older (≥ 35 year) adult males (25%), compared to females (7.7%), with ASD. Bowel disorders showed a complex U-pattern accompanied by changes in sex disparity with age. These results highlight crucial differences between cross-sectional comorbidity patterns and their interactions with sex and age, which may aid in the development of effective sex- and age-specific diagnostic/treatment strategies for ASD and comorbid conditions. *Autism Res* 2016, 0: 000–000. © 2016 International Society for Autism Research, Wiley Periodicals, Inc.

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Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by social and communication impairments, as well as repetitive/stereotyped behaviors. A notable feature of ASD is that individuals diagnosed with it frequently experience one or more other somatic or physical health problems [Mannion & Leader, 2013]. It is important to understand and accurately identify patterns of comorbidity in the ASD population as these co-occurring problems affect the overall prognosis and degree of long-term adaptation of individuals on the spectrum. For example, one study found that individuals with ASD who had a diagnosis of attention deficit hyperactivity disorder (ADHD) experienced greater impairment in executive control function and daily living skills than individuals with ASD who did not have a diagnosis of ADHD [Yerys, Wallace, Sokoloff, Shook, James, & Kenworthy, 2009]. They also exhibited more severe autism-related traits and externalizing maladaptive behaviors. Similar links have been made between ASD and comorbid epilepsy, another condition that further worsens autistic symptoms and social adaptability. Seizure episodes in individuals with

epilepsy and ASD occur at much earlier ages as compared to individuals with epilepsy but not ASD [Spence & Schneider 2009]. Notably, mortality rate is increased in individuals with ASD who also have epilepsy [Pickett, Xiu, Tuchman, Dawson, & Lajonchere, 2011]. Thus, comorbid conditions can have a prominent effect on ASD, and accurate characterization of the prevalence of multiple comorbid conditions across the ASD population is essential for developing more effective diagnostic and treatment strategies in affected individuals.

Despite the need for assessing the rates of comorbid conditions associated with ASD, few comprehensive, large-scale studies exist in this area. To date, very few studies have examined prevalence of comorbid conditions over the ASD population as a whole, covering the entire range of ages, cognitive abilities, and sex. Critically, small samples—some as few as one to two hundred total subjects—have precluded a careful analysis of comorbid prevalence rates across sex and age, two important, yet understudied factors [Gadow, 2012; Kantzer, Fernell, Gillberg, & Miniscalco, 2013; Kohane et al., 2012; Leyfer et al., 2006; Simonoff et al., 2008; Steensel, Bögels, & Bruin, 2012; Volkmar & Cohen, 1991]. Most studies have included small numbers of females, some

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with twenty to thirty female subjects in contrast to over one hundred male subjects [Kantzer et al., 2013; Volkmar & Cohen, 1991], and others with male-to-female ratios as large as ninety percent [Steensel et al., 2012]. The small female sample sizes do not allow teasing out sex effects and therefore may lead to conclusions that do not accurately represent the ASD population as a whole. Furthermore, the few studies that have examined comorbidity prevalence as a function of age have primarily focused on children and young adults with almost no investigation of the comorbidity profiles in older adults [Abdallah et al., 2011; Esbensen, Seltzer, Lam, & Bodfish, 2008; Katoh-Semba et al., 2007; Kohane et al., 2012; Ramsey et al., 2013; Viscidi et al., 2013].

The potential effects of sex and age on comorbidity in ASD are poorly understood. Given the current lack of knowledge about the biological origins of ASD, and the underlying heterogeneity of the disorder, studies of age and sex and their association with comorbidity can shed light on symptom profiles and heterogeneity that characterize the disorder. The substantially higher prevalence rate of ASD in males—male to female ratio is 4–5:1 [Fombonne, 2003, 2009; Yau et al., 2013]—has made it difficult to obtain adequate numbers of females to investigate sex-specific comorbidity in the disorder. Importantly, it is well known that the incidence of many comorbid conditions in the general population is highly sex specific. For example, males are approximately two to three times more likely to have ADHD than females [Grossman, Harrow, Rosen, Faull, & Strauss, 2008; Ramtekkar, Reiersen, Todorov, & Todd, 2010]; females are widely recognized to be more susceptible to anxiety and depression than males [Castro-Sánchez et al., 2012; Centers for Disease Control and Prevention (CDC), 2010; Hsiao, Lin, Liu, & Beck Schatz, 2013]. The variation, if any, in the prevalence rates of these and other comorbid conditions in males and females with ASD is currently unknown. Also, it is crucial to characterize ASD comorbidities across age groups. Despite the fact that ASD is a neurodevelopmental disorder, few studies have examined the relationship between age and comorbidity in ASD [Esbensen, Seltzer, Lam, & Bodfish, 2008; Katoh-Semba et al., 2007; Ramsey et al., 2013; Viscidi et al., 2013]. Increasing the depth of cross-sectional studies, particularly by including age and sex covariates along with more comorbid psychiatric and medical conditions, can help more accurately identify how the profile of ASD changes across age-groups and sex, and aid in the development of more particular targeted interventions.

Here, we attempt to address critical gaps in our knowledge of comorbidity in ASD by assessing sex and age differences across ten comorbid conditions in a very large database of 1.8M individuals (4790 ASD; 1,842,575 without ASD). Based on aforementioned

studies, we included ADHD, schizophrenia, and epilepsy. Additionally, we also included other commonly occurring comorbid conditions including bowel disorders, inflammatory bowel disorder, sleep disorders, autoimmune disorders, diabetes mellitus (DM1), and muscular dystrophy. We only examined comorbid conditions encoded in ICD-9; the use of ICD-9 provides standardization and a possibility of replication studies that use data from several other healthcare systems, which employ the widely used ICD-9 standard. We compared prevalence rates across sex and age in individuals with ASD and those without ASD. Previous studies have consistently reported influences of age and sex on the prevalence of the comorbid conditions in non-ASD individuals. For example, the prevalence of ADHD in boys (13.2%) is reported to be higher than girls (5.6%) [Willcutt, 2012]; schizophrenia is diagnosed 1.4 times more frequently in males than females and typically appears earlier in men [Picchioni & Murray, 2007]; prevalence of epilepsy varies by age with higher incidence of epilepsy in older adults than younger adults [Savage, 2014]. Comparison of the prevalence rates in individuals with ASD and without ASD allowed us to assess the degree to which ASD impacts the prevalence of comorbid conditions.

We used a unique cohort of data from over 1.8M individuals available through the Stanford Translational Research Integrated Database Environment (STRIDE). STRIDE is an online database of pediatric as well as adult cases treated at Stanford University Medical Center from 1995 to present [Lowe, Ferris, Hernandez, & Weber, 2009]. STRIDE receives clinical data of patients from both Stanford University Medical Centre hospitals: Lucile Packard Children's Hospital and Stanford Hospital and Clinics. The database categorizes diseases by the International Classification of Diseases (ICD)–9 billing codes making it possible to assess prevalence rates in a wide range of comorbid conditions. This large sample size allowed us to investigate comorbidity across sex and age in ways that were not previously possible [Gadow & DeVincent, 2012; Gadow, 2012; Kantzer et al., 2013; Steensel et al., 2012; Volkmar & Cohen, 1991]. To our knowledge, this is the first study that examines prevalence of ASD comorbidities across sex and age groups in such a large population, and our findings should prove helpful in better understanding the profile of comorbid conditions in the disorder.

Methods

Participants—STRIDE Cohort

We utilized the STRIDE's Cohort Discovery Tool (CDT) to query data from 1,847,365 participants. Four thousand seven hundred and ninety of whom had a diagnosis of

ASD (hereafter referred to as the ASD population) and 1,842,575 of whom did not receive a diagnosis of ASD (hereafter referred to as the non-ASD population). All participants were cared for at one of the two Stanford University Medical Center Hospitals: Lucile Packard Children’s and Stanford Hospital and Clinics. Socioeconomic status of the participants was not made available due to HIPAA regulations. 0.2% of the participants were American Indians, 8% Asian, 2% Black, 35% White, and 8% Others. Forty-four percent of the participants were males and 56% were females. The participants were not specifically recruited for research projects although they might have been included in research projects including ours, retrospectively.

Data was constrained by restricting the range of the “Sex” and “Current Age” variables within each query. Sex was specified as either male or female, and age categories were defined as 0–18 years, 18–35 years, and ≥ 35 years.

CDT provides an easy platform for Stanford University researchers to query the STRIDE Clinical Data Warehouse (CDW) to answer questions such as “Does the STRIDE CDW contain a cohort of patients with ASD and ADHD?” The search criteria can include patient demographics, ICD coded diagnoses, and ICD-9 and Current Procedural Terminology (CPT) coded procedures. The STRIDE Cohort Discovery Tool is available to Stanford faculty, Postdoctoral fellows and Academic Staff.

Our analysis focused on the following 10 conditions in individuals with and without ASD: ADHD, autoimmune disorder, bowel disorders, CNS/cranial anomalies, diabetes mellitus, epilepsy, inflammatory bowel disorders (IBD), muscular dystrophy, schizophrenia, and sleep disorders, based on ICD-9 healthcare billing codes.

STRIDE does not provide access to individual patient data as in compliance with patient privacy and Health Insurance Portability and Accountability Act (HIPAA) regulations.

Statistical Analyses

Data analysis was carried out using IBM’s SPSS statistical analysis software. We performed chi-square and Fisher exact probability tests to determine whether potential differences in prevalence for each comorbid condition differed across sex and age-groups. The percentage of individuals presenting each comorbid disorder was calculated for each sex and age group within each population. The *P* values, associated with each comorbid condition, were corrected for multiple comparisons using a false discovery rate (FDR) control procedure. FDR level was set to 0.05.

Results

Prevalence Rates of ASD

From the full sample, 4790 participants had a diagnosis of ASD. ASD prevalence rates for males and females in the three age groups are described in Table 1.

Comorbid Conditions in Participants with and without ASD

We first examined the prevalence rates of ten conditions in the ASD and the non-ASD populations across all ages. Six out of ten conditions—ADHD, bowel disorders, CNS/cranial anomalies, epilepsy, schizophrenia, and sleep disorders—showed significantly higher prevalence in ASD compared to the non-ASD group (Fig. 1).

Comorbid Conditions in Males and Female Participants with and without ASD

We next examined the prevalence of each comorbid condition as a function of sex in the ASD as well as the non-ASD population. Consistent with the prevalence patterns of comorbidities observed in the overall ASD vs. non-ASD population, the prevalence rates of six out of ten conditions—ADHD, bowel disorders, CNS/cranial anomalies, epilepsy, schizophrenia, and sleep disorders—were higher in both males and females with ASD compared to the respective non-ASD sample.

We then compared the prevalence of comorbid conditions between males and females in the ASD population only. These analyses revealed statistically significant sex differences in two comorbid conditions: (i) ADHD ($P < 0.05$; FDR corrected), which was more prevalent in males with ASD compared to females with ASD, and (ii) epilepsy ($P < 0.05$; FDR corrected), which was more prevalent in females with ASD compared to males with ASD (Fig. 2). These observed sex differences in the prevalence rates for ADHD and epilepsy in ASD were also significantly greater compared to those sex differences observed in the non-ASD population ($P < 0.05$; FDR corrected).

Comorbid Conditions at Different Age-Groups in Participants with and without ASD

We also examined the prevalence of comorbid conditions as a function of age in the ASD as well as the non-ASD population. Specifically, we assessed the

Table 1. ASD Prevalence Rates for Males and Females in the Three Age Groups

| Age group | Males | Females |
|-----------------|-------|---------|
| 0–18 years | 1.26% | 0.35% |
| 18–35 years | 0.40% | 0.08% |
| ≥ 35 years | 0.02% | 0.005% |

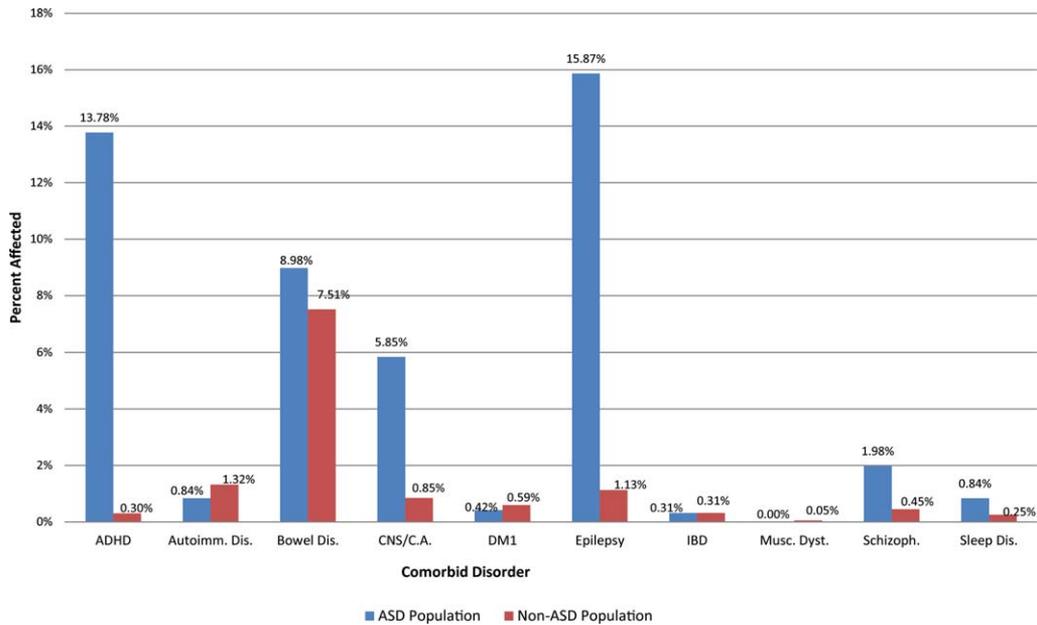


Figure 1. Comorbid conditions in participants with and without ASD. The prevalence of six out of ten conditions—ADHD, bowel disorders, CNS/cranial anomalies, epilepsy, schizophrenia, and sleep disorders—was higher in the ASD population, as compared to the general (non-ASD) population ($P < 0.05$, FDR corrected). ADHD: Attention-deficit/hyperactivity disorder; Autoimm. Dis.: Autoimmune disorder; Bowel Dis.: Bowel disorder; CNS/C.A.: Central nervous system/Cranial abnormalities; DM1: Diabetes mellitus; IBD: Inflammatory bowel disorders; Musc. Dyst: Muscular dystrophy; Schizoph: Schizophrenia; Sleep Dis.: Sleep disorders.

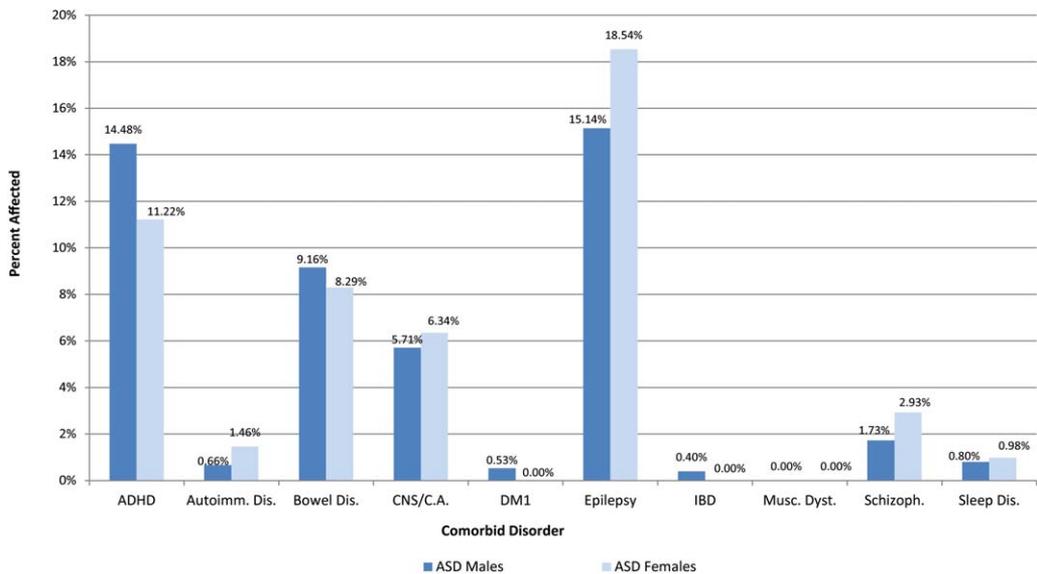


Figure 2. Comorbid conditions in Male and Female participants with ASD. ADHD ($P < 0.05$; FDR corrected), was more prevalent in males with ASD, compared to females with ASD. Epilepsy ($P < 0.05$; FDR corrected) was more prevalent in females with ASD, as compared to males with ASD. Other comorbid conditions did not show any significant sex differences.

prevalence of comorbidities in three age groups: 0–18 years, 18–35 years, and ≥ 35 years. In the 0–18 years age group, the prevalence rates of six out of ten conditions: ADHD, bowel disorders, CNS/cranial anomalies, epilepsy, schizophrenia, and sleep disorders were significantly higher in the ASD than in the non-ASD

population. In the 18–35 years age group, the prevalence rates of five out of 10 conditions: ADHD, bowel disorders, CNS/cranial anomalies, epilepsy, and schizophrenia were higher in the ASD than in the non-ASD population. In the ≥ 35 years age group, three out of ten conditions: bowel disorders, epilepsy, and

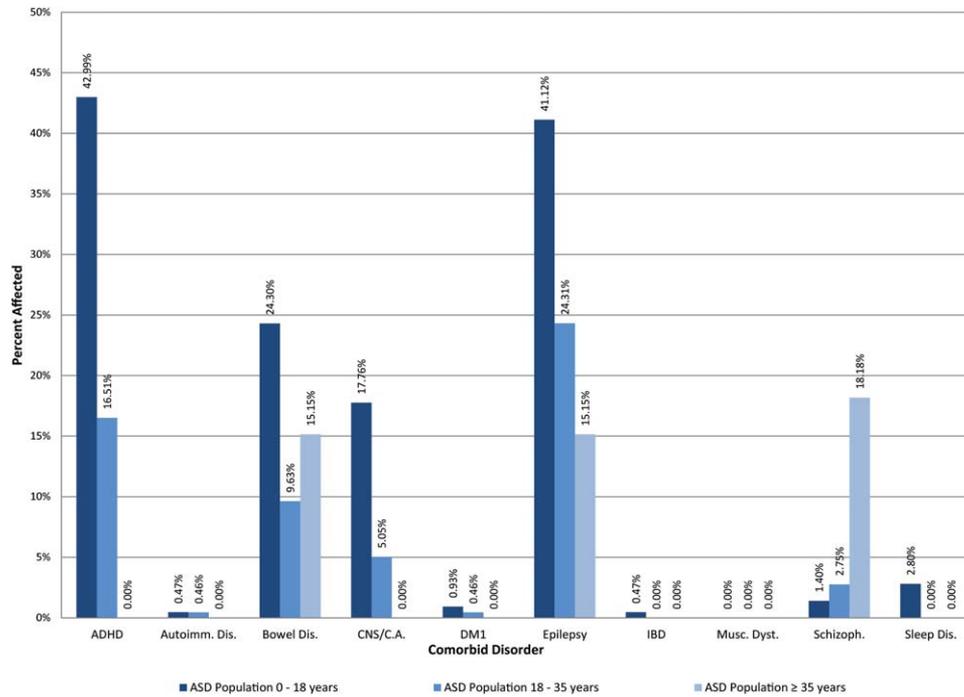


Figure 3. Comorbid conditions at different age-groups in participants with ASD. ADHD, CNS/cranial and epilepsy decreased in prevalence as age increased ($P < 0.05$; FDR corrected). Notably, these conditions were staggeringly large in proportion in the younger group (0–18 age range), with ADHD affecting 42.99% of individuals with ASD, CNS/cranial anomalies affecting 24.3% of individuals with ASD, and epilepsy affecting 41.12% of individuals with ASD. Schizophrenia prevalence rates increased with age, affecting just 1.40% of 0–18 year olds as compared to 18.18% of individuals over the age of 35 ($P < 0.05$; FDR corrected). Bowel disorders showed a nonlinear pattern of prevalence rate as a function of age, decreasing in prevalence from the 0–18 age group to the 18–35 age group before increasing again in the ≥ 35 age group; with the highest proportion of subjects affected by bowel disorders in the 0–18 group ($P < 0.05$; FDR corrected).

schizophrenia, showed significantly higher prevalence in ASD relative to the non-ASD population.

We then compared the prevalence of comorbid conditions across the three age groups in the ASD population only. These analyses revealed that ADHD, CNS/cranial anomalies and epilepsy decreased in prevalence as the age increased ($P < 0.05$; FDR corrected) (Fig. 3). Notably, these conditions were staggeringly large in proportion in the younger group (0–18 age range), with ADHD affecting 42.99% of individuals with ASD, CNS/cranial anomalies affecting 24.3% of individuals with ASD, and epilepsy affecting 41.12% of individuals with ASD. Schizophrenia prevalence rates increased with age, affecting just 1.40% of 0–18 year olds as compared to 18.18% of individuals over the age of 35 ($P < 0.05$; FDR corrected; Fig. 3). Bowel disorders showed a nonlinear pattern of prevalence rate as a function of age, decreasing in prevalence from the 0–18 age group to the 18–35 age group before increasing again in the ≥ 35 age group; with the highest proportion of subjects affected by bowel disorders in the 0–18 group ($P < 0.05$; FDR corrected; Fig. 3). Furthermore, variation in the prevalence rates across age groups was far greater in ASD than in the non-ASD population. The largest differences were

apparent in ADHD and epilepsy, as ADHD decreased by 42% in the ASD population vs. 0.8% in the non-ASD population, and epilepsy decreased about 26% for ASD vs. 1% for non-ASD.

Comorbid Conditions as a Function of Sex and Age in Participants with and without ASD

We lastly examined prevalence of comorbid conditions across both sex and age groups in the ASD population and the non-ASD population. Table 2 and Supporting Information Figure S1 describe in detail the prevalence rate of 10 comorbid conditions in males and females in each of the three age groups in the ASD and non-ASD population.

As shown in Figure 4, the number of comorbid conditions that showed significant influences of sex on prevalence rates fluctuated over age groups in the ASD population: the 0–18 age group showed significant sex differences for ADHD, bowel disorders, and schizophrenia ($P < 0.05$, FDR corrected), the 18–35 age group exhibited no significant differences between males and females, and the ≥ 35 group displayed significant differences in bowel disorders, epilepsy, and schizophrenia ($P < 0.05$, FDR corrected). The non-ASD population

Table 2. Prevalence Rates of Ten Comorbid Conditions in Males and Females in Each of the Three Age Groups in the ASD and the Non-ASD Population

| | ADHD | Bowel Disorders | CNS/Cranial Anomalies | DM1 | Epilepsy | IBD | Muscular Dystrophy | Schizophrenia | Sleep Disorders |
|--|--------|-----------------|-----------------------|-------|----------|-------|--------------------|---------------|-----------------|
| ASD males 0–18 years | 46.39% | 25.90% | 18.67% | 1.20% | 40.36% | 0.60% | 0.00% | 0.60% | 3.01% |
| ASD females 0–18 years | 31.25% | 18.75% | 14.58% | 0.00% | 43.75% | 0.00% | 0.00% | 4.17% | 2.08% |
| ASD males 18–35 years | 17.26% | 10.71% | 5.36% | 0.60% | 23.81% | 0.00% | 0.00% | 2.98% | 0.00% |
| ASD females 18–35 years | 14.00% | 6.00% | 4.00% | 0.00% | 26% | 0.00% | 0.00% | 2.00% | 0.00% |
| ASD males ≥35 years | 0.00% | 10.00% | 0.00% | 0.00% | 20% | 0.00% | 0.00% | 25.00% | 0.00% |
| ASD females ≥35 years | 0.00% | 23.08% | 0.00% | 0.00% | 7.69% | 0.00% | 0.00% | 7.69% | 0.00% |
| Non-ASD population males 0–18 years | 1.078% | 5.13% | 2.42% | 0.36% | 1.91% | 0.13% | 0.11% | 0.04% | 0.16% |
| Non-ASD population females 0–18 years | 0.400% | 4.56% | 2.34% | 0.35% | 1.77% | 0.11% | 0.06% | 0.03% | 0.15% |
| Non-ASD population males 18–35 years | 0.997% | 4.44% | 1.02% | 0.65% | 1.93% | 0.50% | 0.13% | 0.57% | 0.28% |
| Non-ASD population females 18–35 years | 0.364% | 3.73% | 1.12% | 0.54% | 1.31% | 0.32% | 0.03% | 0.27% | 0.19% |
| Non-ASD population males ≥35 years | 0.083% | 10.57% | 0.24% | 0.80% | 0.86% | 0.40% | 0.04% | 0.69% | 0.31% |
| Non-ASD population females ≥35 years | 0.051% | 8.50% | 0.39% | 0.56% | 0.73% | 0.29% | 0.03% | 0.50% | 0.26% |

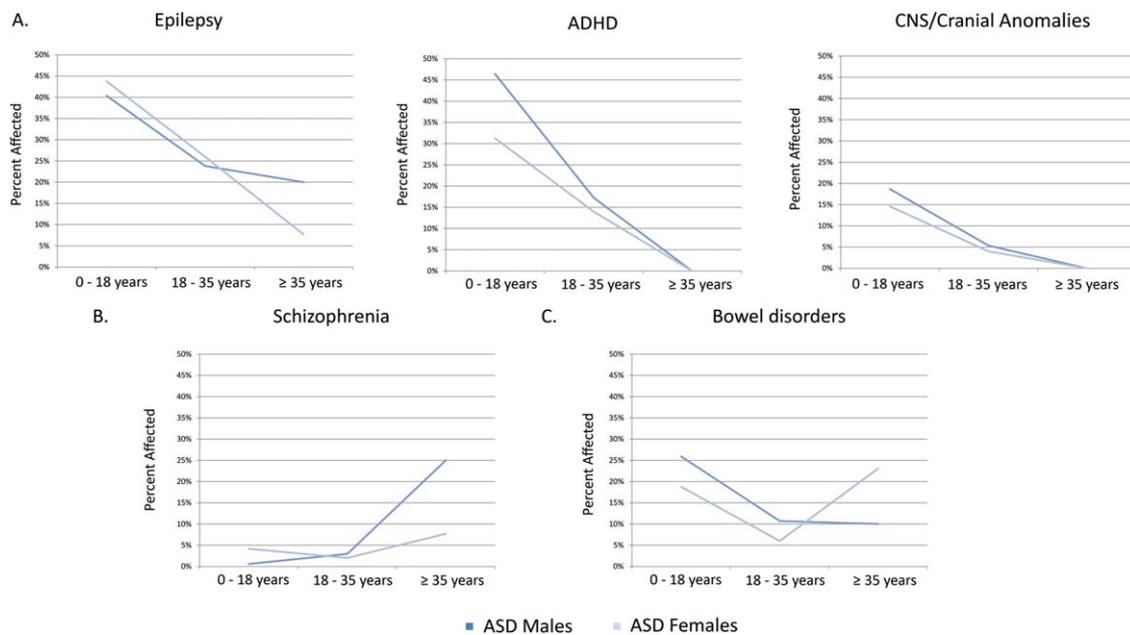


Figure 4. Comorbid conditions as a function of sex and age in participants with ASD. Epilepsy, ADHD, and CNS/cranial anomalies showed exceptionally large proportions in both male (>19%) and female (>15%) 0–18 year ASD. Notably, these prevalence rates decreased drastically with age. In contrast, the prevalence of schizophrenia increased with age affecting a disproportionately large number of older adult males (25%), as compared to females (7.7%), with ASD. Bowel disorders showed a complex U-pattern accompanied by changes in sex disparity with age.

showed significant sex differences in rates of all ten comorbid conditions in the 18–35 and ≥35 age groups, but not in the 0–18 age group. A direct comparison

between ASD and non-ASD groups showed that sex differences in prevalence rates were significantly larger in ASD as compared to the non-ASD population.

Comparing the sex rate differences across age groups, we observed that the ASD population showed a sex effect in the prevalence of comorbidities across age groups: bowel disorders exhibited higher male prevalence in 0–18 and 18–35 groups and higher female prevalence in the ≥ 35 group, epilepsy switched from females in the 0–18 and 18–35 age groups to males in the ≥ 35 group, and schizophrenia switched from females in the 0–18 group to males in the 18–35 and ≥ 35 groups. In the non-ASD population, CNS/cranial anomalies were the only disorder to display a sex effect, exhibiting higher male prevalence in the 0–18 group and higher female prevalence in the 18–35 and ≥ 35 groups. Thus, the non-ASD population tended to be more consistent in sex differences across age groups.

Discussion

Analyses of comorbidity with large datasets are crucial for refining our understanding of ASD. Our study, which encompasses 1,842,575 non-ASD subjects and 4,790 ASD subjects from the STRIDE clinical database, is the first evaluation to date that examines the prevalence of 10 common comorbid conditions across both sex and age groups in a large cohort of ASD and non-ASD populations. Overall, we found that epilepsy, ADHD, CNS/cranial anomalies, sleep disorders, schizophrenia, and bowel disorders were more prevalent in the ASD population than in the non-ASD population, providing further corroborating evidence that a significant portion of individuals with ASD experience an additional burden of comorbid conditions.

By examining ASD comorbidity rates across sex and age, we found that epilepsy, ADHD, and CNS/cranial anomalies were evident in surprisingly large proportions ($>15\%$) in our youngest ASD population group (i.e. 0–18 years). Crucially, however, their prevalence rates decreased drastically with age. In contrast, the prevalence of schizophrenia increased significantly with age affecting a disproportionately large number of older males (≥ 35 years) with ASD. Bowel disorders showed a U-shaped pattern characterized by complex changes in sex disparity with age. Importantly, these patterns were quite distinct from those observed in the non-ASD population. Our findings discussed in detail below (a) highlight crucial differences between comorbidity patterns and their interactions with sex and age in ASD and (b) emphasize the importance of comorbidity in ASD research for better characterization of the biological bases of the disorder.

ASD and Comorbid Epilepsy

One of the most widely reported comorbid conditions associated with ASD is epilepsy. In our sample, we

found that 16% of individuals with ASD also had a diagnosis of epilepsy, well above the prevalence of epilepsy in the non-ASD population and the general population. The previously reported prevalence rates of epilepsy in the ASD population have varied widely, with estimates ranging from as low as 5% to as much as 46%. It has been argued that this large variation could be due to heterogeneity of samples with respect to age and sex, that increase or decrease the risk of epilepsy [Spence & Schneider, 2009]. Examining epilepsy rates in the stratified samples, we observed three key patterns, which are consistent with, and extend previous work. First, we found that the prevalence of epilepsy is highest in childhood and adolescence. This result is consistent with the finding that age at onset of epilepsy in ASD has two peaks, first in early childhood and second in adolescence [Kawasaki, Yokota, Shinomiya, Shimizu, & Niwa, 1997; Giovanardi, Posar, Parmeggiani, 2000; Danielsson, Gillberg, Billstedt, Gillberg, & Olsson, 2005; Hughes and Melyn, 2005, Hara, 2007). Multiple studies have shown that the primary age at epilepsy onset in ASD is early childhood (<3 years) [Viscidi et al., 2013, El Achkar & Spence, 2015]. A long-term follow-up study of individuals with ASD points to a second peak of epilepsy onset between the ages of 10 and 14. Specifically, Bolton and colleagues found that 50% of the patients with ASD had epilepsy onset after the age of 10 years [Bolton et al., 2011]. A subset of the aforementioned studies also reported a decline in epilepsy rates in individuals with ASD post adolescence [El Achkar & Spence, 2015]. The pattern of age-related decline in the prevalence of epilepsy was also observed in the non-ASD population. Second, we observed that females with ASD, compared to males with ASD, show higher incidence of epilepsy. This result is consistent with epidemiological studies that have suggested increased risk of epilepsy in females with ASD than males with ASD [Elia, Musumeci, Ferri, & Bergonzi, 1995; Danielsson et al., 2005; Hughes & Melyn, 2005]. A recent meta-analysis reported that the prevalence of epilepsy in males with ASD was 18% as compared to 34.5% in females with ASD [Amiet et al., 2008]. The study also reported that the male to female ratio in autism without epilepsy is high (M:F = 4:1), the sex disparity decreases (M:F = 2:1) in the ASD subpopulation with comorbid epilepsy [Amiet et al., 2008]. Finally, we present novel evidence that the sex differences are largest in the older adults with ASD (≥ 35 year). Notably, we find that in the ≥ 35 year group the epilepsy rates in males with ASD were higher than females with ASD. Given that epilepsy is a childhood/adolescent onset disorder which tends to remit with age, this finding suggests, for the first time, that epilepsy might be more difficult to treat in older adult males with ASD. The reasons behind this pattern are unclear and warrant

further investigation. Taken together, these results characterize sex-specific features of epilepsy comorbidity in the ASD population, which may inform future studies focused on specific risk factors for both the ASD phenotype and comorbid epilepsy, with important implications for a tailored treatment of the disorder. For example, based on our finding of an increased incidence of epilepsy in females with ASD compared to males with ASD, it may be worthwhile to investigate sex-specific treatments of epilepsy in ASD.

ASD and Psychiatric Comorbidities

The second most commonly comorbid condition in individuals with ASD was ADHD. We found that 14% of individuals with ASD also had a diagnosis of ADHD, well above the prevalence of ADHD in the non-ASD population and the general population. Examining the rates across age groups, we observed that the prevalence of ADHD in individuals with ASD is highest in the 0–18 year group. The most recent meta-analysis of 33 research studies showed that the prevalence of ADHD in children with ASD was 33–37% [Berenguer-Forner, Miranda-Casas, Pastor-Cerezuela, & Rosello-Miranda, 2015], consistent with our finding that 43% of 0–18-year-old individuals with ASD also had a diagnosis of ADHD. Studies in older individuals have reported lower ADHD percentages in adults with ASD [Lai, Lombardo, Baron-Cohen, 2014], compared with children with ASD. The pattern of age-related decline in the prevalence of ADHD was also observed in the non-ASD population. Examining sex differences in comorbid ADHD patterns, one study found that ADHD was more prevalent in boys than in girls and reported the prevalence of ASD children affected with comorbid ADHD at 17.3%, consistent with our finding [Suren et al., 2012]. Similarly, a study of 7 to 12 year-olds with ASD found that males had higher levels of hyperactivity and impulsivity than females [May et al., 2012]. No study, however, has investigated ADHD comorbidity rates in the ASD population across sex and age, making it difficult to compare our finding to prior reports.

Comorbidity analyses of other psychiatric conditions, most notably schizophrenia within the ASD population are also noticeably missing in the extant literature. Theoretical models have suggested that the neurodevelopmental deficits underlying ASD may put individuals with ASD at risk for developing psychosis later in life [Toal et al., 2009]. Consistent with this model, we found that prevalence rates of schizophrenia were higher in ASD, and it increased drastically with age, affecting just 1.40% of 0–18 year-olds and 2.75% of 18–35 year-olds, compared to 18.18% of individuals over the age of 35. The rates of schizophrenia in the 0–18 year group were significantly lower than the ≥ 35 year group and were not different

than the 18–35 year group of individuals with ASD. The latter result is contrary to our prediction based on previous evidence that schizophrenia has an onset typically in late adolescence or early adulthood in non-ASD individuals. Further work is required to investigate whether the risk/age of onset is shifted in individuals with ASD, and if so why. Stratifying the age groups by sex, we found that the proportion of ≥ 35 year males with ASD with schizophrenia was significantly greater than the proportion of ≥ 35 year females with ASD with schizophrenia. There were no sex differences in the other two age groups. Our findings suggest the possibility that neuroprotective factors in females with ASD may reduce the risk of schizophrenia at older ages.

ASD and Gastrointestinal Comorbidities

Past studies have suggested that gastrointestinal difficulties, including constipation and diarrhea are common in individuals with ASD [Valicenti-McDermott et al., 2006; Nikolov et al., 2009] with the latest study by the Centers for Disease Control and Prevention reporting that individuals with ASD are more than three times likely to experience gastrointestinal difficulties than are their typical peers [Schieve et al., 2012]. These studies are, however, based on samples of children with ASD. Little is known about the prevalence of these difficulties across age-groups and sex. We found very high incidence of bowel disorders in children with ASD (24%). Notably, the prevalence rate declined drastically in the 18–35 year group and rose again to high levels in ≥ 35 year group. These remarkable age-related changes were also sex specific: Males showed higher prevalence of comorbid bowel disorder in the younger cohort of ASD than females; in contrast, females showed higher prevalence in the older adult group. Future studies examining the causes underlying this complex sex-influenced developmental trajectory of bowel disorder comorbidity in the ASD population are warranted to provide new insights in to more effective and targeted treatments that reduce GI complications and associated behavioral symptoms.

ASD and Other Comorbidities

There is a dearth of studies examining how the prevalence of the other common comorbid conditions—autoimmune disorders, DM1, sleep disorders, muscular dystrophy, and CNS/cranial anomalies—are influenced by sex and age in the ASD population. This precludes us from contrasting our findings in these domains against extant literature. We hope that our investigation will lead to further studies addressing sex- and age-dependent differences within these conditions. A notable finding regarding these conditions is the observed

high prevalence of CNS/cranial anomalies in childhood ASD.

Summary of Sex Differences in Comorbid Conditions in ASD

We found sex differences in comorbid conditions within the ASD population—ADHD was more prevalent in males with ASD, as compared to females with ASD, and epilepsy was more prevalent in females with ASD, as compared to males with ASD. Examining specific age groups, statistically significant sex differences were found to be most prevalent in the ASD population in the 0–18 and ≥ 35 age groups. Furthermore, across three consecutive age groups we found that sex differences in comorbid conditions follow substantially different patterns in the ASD and non-ASD populations, especially in the 0–18 age group. Thus, it is imperative to carry out further evaluations of sex-specific symptoms over distinct age groups and comorbid conditions in the ASD population, as it cannot be assumed that individuals with ASD would follow sex prevalence patterns of comorbidity similar to those seen in the non-ASD population.

Changing Profile of ASD Comorbidities with Age

Our results extend prior findings [Kohane et al., 2012], and provide strongest evidence to date for changing profiles of comorbidity with age in the ASD population. Kohane and colleagues examined comorbidity patterns in two age groups: 0–18 years and 18–34 years, and reported that schizophrenia, DM1, and IBD increased with age whereas sleep disorders, bowel disorders (without IBD) and epilepsy did not change significantly. The results are consistent with our finding of an age-related increase in prevalence of comorbid schizophrenia, in the ASD population; however, they are inconsistent with our findings of a decrease in prevalence of epilepsy, ADHD, and CNS/cranial anomalies. These inconsistencies could partly be attributed to the differences in the age-range examined in the two studies: we examined comorbidity patterns across the lifespan as compared to Kohane and colleagues which examined a narrow range from 0 to 34 years [Kohane et al., 2012]. Additionally, Kohane et al. examined a subset of comorbid conditions excluding key conditions such as ADHD, which was examined in our study [Kohane et al., 2012]. Finally, this study, in stark contrast to Kohane et al., investigated the effect of sex—a key factor in ASD—on the overall as well as age-group specific comorbidity rates [Kohane et al., 2012]. By including sex, we were able to specifically show that certain effects were sex-specific; for example, prominent age-related increases in the prevalence of comorbid schizophrenia in individuals with ASD were observed only in females but not males. Critically, the observed

differences between the age groups might also be explained by age-related differences in patient care and other environmental factors.

Limitations and Future Work

The study has several limitations which merit discussion. First, although our study uses data from a large database, it is important to note that the scope of the study was limited to patients treated at the Stanford University Medical Center. It is possible that our findings would have been altered slightly with a broader and more diverse population from multiple sites.

Second, in the interests of patient privacy, the STRIDE Discovery Cohort Tool does not provide researchers with comprehensive demographic and cognitive assessment information of the participants. It is well acknowledged that the various comorbid conditions, including epilepsy and schizophrenia can influence cognitive ability and adaptive functioning. Research examining the collective influence on these factors has been very limited and needs to be addressed by future work. Furthermore, investigation of co-occurrence among comorbid conditions is an important avenue for future work.

Third, there is currently some debate surrounding the reliability of ICD-9 billing codes in accurately characterizing the prevalence of various disorders and diseases [Drahos, Vanwormer, Greenlee, Landgren, & Koshiol, 2013; Muir, 2013; Surie et al., 2013; Tanpowpong et al., 2013]. ICD-9 codes do not permit distinguishing between disease and symptom-complex. For example, while it can be assumed that diagnoses were made by trained clinicians, from the ICD-9 codes alone we cannot determine whether or not parent report, standardized instruments, and/or clinical impression were used to make the diagnosis. Moreover, other inherent biases in the use of the codes include the fact that the assignments of the codes are at least in part determined by the expertise of the treating specialist.

Fourth, our study examined three large age groups each spanning the development periods—early childhood to adolescence, adolescence to middle adulthood, middle adulthood, and beyond. The use of these wide spanning age ranges raises the possibility that the reported developmental changes may still reflect cohort/group differences as the comorbidity characteristics are likely to vary within these groups. Additionally, we used a cross-sectional design and report age-related increases or decreases in the prevalence of ASD comorbidities. Longitudinal studies are needed to more accurately estimate the changes in the prevalence rates of comorbid conditions in individuals with ASD with time.

Fifth, we only examined comorbid conditions encoded in ICD-9. The use of ICD-9 provides standardization and a possibility of replication studies that use data from several other healthcare systems, which employ the widely used ICD-9 standard.

Sixth, in contrast to conventional small-scale studies, the large-scale approach used in our study allows examination of a wider range of comorbid conditions across a wider range of age-groups and sex. Unlike large-scale investigations such as ours, small-scale studies typically perform more careful diagnostic and phenotypic assessments.

Seventh, further work is needed to investigate the influence of cognitive factors, most importantly IQ on the prevalence rates of comorbid conditions in individuals with ASD.

Lastly, analysis of archived data collected over a period of 20 years imposes a unique set of limitations. For example, individuals diagnosed with ASD may have been assessed using different diagnostic criteria, as the criteria for ASD has changed over the years, necessitating the analysis of the prevalence rates in clinical data collected during a shorter interval of time wherein the diagnosis criteria for ASD is more likely to be similar across all individuals diagnosed with the disorder.

Conclusions

By leveraging a large dataset of 1.8 M individuals (4790 ASD; 1,842,575 without ASD), our study provides critical new information on the prevalence of comorbid conditions in ASD as a function of sex and age. Our data illustrates crucial differences between the patterns of comorbidities in male and female, children/adolescents, adults, and older adults that are distinct in the ASD and non-ASD populations, pointing to a need for further characterization of comorbid conditions in these populations. Further studies are needed to investigate longitudinal patterns in comorbidity across sexes and to understand the genetic, epigenetic and neurobiological basis of sex differences and age-dependent changes in comorbidity.

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Supporting Information

Additional Supporting Information may be found in the online version of this article.

Figure S1. Prevalence rates of ten comorbid conditions in males and females in each of the three age groups in the ASD and the non-ASD population.