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Prevalence of Developmental, Psychiatric, and Neurologic Conditions in Older Siblings of Children with and without Autism Spectrum Disorder: Study to Explore Early Development

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Abstract

This study evaluated developmental, psychiatric, and neurologic conditions among older siblings of children with and without autism spectrum disorder (ASD) to understand the extent of familial clustering of these diagnoses. Using data from the Study to Explore Early Development, a large multi-site case-control study, the analyses included 2,963 children aged 2–5 years with ASD, other developmental disabilities (DD group), and a population-based control group (POP). Percentages of index children with older siblings with select developmental, psychiatric, and neurologic conditions were estimated and compared across index child study groups using chi-square tests and multivariable modified Poisson regression. In adjusted analyses, children in the ASD group were significantly more likely than children in the POP group to have one or more older siblings with ASD, developmental delay, attention-deficit/hyperactivity disorder, intellectual disability, sensory integration disorder (SID), speech/language delays, or a psychiatric diagnosis (adjusted prevalence ratio [aPR] range: 1.4–3.7). Children in the DD group were significantly more likely

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Ethics Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Obtained from all individual participants included in the study.

Conflict of Interest Victoria L. Fields, Lin H. Tian, Lisa D. Wiggins, Gnakub N. Soke, Katherine Overwyk, Eric Moody, Nuri Reyes, Stuart K. Shapira, Laura A. Schieve declare that they have no conflict of interest

than children in the POP group to have an older sibling with most of the aforementioned conditions, except for intellectual disability and psychiatric diagnosis (aPR range: 1.4–2.2). Children in the ASD group were significantly more likely than children in the DD group to have one or more older siblings with ASD, developmental delay, SID, or a psychiatric diagnosis (aPR range: 1.4–1.9). These findings suggest that developmental disorders cluster in families. Increased monitoring and screening for ASD and other DDs may be warranted when an older sibling has a DD diagnosis or symptoms.

Keywords

Autism spectrum disorder; Developmental disabilities; Siblings; Conditions; Diagnoses

Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder marked by impairments in social interaction and communication, and restricted and repetitive interests and behaviors. While the etiology of ASD is not well understood, studies suggest contributions from both genetic and environmental factors (McGuinn et al., 2020; Hallmayer et al., 2011; Colvert et al., 2015).

Later-born siblings of children with ASD are more likely to be diagnosed with ASD than later-born siblings of children not diagnosed with ASD (Miller et al., 2019). Both sibling concordance rates and the results from genetic linkage analyses are consistent with a polygenic mode of transmission (Hallmayer et al., 2011; Colvert et al., 2015; Constantino et al., 2010; Nordenbæk et al., 2014). Additionally, epidemiologic studies have reported associations between ASD and early life air pollution exposure (McGuinn et al., 2020; Flores-Pajot et al., 2016; Volk et al., 2020) and maternal health conditions, such as autoimmune conditions, infertility disorders, obesity, and pregnancy complications (e.g., hypertension), all of which can recur in subsequent pregnancies (Croen et al., 2019; Schieve et al., 2017; Matias et al., 2021; Cordero et al., 2019). Thus, both genetic and non-genetic environmental and maternal factors may explain the high rates of ASD within sibling groups (Croen et al., 2019; Schieve et al., 2017; Matias et al., 2021; Cordero et al., 2019).

Previous studies that evaluated the health and development of siblings of individuals with ASD report familial clustering of ASD (Miller et al., 2019; Jokiranta-Olkonienmi et al., 2016; Ozonoff et al., 2011; Shephard et al., 2017). Studies also report other (non-ASD) developmental disabilities in siblings of children with ASD, most notably attention-deficit/hyperactivity disorder (ADHD) and/or ADHD-related symptomatology (Lin et al., 2021; Miller et al., 2019; Septier et al., 2019; Ghirardi et al., 2018; Chien et al., 2017; Shephard et al., 2017; Jokiranta-Olkonienmi et al., 2016). Using medical records data from two large US health care systems, Miller et al. (2019) found that later-born siblings of children with ASD or ADHD were at elevated risk for the same disorder, and also of being diagnosed with the other disorder (Miller et al., 2019). In a case-control study conducted at three clinical centers in France, ADHD was found to be 3–4 times more frequent in relatives of children with ASD than in relatives of a control group of unaffected children (Septier

et al., 2019). Studies based on registry-based data in Sweden (Ghiradi et al., 2018) and Finland (Jokiranta-Olkonemi et al., 2016) reported a strong co-aggregation between ASD and ADHD among individuals from the same family. Chien et al. (2017) assessed sibling pairs enrolled through a clinical center in Taiwan and found that siblings of children with ASD had higher than expected levels of hyperactivity and impulsivity, and reduced levels of attention (Chien et al., 2017). A subsequent longitudinal study using Taiwan's National Health Insurance Research Database also found that unaffected siblings of children with ASD were more likely to develop ADHD compared with a control group (7.8% vs. 2.3% in controls; Lin et al., 2022).

Smaller case series with in-depth developmental assessments support the findings from larger studies, demonstrating a high proportion of ASD case siblings have ADHD and anxiety symptomatology (Shephard et al., 2017). The purported mechanism for ADHD in siblings of ASD cases is that the two conditions partially share both genetic and other biological causes (Miller et al., 2019; Musser et al., 2014; Oerlemans et al., 2015).

Studies of other non-ADHD developmental outcomes in siblings include the longitudinal study from Taiwan, which reported increased diagnoses of speech or language disorder, developmental coordination disorder, intellectual disability (ID), anxiety disorder, and depression among siblings of individuals with ASD (Lin et al., 2022). A nested case-control study within the Finish registry reported increased diagnoses of learning disorders, coordination disorders, ID, oppositional defiant disorder, and emotional disorders among siblings of children with ASD (Jokiranta-Olkonemi et al., 2016). Various small clinical studies demonstrate that siblings of children with ASD manifest cognitive, language, or learning difficulties (Gamliel et al., 2009; Georgiades et al., 2013; Piven et al., 1990; Fombonne et al., 1997; Folstein et al., 1999). Additionally, a meta-analysis that assessed numerous studies of developmental and psychological outcomes reported that overall, siblings of individuals with ASD were significantly more likely to have internalizing behavioral problems and psychological problems than comparison groups; however, the authors note the effect size was small and that across studies inconsistent outcome measures were used and there was variation in the findings for individual studies, with numerous studies reporting no significant differences between sibling groups (Shivers et al., 2019).

In sum, while the co-aggregation of ASD and ADHD among sibling groups has been fairly well-established, non-ADHD developmental and psychological outcomes in siblings has been less well studied. Moreover, studies to date have been hampered to varying extents by limitations including small non-generalizable clinical samples, lack of/limited comparison groups, non-standardized measures of ASD and other DD diagnoses among both index children and siblings, and passive outcome ascertainment methods based on clinical diagnoses. Indeed, one of the most robust studies to date, which used a longitudinal design, did not prospectively evaluate study participants with standardized developmental assessments, but instead relied on diagnoses in children's medical records; given the timeframe for This study was more than 20 years ago, the presence of DDs among siblings was likely underestimated and potentially biased given parents who already had one child with ASD might have differentially sought clinical developmental evaluations for their other children (Lin et al., 2022).

We examined ASD and other developmental, psychiatric, and neurological conditions among the siblings of children with or without ASD who were included in the Study to Explore Early Development (SEED), a large case-control study of ASD conducted in several US states. In addition to its large size, SEED'S population-based methodology enrolled a much more racially diverse sample than most previous studies assessing this topic. SEED also collected a much larger number of developmental, psychiatric, and neurologic conditions among siblings than most previous studies. Additionally, SEED has several unique features that add to the robustness of this study. ASD case classification in index children did not rely on past diagnoses but instead included children with symptomatology without a diagnosis as all children's final case status was based on an in-person standardized developmental assessment. SEED included two control groups – children from the general population, and children with non-ASD developmental conditions – that provided data to help disentangle familial clustering that was specific to ASD from that common to developmental disorders generally. Thus, this study adds to the current understanding of the extent of familial clustering of developmental diagnoses in children, and the findings inform the comprehensive family care needs for children with developmental disorders.

Methods

Study Design and Data Collection

SEED was designed to better understand the risk factors and phenotypes associated with ASD. This analysis describes data collected in SEED Phase 1 (2007–2012) and SEED Phase 2 (2012–2016). The same six study sites (located in California, Colorado, Georgia, Maryland, North Carolina, and Pennsylvania) completed SEED Phases 1 and 2 following a common protocol that included the same data collection methodology and forms (Schendel et al., 2012). Children eligible for SEED were aged 2–5 years at the time of study enrollment, lived in the respective site's study area both at birth and at study enrollment, and lived with a caregiver since at least 6 months of age who could provide legal consent and communicate in English (all sites) or Spanish (California and Colorado only). The respondent was required to be the biological mother in SEED Phase 2 in order to improve data collection of pregnancy-related risk factors in this phase; nonetheless, the respondent for 98% of children in the first phase was the biological mother. This study was limited to children whose biological mother was the respondent because data on siblings were collected as part of the mother's reproductive health history, which was not collected from respondents other than the biological mother. SEED included three study groups: children with ASD, children with DDs other than ASD comprising the DD group, and non-ASD children from the general population (POP group). Children with ASD or with other DDs were recruited from multiple clinics and schools at each site. POP controls were recruited from randomly-selected birth records at each site.

Upon enrollment, the mother completed the Social Communication Questionnaire (SCQ), (Rutter et al., 2003) to screen for ASD symptoms in the sampled child. Children with SCQ scores ≥ 11 and/or a previous ASD diagnosis or special education classification underwent in-depth developmental assessments, including the Autism Diagnostic Observation Schedule (ADOS; Lord et al., 2000), and ADOS-2 (for Phase 2), and their caregivers completed

the Autism Diagnostic Interview–Revised (ADI-R; Lord et al., 1994). Final ASD classification was determined by ADOS/ADOS-2 and ADI-R scores (Wiggins et al., 2015a). Further details on the SEED developmental assessment methodology, including the case classification algorithm, psychometric properties of this algorithm, the qualifications of the clinicians who administered the developmental assessments to children enrolled in SEED, and the quality assurance practices to assure instrument administration fidelity and ongoing reliability, have been previously published (Wiggins et al., 2015a).

Mothers also completed structured telephone interviews and self-administered forms assessing sociodemographic characteristics and child health conditions and behaviors. This analysis used data from the maternal telephone interview. Mothers were asked questions pertaining to their pregnancy history, including pregnancies and births with partners other than the index child's father. For the index child and all other liveborn children, the mother was asked a series of questions about diagnoses of developmental conditions. The mother was asked if "a doctor or health care provider ever told you that (CHILD'S NAME) had or has any of the conditions"; a list of conditions was then read by the interviewer (see Appendix A for full list of conditions). Additionally, the mother was asked to specify any other developmental conditions the child had that were not listed. These reports were reviewed by the author group and recoded to one of the listed conditions when the wording described the condition or corresponded verbatim. The mother was instructed that a health care provider at the child's school, such as a child psychologist, physical therapist, occupational therapist, or school nurse, was also considered a qualified health care professional in answering the questions; however, the child's teachers were not to be considered health care providers.

The analysis included index children with a final classification of ASD, DD, or POP who had one or more older siblings from any live births reported by the mother. Thus, only index children with half or full older siblings were included in the study for all analyses. Younger siblings were not considered in this analysis because given the young age of the index children (2 to 5 years), many younger siblings may not have had sufficient time for diagnosis of a developmental disorder.

This study was approved by institutional review boards at the Centers for Disease Control and Prevention and by participating sites. The study has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Written informed consent was obtained from the parents of all study participants.

Data Analysis

In This analysis, we only assessed conditions for which there were ≥ 10 "YES" responses for older siblings of index children in the ASD and DD study groups. Conditions excluded from analysis because they did not meet This threshold included cerebral palsy, Down syndrome, fragile X syndrome, Rett syndrome, and Tourette syndrome or tic disorders. Additionally, we excluded two conditions—reading difficulty and behavioral problem—because they are general descriptions of developmental problems that do not completely align with a specific diagnosis. Finally, we excluded two conditions—sleep disorder and

self-injurious behavior—with a high likelihood of under-reporting because the question series pertaining to siblings' conditions required a health care provider diagnosis for an affirmative response. Indeed, among index children, we found the prevalence of maternal reports of diagnoses for sleep disorder and self-injurious behavior were much lower than maternal reports on other more in-depth developmental forms that had asked about index children's sleeping patterns and sleep disturbances (regardless of health care diagnosis) and specific self-injurious behavior symptomatology. (This more detailed information was not ascertained for the siblings.)

We categorized the conditions that were included in This analysis as developmental, psychiatric, or neurologic in keeping with the classification scheme used in a previous surveillance study (Levy et al., 2010). Developmental diagnoses included ASD (Asperger syndrome, autism, and pervasive developmental disorder not otherwise specified were combined into one category), developmental delay, ADHD, ID, sensory integration disorder (SID, dysfunctional sensory system where one or more senses are either over- or under-reactive to stimulation), learning disabilities, speech/language delays, and movement or coordination problems or motor delays. Psychiatric diagnoses included anxiety, obsessive-compulsive disorder, bipolar disorder, depression, and mood disorder not otherwise specified, which were combined into a single variable—psychiatric condition—for analysis because of small sample sizes for individual psychiatric diagnoses. Neurologic diagnoses included epilepsy or seizure disorder, vision problems (uncorrectable), and hearing problems. We also assessed a combined category of any of the conditions that were included in the analysis. Conditions were not mutually exclusive (i.e., older siblings could be reported to have multiple conditions). While we lacked information to inform the underlying cause of vision and hearing problems, we included these conditions within the broader “neurologic disorders” heading in keeping with the classification scheme for neurodevelopmental disorders in children utilized by Levy et al. (2010), in which they distinguished developmental disorders (consisting of behaviorally-related disorders, cognitive and learning disorders, and various types of developmental delays) from other “medical” neurologic disorders.

We compared the distribution of sociodemographic factors by study group (ASD vs. POP, DD vs. POP, ASD vs. DD) using chi-square tests. For each study group (ASD, DD, or POP), we calculated the percentage of index children who had one or more older siblings with each of the aforementioned conditions and used chi-square tests for comparing between study groups. Adjusted prevalence ratios were estimated to quantify differences between groups using modified Poisson regression (Zou, 2004), which is a frequently applied method to estimate risk ratios for binary outcomes and is robust to issues of convergence. In addition to study group, models included index child's sex and age, mother's race/ethnicity, education, age at study enrollment, primary language spoken, and birth location, and household income, as independent variables. Multicollinearity diagnostic statistics, variance inflation factors, tolerances, and correlation coefficients were used to detect multicollinearity of the independent variables.

We carried out two series of supplemental analyses. First, we assessed the percentages of index children with older siblings (one, two, or three or more) who had ASD. While not

a recurrence risk assessment per se, this analysis provides insight into the extent of ASD clustering, or the finding of more than one occurrence of ASD, in some families. Second, we excluded index children whose older sibling was reported to have ASD and then assessed the percentage of index children with older siblings with each of the other conditions with p-values derived from chi-square or Fisher's exact tests for comparing between study groups. This analysis provides insight into which conditions, beyond ASD, are more likely to occur in older siblings of children with ASD (i.e., conditions which appear to occur independently of ASD).

Results

For the analysis, we excluded children with only younger siblings or no siblings ($n = 2,379$), as well as children whose parent did not respond to the questions on conditions in siblings ($n = 3$) or responded "don't know" for all conditions ($n = 13$). Our analytic sample included 738 index children with ASD, 1,186 index children with another DD, and 1,039 index children in the POP group.

When compared to POP group children, children with ASD or another DD were less likely to have been born to non-Hispanic white mothers, mothers with a bachelor's degree or higher, and in high income families. Over 70% of index children in all groups were 48 months of age or older. ASD and DD group children were more likely to be male (82.0% and 66.0%) than POP group children (53.8%; p -values < 0.05). Over 75% of mothers in all groups were born in the United States and more than 85% reported English as their primary language, although mothers of POP children were more likely than mothers of ASD or DD children to be born in the United States and to speak English. Across study groups, most index children had only 1 older sibling, with a descending percentage having 2 or 3 or more older siblings (Table 1).

Index children in the ASD group were significantly more likely ($p < 0.05$) than index children in the POP group to have one or more older siblings with the following conditions: ASD, developmental delay, ADHD, ID, SID, learning disabilities, speech/language delays, and/or psychiatric diagnoses (Table 2). Index children in the DD group were significantly more likely than index children in the POP group to have one or more older siblings with all of the same conditions except psychiatric diagnoses. Index children in the ASD group were significantly more likely than index children in the DD group to have one or more older siblings with two conditions—ASD and developmental delay.

Overall, most results were consistent between unadjusted and adjusted analyses. The adjusted prevalence ratios (aPRs) comparing study groups (ASD, DD, POP) on whether index children had one or more older siblings with a developmental, psychiatric, or neurologic condition are shown in Fig. 1. The aPRs indicate that children with ASD were significantly more likely than children in the POP group to have one or more older siblings with ASD, developmental delay, ADHD, ID, SID, speech/language delays, and/or a psychiatric diagnosis, with point estimates ranging from 1.4 (for ADHD) to 3.7 (for ID and SID). Children in the DD group were also significantly more likely than children in the POP group to have an older sibling with most of the aforementioned conditions, with

the exception of a psychiatric diagnosis, and most aPR point estimates were attenuated relative to those comparing ASD to POP, ranging from 1.4 (ADHD) to 2.2 (SID). Children with ASD were significantly more likely than children with other DDs to have an older sibling with an ASD (aPR = 1.9), developmental delay (aPR = 1.4), SID (aPR = 1.6), or a psychiatric diagnosis (aPR = 1.9).

The number of index children with one or more older siblings with parent-reported diagnosis of ASD is reported in Supplemental Table 1. Among index children with only one older sibling, we found that the percentage of older siblings with ASD varied significantly by index child study group—54 (11.1%) for the ASD group, 47 (6.9%) for the DD group, and 25 (3.7%) for the POP group. Among index children with two or more older siblings the likelihood of having an older sibling with ASD was even higher, particularly for the ASD study group. Among ASD index children with two older siblings, the percentage who had one or more older siblings with ASD was 20%.

When index children who had an older sibling with ASD were excluded from analyses, there were fewer significant differences between study groups in the percentage having an older sibling with a psychiatric or most developmental conditions (Supplemental Table 2). Index children with ASD remained significantly ($p < 0.05$) more likely than index children in the POP group to have one or more older siblings with ADHD (13.7% vs. 10.5%) or speech/language delays (13.3% vs. 9.2%). Index children in the DD group were significantly more likely than index children in the POP group to have an older sibling with developmental delay (6.1% vs. 3.5%), ADHD (16.4% vs. 10.5%), learning disabilities (7.8% vs. 4.2%), and/or speech/language delays (14.8% vs. 9.2%). Additionally, index children in the DD group were more likely than index children in the ASD group to have an older sibling with learning disabilities (7.8% vs. 4.6%). Among the three study groups, the most common conditions seen in older siblings without ASD were developmental delays, ADHD, learning disabilities, and speech/language delays.

Discussion

Previous SEED analyses examined the prevalence of co-occurring developmental conditions and symptomatology in SEED index children and found that over half of the children in the ASD case group had one or more behavioral, developmental, medical, or psychiatric condition other than ASD (Wiggins et al., 2015a, 2022). Here, we compared developmental, psychiatric, and neurologic conditions among older siblings of children with ASD, children with other DDs, and children from the general population. We found that older siblings of children with ASD or with other DDs were more likely to have developmental conditions than older siblings of children in the POP comparison group. Older siblings of children with ASD were also more likely to have psychiatric conditions than either older siblings of children in the POP group or older siblings in the DD group. However, there was little variation between study groups in the three neurologic conditions we assessed — epilepsy and vision and hearing problems. Overall, our findings suggest that developmental disorders cluster in families. Thus, once a child is diagnosed with ASD or other DDs, enhanced monitoring of developmental and psychiatric problems in siblings might be warranted. While the current analysis also provides some insight into heritability, the data should be

interpreted cautiously in that regard, given the small sample size of some conditions found in older siblings and that we were limited to using parent-reported data on conditions in siblings.

The rate of ASD among older siblings of index children with ASD in our study (i.e., the likelihood that ASD was also diagnosed in one or more older siblings if the index child had ASD) was 14%, which is within the range of the prevalence of recurrence (10–20%) reported in other studies (Miller et al., 2019; Jokiranta-Olkonemi et al., 2016; Ozonoff et al., 2011; Sandin et al., 2014; Grønberg et al., 2013), although to be clear, our study did not measure recurrence of ASD, but rather what would be considered “pre-occurrence” in families. For index children with only one older sibling, siblings in the ASD group were 3 times more likely to be diagnosed with ASD compared to older siblings in the POP group and 1.6 times more likely compared to older siblings in the DD group. Although few children in the study group had more than one older sibling with ASD, we found that the likelihood of an index child with ASD having one or more older siblings with ASD nearly doubled (from 11 to 20%) when the number of older siblings increased from one to two. These findings could be due to genetic risks of ASD but also to non-genetic maternal risks equally common across pregnancies of the index child and their siblings.

Our finding of increased prevalence of diagnosed SID in older siblings of children with ASD supports previous results from several large, population-based samples that have indicated a high prevalence of sensory features in children with ASD (Wiggins et al., 2015a, 2022; Kirby et al., 2022). Assessments of sensory traits in the broader autism phenotype have found that parents and siblings of individuals with ASD show higher levels of self-reported sensory traits relative to the general population (Robertson & Baron-Cohen, 2017). Atypical sensory experience is estimated to occur in as many as 90% of individuals with ASD and to affect every sensory modality, and the latest diagnostic criteria for ASD include sensory sensitivities as a diagnostic feature (Robertson & Baron-Cohen, 2017). Notably, in our supplemental analyses in which we excluded older siblings who had an ASD diagnosis, SID was no longer differential between the siblings of ASD, DD, and POP group index children. These findings support the supposition that SID may be specific to the ASD phenotype.

Previous clinical studies have reported lower cognitive abilities among siblings of children with ASD (Georgiades et al., 2013; Piven et al., 1990; Folstein et al., 1999); however, other studies have reported no association, (Szatmari et al., 1993; Pilowsky et al., 2007; Ozonoff et al., 1993) or higher verbal intelligence quotient levels among siblings of children with ASD (Fombonne et al., 1997; Pilowsky et al., 2003). Here, we report a higher percentage of ID in older siblings of children with ASD or with other DDs; however as with SID, this finding was no longer evident when siblings with an ASD diagnosis were excluded from analysis, suggesting it was not an independent association.

As with ID, previous studies of psychiatric disorders (anxiety, depression, and bipolar disorder) in siblings of children with ASD have reported inconsistent findings (Lin et al., 2022; Lovell & Wetherell, 2016; Quintero & McIntyre, 2010; Sullivan et al., 2012; Selten et al., 2015). In the current study, index children in the ASD group were significantly more likely than children in either the POP or DD groups to have a sibling with a psychiatric

condition. However, as with SID and ID, this differential was no longer observed in the sub-sample that excluded older siblings with an ASD diagnosis, which again, suggests that the high level of ASD recurrence in families explained the psychiatric condition finding. Nonetheless, in our and other studies, sample sizes limited the assessment of individual psychiatric conditions and, thus, negative findings should be cautiously interpreted.

In sum, our and previous reports support the possibility of cross-aggregation of ASD and various other conditions including SID, ID, and psychiatric conditions. However, in our study, we conducted supplemental analyses to further disentangle the underlying reasons developmental and psychiatric conditions were more prevalent in siblings. Those findings indicate that the positive findings initially observed for SID, ID, and psychiatric conditions likely reflect ASD clustering within many of those families, rather than independent familial clustering between ASD and the aforementioned conditions.

Nonetheless, we also found that several non-ASD conditions, including ADHD, developmental delay, and speech/language delays, were significantly higher in the older siblings of children with ASD than siblings of POP group children, even after the exclusion of siblings with a diagnosis of ASD. Thus, our finding of clustering of ASD with some non-ASD developmental conditions appears to be robust and not explained by the known high risk for ASD clustering within families. However, we found the same conditions were increased in siblings of children in the (non-ASD) DD group. Thus, the findings might not be specific to ASD co-aggregation.

Still, our findings that children with ASD were more likely than children in the POP group to have one or more older siblings with ADHD align with numerous previous studies and lend support to the hypothesis of some shared biological pathways between ASD and ADHD (Miller et al., 2019; Septier et al., 2019; Lin et al., 2022; Jokiranta-Olkonemi et al., 2016). In addition to co-diagnoses of ASD and ADHD, studies suggest that many children with ADHD have symptomology that includes social and communication difficulties and, likewise, children with ASD commonly exhibit hyperactivity and attention difficulties (Mulligan et al., 2009). An etiologic link between ADHD and ASD symptoms has been supported by family and twin studies (Nijmeijer et al., 2009; Mulligan et al., 2009; Reiersen et al., 2008; Musser et al., 2014) and genetic analyses have documented shared copy number variants (Martin et al., 2014; Williams et al., 2012; Musser et al., 2014) and candidate genes (Zhou et al., 2023) between the two conditions, although the specific genetic findings vary across studies.

The composite findings from this study have implications for service needs of families. Children with ASD use more health services and have more difficulties accessing needed care than children in the general population (Kogan et al., 2018). Because of the multiple types of services needed by children with ASD, care coordination is challenging, and parents are less likely to report that their child's care meets all of the criteria for a medical home than the parents of children without ASD. Particular difficulties include getting needed referrals and access to specialist care, such as mental health services (Kogan et al., 2018). When more than one child is affected with ASD or another DD, there is even greater cumulative health and family resource needs and increased caregiving burden. The data

we report here, that nearly 40% of the older siblings of children with ASD had one or more developmental, psychiatric, or neurologic condition, provides a sense of how often families are caring for multiple children with developmental and mental health conditions and associated specialized service needs. Moreover, our data underscore the importance of monitoring siblings of children diagnosed with ASD or another DD, such that they can be identified and begin interventions as early as possible.

Limitations to this study should be considered in interpreting these findings. Given the young age of the index children in our sample, we excluded younger siblings from the analysis as they may not yet have had sufficient time for symptom manifestation and diagnosis for many developmental, psychiatric, and neurologic conditions examined (Soke et al., 2018). Thus, we may have underestimated the magnitude of clustering among siblings for some conditions. Additionally, some conditions, such as ADHD, may not be diagnosed until school-age (Soke et al., 2018); thus, while we may have limited misclassification by including only index children with older siblings in our study sample, it is possible that some older siblings who have ADHD were not yet diagnosed by the time of their family's SEED participation. Conversely, having a child with an ASD or other developmental diagnosis may prompt families to pro-actively seek an evaluation and obtain a diagnosis for their other children. That is, for parents who have raised a child with ASD or another developmental condition, there may be increased sensitivity to mental and developmental symptoms found in other siblings (Lin et al., 2022). As parents' awareness about developmental disorders increases through treating their child's ASD or other DD, they may more readily seek help for siblings than parents who do not have a child with ASD or other DD diagnosis (Jokiranta-Olkonemi et al., 2016). These parents also may more likely recall their other children's health conditions than parents who do not have a child with a developmental disability. However, parents were provided with a preparation guide before the interview so they could collect information to reduce recall bias. Additionally, it's also possible that some parents with more than one child with DD/ID, or ASD might not have participated in SEED due to time constraints caused by their high caregiving burden. However, a previous SEED analysis in one study site compared children who did and did not participate in the study and found little impact on several key birth characteristics or outcomes, suggesting the final study sample was robust (Schieve et al., 2018). We did not have the data to determine the genetic and non-genetic environmental contributions to the familial clustering of developmental disabilities that we observed in this study. Additionally, sample size constraints precluded us from adjusting for sex of the sibling when examining associations for each condition; given some conditions are more commonly diagnosed in males (Maenner et al., 2020; Arnett et al., 2015), our findings may have been influenced by unmeasured confounding. Finally, siblings' diagnoses were reported by parents, and we did not have access to medical records or conduct study developmental assessments on siblings to confirm parent reports; nonetheless, question verbiage specified that conditions reported should have been diagnosed by a health care provider.

Despite these limitations, the SEED sample had many strengths, including recruitment methods that resulted in a diverse sample of children in all three study groups that better represented the racial, ethnic, and socioeconomic diversity in the US than previous studies on this topic (DiGuseppi et al., 2016). While our sample size was not sufficient to examine

all conditions of interest in siblings of index children, it is nonetheless one of the largest studies to date with detailed data on developmental, psychiatric, and neurologic conditions reported in siblings of study group children.

Our results suggest that increased monitoring and screening for ASD and other DDs may be warranted when an older sibling has a diagnosis or symptomatology of ASD or another DD. Future research could explore the contributions of both genetic and non-genetic environmental factors to the clustering of developmental conditions within families (e.g., Matias et al., 2021). Our results also suggest the need to consider the impacts when multiple children are diagnosed with conditions within one family, i.e., the implications of how both family burden and resource needs might increase. Additionally, this study demonstrates that having more than one child affected by a disability is not uncommon and, thus, highlights the importance of health care and other service providers considering the total family needs when treating a child with ASD or other DD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

- Arnett AB, Pennington BF, Willcutt EG, DeFries JC, & Olson RK (2015). Sex differences in ADHD symptom severity. *Journal of Child Psychology and Psychiatry and Allied Disciplines*, 56(6), 632–639. 10.1111/jcpp.12337. [PubMed: 25283790]
- Chien YL, Chou MC, Chiu YN, Chou WJ, Wu YY Tsai WC, & Gau SS (2017). ADHD-related symptoms and attention profiles in the unaffected siblings of probands with autism spectrum disorder: Focus on the subtypes of autism and Asperger's disorder. *Molecular Autism*, 8, 37. 10.1186/s13229-017-0153-9. [PubMed: 28770037]
- Colvert E, Tick B, McEwen F, Stewart C, Curran SR, Woodhouse E, Gillan N, Hallett V, Lietz S, Garnett T, Ronald A, Plomin R, Rijsdijk F, Happé F, & Bolton P (2015). Heritability of autism

- spectrum disorder in a UK population-based twin sample. *JAMA Psychiatry*, 72(5), 415–423. 10.1001/jamapsychiatry.2014.3028. [PubMed: 25738232]
- Constantino JN, Zhang Y, Frazier T, Abbacchi AM, & Law P (2010). Sibling recurrence and the genetic epidemiology of autism. *The American Journal of Psychiatry*, 167(11), 1349–1356. 10.1176/appi.ajp.2010.09101470. [PubMed: 20889652]
- Cordero C, Windham GC, Schieve LA, Fallin MD, Croen LA, Siega-Riz AM, Engel SM, Herring AH, Stuebe AM, Vladutiu CJ, & Daniels JL (2019). Maternal diabetes and hypertensive disorders in association with autism spectrum disorder. *Autism Research: Official Journal of the International Society for Autism Research*, 12(6), 967–975. 10.1002/aur.2105. [PubMed: 30969030]
- Croen LA, Qian Y, Ashwood P, Daniels JL, Fallin D, Schendel D, Schieve LA, Singer AB, & Zerbo O (2019). Family history of immune conditions and autism spectrum and developmental disorders: Findings from the study to explore early development. *Autism Research: Official Journal of the International Society for Autism Research*, 12(1), 123–135. 10.1002/aur.1979. [PubMed: 30095240]
- DiGuseppi CG, Daniels JL, Fallin DM, Rosenberg SA, Schieve LA, Thomas KC, Windham GC, Goss CW, Soke GN, Currie DW, Singer AB, Lee LC, Bernal P, Croen LA, Miller LA, Pinto-Martin JA, Young LM, & Schendel DE (2016). Demographic profile of families and children in the study to explore Early Development (SEED): Case-control study of autism spectrum disorder. *Disability and Health Journal*, 9(3), 544–551. 10.1016/j.dhjo.2016.01.005. [PubMed: 26917104]
- Flores-Pajot MC, Ofner M, Do MT, Lavigne E, & Villeneuve PJ (2016). Childhood autism spectrum disorders and exposure to nitrogen dioxide, and particulate matter air pollution: A review and meta-analysis. *Environmental Research*, 151, 763–776. 10.1016/j.envres.2016.07.030. [PubMed: 27609410]
- Folstein SE, Santangelo SL, Gilman SE, Piven J, Landa R, Lainhart J, Hein J, & Wzorek M (1999). Predictors of cognitive test patterns in autism families. *Journal of Child Psychology and Psychiatry and Allied Disciplines*, 40(7), 1117–1128. [PubMed: 10576540]
- Fombonne E, Bolton P, Prior J, Jordan H, & Rutter M (1997). A family study of autism: Cognitive patterns and levels in parents and siblings. *Journal of Child Psychology and Psychiatry and Allied Disciplines*, 38(6), 667–683. 10.1111/j.1469-7610.1997.tb01694.x. [PubMed: 9315977]
- Gamliel I, Yirmiya N, Jaffe DH, Manor O, & Sigman M (2009). Developmental trajectories in siblings of children with autism: Cognition and language from 4 months to 7 years. *Journal of Autism and Developmental Disorders*, 39(8), 1131–1144. 10.1007/s10803-009-0727-2. [PubMed: 19326200]
- Georgiades S, Szatmari P, Zwaigenbaum L, Bryson S, Brian J, Roberts W, Smith I, Vaillancourt T, Roncadin C, & Garon N (2013). A prospective study of autistic-like traits in unaffected siblings of probands with autism spectrum disorder. *JAMA Psychiatry*, 70(1), 42–48. 10.1001/2013.jamapsychiatry.1. [PubMed: 22945359]
- Ghirardi L, Brikell I, Kuja-Halkola R, Freitag CM, Franke B, Asherson P, Lichtenstein P, & Larsson H (2018). The familial co-aggregation of ASD and ADHD: A register-based cohort study. *Molecular Psychiatry*, 23(2), 257–262. 10.1038/mp.2017.17. [PubMed: 28242872]
- Grønberg TK, Schendel DE, & Parner ET (2013). Recurrence of autism spectrum disorders in full- and half-siblings and trends over time: A population-based cohort study. *JAMA Pediatrics*, 167(10), 947–953. 10.1001/jamapediatrics.2013.2259. [PubMed: 23959427]
- Hallmayer J, Cleveland S, Torres A, Phillips J, Cohen B, Torigoe T, Miller J, Fedele A, Collins J, Smith K, Lotspeich L, Croen LA, Ozonoff S, Lajonchere C, Grether JK, & Risch N (2011). Genetic heritability and shared environmental factors among twin pairs with autism. *Archives of General Psychiatry*, 68(11), 1095–1102. 10.1001/archgenpsychiatry.2011.76. [PubMed: 21727249]
- Jokiranta-Olkonien E, Cheslack-Postava K, Sucksdorff D, Suominen A, Gyllenberg D, Chudal R, Leivonen S, Gissler M, Brown AS, & Sourander A (2016). Risk of psychiatric and neurodevelopmental disorders among siblings of probands with autism spectrum disorders. *JAMA Psychiatry*, 73(6), 622–629. 10.1001/jamapsychiatry.2016.0495. [PubMed: 27145529]
- Kirby AV, Bilder DA, Wiggins LD, Hughes MM, Davis J, Hall-Lande JA, Lee LC, McMahon WM, & Bakian AV (2022). Sensory features in autism: Findings from a large population-based surveillance system. *Autism Research: Official Journal of the International Society for Autism Research*, 15(4), 751–760. 10.1002/aur.2670. [PubMed: 35040592]
- Kogan MD, Vladutiu CJ, Schieve LA, Ghandour RM, Blumberg SJ, Zablotsky B, Perrin JM, Shattuck P, Kuhlthau KA, Harwood RL, & Lu MC (2018). The prevalence of parent-reported autism

spectrum disorder among US children. *Pediatrics*, 142(6), e20174161. 10.1542/peds.2017-4161. [PubMed: 30478241]

- Levy SE, Giarelli E, Lee LC, Schieve LA, Kirby RS, Cunniff C, Nicholas J, Reaven J, & Rice CE (2010). Autism spectrum disorder and co-occurring developmental, psychiatric, and medical conditions among children in multiple populations of the United States. *Journal of Developmental and Behavioral Pediatrics: JDBP*, 31(4), 267–275. 10.1097/DBP.0b013e3181d5d03b. [PubMed: 20431403]
- Lin HC, Cheng CM, Huang KL, Hsu JW, Bai YM, Tsai SJ, Chen TJ, & Chen MH (2022). Developmental and mental health risks among siblings of patients with autism spectrum disorder: A nationwide study. *European Child & Adolescent Psychiatry*, 31(9), 1361–1366. 10.1007/s00787-021-01784-9. [PubMed: 33870447]
- Lord C, Rutter M, & Le Couteur A (1994). Autism Diagnostic Interview-Revised: A revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. *Journal of Autism and Developmental Disorders*, 24(5), 659–685. 10.1007/BF02172145. [PubMed: 7814313]
- Lord C, Risi S, Lambrecht L, Cook EH Jr, Leventhal BL, DiLavore PC, Pickles A, & Rutter M (2000). The autism diagnostic observation schedule-generic: A standard measure of social and communication deficits associated with the spectrum of autism. *Journal of Autism and Developmental Disorders*, 30(3), 205–223. [PubMed: 11055457]
- Lovell B, & Wetherell MA (2016). The psychophysiological impact of childhood autism spectrum disorder on siblings. *Research in developmental disabilities*, 49–50, 226–234. 10.1016/j.ridd.2015.11.023.
- Maenner MJ, Shaw KA, Baio J, Ed S1, Washington A, Patrick M, DiRienzo M, Christensen DL, Wiggins LD, Pettygrove S, Andrews JG, Lopez M, Hudson A, Baroud T, Schwenk Y, White T, Rosenberg CR, Lee LC, Harrington RA, Huston M, & Dietz PM (2020). Prevalence of autism spectrum disorder among children aged 8 years - Autism and Developmental Disabilities Monitoring Network, 11 sites, United States, 2016. *Morbidity and mortality weekly report. Surveillance summaries (Washington, D.C.: 2002)*, 69(4), 1–12. 10.15585/mmwr.ss6904a1.
- Martin J, Cooper M, Hamshire ML, Pocklington A, Scherer SW, Kent L, Gill M, Owen MJ, Williams N, O'Donovan MC, Thapar A, & Holmans P (2014). Biological overlap of attention-deficit/hyperactivity disorder and autism spectrum disorder: Evidence from copy number variants. *Journal of the American Academy of Child and Adolescent Psychiatry*, 53(7), 761–70e26. 10.1016/j.jaac.2014.03.004. [PubMed: 24954825]
- Matias SL, Pearl M, Lyall K, Croen LA, Krai TVE, Fallin D, Lee LC, Bradley CB, Schieve LA, & Windham GL (2021). Maternal prepregnancy weight and gestational weight gain in association with autism and developmental disorders in offspring. *Obesity (Silver Spring Md)*, 29(9), 1554–1564. 10.1002/oby.23228. [PubMed: 34347372]
- McGuinn LA, Windham GC, McGuinn LA, Windham GC, Kalkbrenner AE, Bradley C, Di Q, Croen LA, Fallin MD, Hoffman K, Ladd-Acosta C, Schwartz J, Rappold AG, Richardson DB, Neas LM, Gammon MD, Schieve LA, & Daniels JL (2020). Early life exposure to air pollution and autism spectrum disorder: Findings from a multisite case-control study. *Epidemiology (Cambridge Mass)*, 31(1), 103–114. 10.1097/EDE.0000000000001109. [PubMed: 31592868]
- Miller M, Iosif AM, Young GS, Hill M, Phelps Hanzel E, Hutman T, Johnson S, & Ozonoff S (2016). School-age outcomes of infants at risk for autism spectrum disorder. *Autism Research: Official Journal of the International Society for Autism Research*, 9(6), 632–642. 10.1002/aur.1572.
- Miller M, Musser ED, Young GS, Olson B, Steiner RD, & Nigg JT (2019). Sibling recurrence risk and cross-aggregation of attention-deficit/hyperactivity disorder and autism spectrum disorder. *JAMA Pediatrics*, 173(2), 147–152. 10.1001/jamapediatrics.2018.4076. [PubMed: 30535156]
- Mulligan A, Anney RJ, O'Regan M, Chen W, Butler L, Fitzgerald M, Buitelaar J, Steinhausen HC, Rothenberger A, Minderaa R, Nijmeijer J, Hoekstra PJ, Oades RD, Roeyers H, Buschgens C, Christiansen H, Franke B, Gabriels I, Hartman C, Kuntsi J, & Gill M (2009). Autism symptoms in attention-deficit/hyperactivity disorder: A familial trait which correlates with conduct, oppositional defiant, language and motor disorders. *Journal of Autism and Developmental Disorders*, 39(2), 197–209. 10.1007/s10803-008-0621-3. [PubMed: 18642069]

- Musser ED, Hawkey E, Kachan-Liu SS, Lees P, Rouillet JB, Goddard K, Steiner RD, & Nigg JT (2014). Shared familial transmission of autism spectrum and attention-deficit/hyperactivity disorders. *Journal of Child Psychology and Psychiatry and Allied Disciplines*, 55(7), 819–827. 10.1111/jcpp.12201. [PubMed: 24444366]
- Nijmeijer JS, Hoekstra PJ, Minderaa RB, Buitelaar JK, Altink ME, Buschgens CJ, Fliers EA, Rommelse NN, Sergeant JA, & Hartman CA (2009). PDD symptoms in ADHD, an independent familial trait? *Journal of Abnormal Child Psychology*, 37(3), 443–453. 10.1007/s10802-008-9282-0. [PubMed: 19051006]
- Nordenbæk C, Jørgensen M, Kyvik KO, & Bilenberg N (2014). A Danish population-based twin study on autism spectrum disorders. *European Child & Adolescent Psychiatry*, 23(1), 35–43. 10.1007/s00787-013-0419-5. [PubMed: 23661220]
- Oerlemans AM, Hartman CA, De Bruijn YG, Van Steijn DJ, Franke B, Buitelaar JK, & Rommelse NN (2015). Simplex and multiplex stratification in ASD and ADHD families: A promising approach for identifying overlapping and unique underpinnings of ASD and ADHD? *Journal of Autism and Developmental Disorders*, 45(3), 645–657. 10.1007/s10803-014-2220-9. [PubMed: 25173102]
- Ozonoff S, Rogers SJ, Farnham JM, & Pennington BF (1993). Can standard measures identify subclinical markers of autism? *Journal of Autism and Developmental Disorders*, 23(3), 429–441. 10.1007/BF01046049. [PubMed: 8226580]
- Ozonoff S, Young GS, Carter A, Messinger D, Yirmiya N, Zwaigenbaum L, Bryson S, Carver LJ, Constantino JN, Dobkins K, Hutman T, Iverson JM, Landa R, Rogers SJ, Sigman M, & Stone WL (2011). Recurrence risk for autism spectrum disorders: A Baby Siblings Research Consortium study. *Pediatrics*, 128(3), e488–e495. 10.1542/peds.2010-2825. [PubMed: 21844053]
- Pilowsky T, Yirmiya N, Shalev RS, & Gross-Tsur V (2003). Language abilities of siblings of children with autism. *Journal of Child Psychology and Psychiatry and Allied Disciplines*, 44(6), 914–925. 10.1111/1469-7610.00175. [PubMed: 12959499]
- Pilowsky T, Yirmiya N, Gross-Tsur V, & Shalev RS (2007). Neuropsychological functioning of siblings of children with autism, siblings of children with developmental language delay, and siblings of children with mental retardation of unknown genetic etiology. *Journal of Autism and Developmental Disorders*, 37(3), 537–552. 10.1007/s10803-006-0185-z. [PubMed: 17016678]
- Piven J, Gayle J, Chase GA, Fink B, Landa R, Wzorek MM, & Folstein SE (1990). A family history study of neuropsychiatric disorders in the adult siblings of autistic individuals. *Journal of the American Academy of Child and Adolescent Psychiatry*, 29(2), 177–183. 10.1097/00004583-199003000-00004. [PubMed: 2324058]
- Quintero N, & McIntyre LL (2010). Sibling adjustment and maternal well-being: An examination of families with and without a child with an autism spectrum disorder. *Focus on Autism and Other Developmental Disabilities*, 25(1), 37–46. 10.1177/1088357609350367. [PubMed: 21037802]
- Reiersen AM, Constantino JN, Grimmer M, Martin NG, & Todd RD (2008). Evidence for shared genetic influences on self-reported ADHD and autistic symptoms in young adult Australian twins. *Twin Research and Human Genetics: The Official Journal of the International Society for Twin Studies*, 11(6), 579–585. 10.1375/twin.11.6.579. [PubMed: 19016613]
- Robertson CE, & Baron-Cohen S (2017). Sensory perception in autism. *Nature Reviews Neuroscience*, 18(11), 671–684. 10.1038/nrn.2017.112. [PubMed: 28951611]
- Rutter M, Bailey A, & Lord C (2003a). SCQ: Social Communication Questionnaire. Western Psychological Services.
- Sandin S, Lichtenstein P, Kuja-Halkola R, Larsson H, Hultman CM, & Reichenberg A (2014). The familial risk of autism. *Journal of the American Medical Association*, 311(17), 1770–1777. 10.1001/jama.2014.4144. [PubMed: 24794370]
- Schendel DE, Diguiseppi C, Croen LA, Fallin MD, Reed RL, Schieve LA, Wiggins LD, Daniels J, Grether J, Levy SE, Miller L, Newschaffer C, Pinto-Martin J, Robinson C, Windham GC, Alexander A, Aylsworth AS, Bernal P, Bonner JD, Blaskey L, & Yeargin-Allsopp M (2012). The study to explore Early Development (SEED): A multisite epidemiologic study of autism by the Centers for Autism and Developmental Disabilities Research and Epidemiology (CADDRE) network. *Journal of Autism and Developmental Disorders*, 42(10), 2121–2140. 10.1007/s10803-012-1461-8. [PubMed: 22350336]

- Schieve LA, Drews-Botsch C, Harris S, Newschaffer C, Daniels J, DiGuseppi C, Croen LA, & Windham GC (2017). Maternal and paternal infertility disorders and treatments and autism spectrum disorder: Findings from the study to explore Early Development. *Journal of Autism and Developmental Disorders*, 47(12), 3994–4005. 10.1007/s10803-017-3283-1. [PubMed: 28900768]
- Schieve LA, Harris S, Maenner MJ, Alexander A, & Dowling NF (2018). Assessment of demographic and perinatal predictors of non-response and impact of non-response on measures of association in a population-based case control study: Findings from the Georgia Study to explore Early Development. *Emerging Themes in Epidemiology*, 15, 12. 10.1186/s12982-018-0081-y. [PubMed: 30147744]
- Selten JP, Lundberg M, Rai D, & Magnusson C (2015). Risks for nonaffective psychotic disorder and bipolar disorder in young people with autism spectrum disorder: A population-based study. *JAMA Psychiatry*, 72(5), 483–189. 10.1001/jamapsychiatry.2014.3059. [PubMed: 25806797]
- Septier M, Peyre H, Amsellem F, Beggato A, Maruani A, Poumeyreau M, Amestoy A, Scheid I, Gaman A, Bolognani F, Honey G, Bouquet C, Ly-Le Moal M, Bouvard M, Leboyer M, Bourgeron T, & Delorme R (2019). Increased risk of ADHD in families with ASD. *European Child & Adolescent Psychiatry*, 28(2), 281–288. 10.1007/s00787-018-1206-0. [PubMed: 30267210]
- Shephard E, Milosavljevic B, Pasco G, Jones EJ, Gliga T, Happé F, Johnson MH, Charman T, & BASIS Team. (2017). Mid-childhood outcomes of infant siblings at familial high-risk of autism spectrum disorder. *Autism Research: Official Journal of the International Society for Autism Research*, 10(3), 546–557. 10.1002/aur.1733. [PubMed: 27896942]
- Shivers CM, Jackson JB, & McGregor CM (2019). Functioning among typically developing siblings of individuals with autism spectrum disorder: A meta-analysis. *Clinical Child and Family Psychology Review*, 22(2), 172–196. 10.1007/s10567-018-0269-2. [PubMed: 30178117]
- Soke GN, Maenner MJ, Christensen D, Kurzius-Spencer M, & Schieve LA (2018). Prevalence of co-occurring medical and behavioral conditions/symptoms among 4- and 8-year-old children with autism spectrum disorder in selected areas of the United States in 2010. *Journal of Autism and Developmental Disorders*, 48(8), 2663–2676. 10.1007/s10803-018-3521-1. [PubMed: 29524016]
- Sullivan PF, Magnusson C, Reichenberg A, Boman M, Dalman C, Davidson M, Fruchter E, Hultman CM, Lundberg M, Långström N, Weiser M, Svensson AC, & Lichtenstein P (2012). Family history of schizophrenia and bipolar disorder as risk factors for autism. *Archives of General Psychiatry*, 69(11), 1099–1103. 10.1001/archgenpsychiatry.2012.730. [PubMed: 22752149]
- Szatmari P, Jones MB, Tuff L, Bartolucci G, Fisman S, & Mahoney W (1993). Lack of cognitive impairment in first-degree relatives of children with pervasive developmental disorders. *Journal of the American Academy of Child and Adolescent Psychiatry*, 32(6), 1264–1273. 10.1097/00004583-199311000-00022. [PubMed: 8282674]
- Volk HE, Park B, Hollingue C, Jones KL, Ashwood R, Windham GC, Lurman F, Alexeeff SE, Kharrazi M, Pearl M, Van de Water J, & Croen LA (2020). Maternal immune response and air pollution exposure during pregnancy: Insights from the early markers for Autism (EMA) study. *Journal of Neurodevelopmental Disorders*, 12(1), 42. 10.1186/s11689-020-09343-0. [PubMed: 33327930]
- Wiggins LD, Reynolds A, Rice CE, Moody EJ, Bernal P, Blaskey L, Rosenberg SA, Lee LC, & Levy SE (2015). Using standardized diagnostic instruments to classify children with autism in the study to explore early development. *Journal of Autism and Developmental Disorders*, 45(5), 1271–1280. 10.1007/s10803-014-2287-3. [PubMed: 25348175]
- Wiggins LD, Levy SE, Daniels J, Schieve L, Croen LA, DiGuseppi C, Blaskey L, Giarelli E, Lee LC, Pinto-Martin J, Reynolds A, Rice C, Rosenberg CR, Thompson P, Yeargin-Allsopp M, Young L, & Schendel D (2015a). Autism spectrum disorder symptoms among children enrolled in the study to explore Early Development (SEED). *Journal of Autism and Developmental Disorders*, 45(10), 3183–3194. 10.1007/s10803-015-2476-8. [PubMed: 26048040]
- Wiggins LD, Tian LH, Rubenstein E, Schieve L, Daniels J, Pazol K, DiGuseppi C, Barger B, Moody E, Rosenberg S, Bradley C, Hsu M, Rosenberg R, Christensen C, Crume D, Pandey TJ, & Levy SE (2022). Features that best define the heterogeneity and homogeneity of autism in preschool-age children: A multisite case-control analysis replicated across two independent samples. *Autism Research: Official Journal of the International Society for Autism Research*, 15(3), 539–550. 10.1002/aur.2663. [PubMed: 34967132]

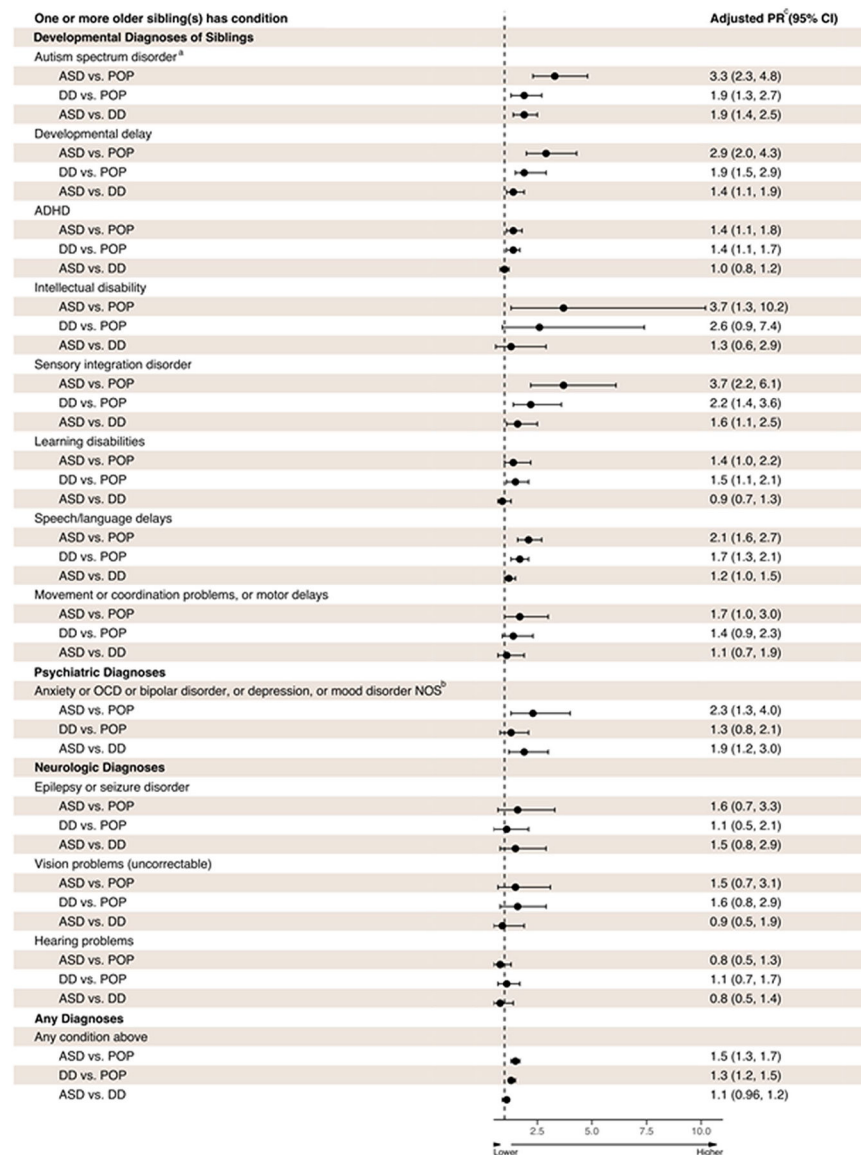
- Williams NM, Franke B, Mick E, Anney RJ, Freitag CM, Gill M, Thapar A, O'Donovan MC, Owen MJ, Holmans P, Kent L, Middleton F, Zhang-James Y, Liu L, Meyer J, Nguyen TT, Romanos J, Romanos M, Seitz C, Renner TJ, & Faraone SV (2012). Genome-wide analysis of copy number variants in attention deficit hyperactivity disorder: The role of rare variants and duplications at 15q13.3. *The American Journal of Psychiatry*, 169(2), 195–204. 10.1176/appi.ajp.2011.11060822.
- Zhou A, Cao X, Mahaganapathy V, Azaro M, Gwin C, Wilson S, Buyske S, Bartlett CW, Flax JF, Brzustowicz LM, & Xing J (2023). Common genetic risk factors in ASD and ADHD co-occurring families. *Human Genetics*, 142(2), 217–230. 10.1007/s00439-022-02496-z. [PubMed: 36251081]
- Zou G. (2004). A modified Poisson regression approach to prospective studies with binary data. *American Journal of Epidemiology*, 159(7), 702–706. 10.1093/aje/kwh090. [PubMed: 15033648]

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**Fig. 1.**

Adjusted prevalence ratios comparing index child study groups (ASD, DD, & POP) on percentage of older siblings with developmental, psychiatric, and neurologic conditions, Study to Explore Early Development. Abbreviations: ADHD, attention-deficit/hyperactivity disorder; aPR, adjusted prevalence ratio; ASD, autism spectrum disorder group; CI, confidence interval; DD, other developmental disabilities group; NOS, not otherwise specified; OCD, obsessive-compulsive disorder; POP, population control group. ^a Autism spectrum disorder category is Asperger syndrome, autism spectrum disorder, and pervasive developmental disorder combined. ^b This category combines the listed diagnoses that were asked about individually in the Maternal Interview. ^c All models included adjustment for index child sex, index child age, maternal age, maternal race-ethnicity, maternal education, household income, maternal country of birth, maternal language, and number of older siblings.

Table 1

Descriptive characteristics of the study population, index children with older siblings, Study to Explore Early Development

Characteristics	ASD (n = 738) N (%)	DD (n = 1186) N (%)	POP (n = 1039) N (%)
Child sex	*	**	
Male	605 (82.0)	783 (66.0)	559 (53.8)
Female	133 (18.0)	403 (34.0)	480 (46.2)
Child age, months	*		
30–47	167(22.6)	298(25.1)	287 (27.6)
48–68	571(77.4)	888 (74.9)	752(72.4)
Maternal age, years		**	
<30	64 (8.7)	125 (10.5)	72 (6.9)
30–34	171 (23.2)	261 (22.0)	216 (20.8)
≥35	503 (68.2)	800 (67.5)	751 (72.3)
Maternal race-ethnicity	*	**	
NHW	331 (45.3)	648 (54.8)	689 (66.4)
NHB	193 (26.4)	251 (21.2)	162 (15.6)
Hispanic	127 (17.4)	189 (16.0)	99 (9.6)
Other/multiracial	80 (10.9)	94 (8.0)	87 (8.4)
Maternal education	*	**	
< Bachelor's	399 (54.1)	581 (49.1)	378 (36.4)
Bachelor's +	339 (45.9)	602(50.9)	661 (63.6)
Household income	*	**	
<\$50,000	302 (41.8)	474 (41.7)	263 (26.3)
\$50–89,999	192 (26.6)	281 (24.7)	232 (23.2)
\$ 90,000 +	228 (31.6)	383 (33.7)	504 (50.5)
Mother US born	*	**	
Yes	555 (75.2)	971 (81.9)	894 (86.1)
No	183 (24.8)	214 (18.1)	144 (13.9)
Maternal language	*	**	
English	640 (86.7)	1037 (87.5)	976 (93.9)
Other language	98 (13.3)	148 (12.5)	63 (6.1)
Older siblings		**	
1	485 (65.7)	680 (57.3)	668 (64.3)
2	168 (22.8)	338 (28.5)	246 (23.7)
3 or more	86 (11.5)	168 (14.1)	125 (12.1)

Abbreviations ASD, autism spectrum disorder group; DD, other developmental disabilities group; POP, population control group; NHW, non-Hispanic white; NHB, non-Hispanic black

* $p < 0.05$ derived from a chi-square test in which ASD study group was compared to the POP group

** $p < 0.05$ derived from a chi-square test in which DD study group was compared to the POP group

Table 2Index children with parent report of a diagnosis of select conditions in older siblings^a, Study to Explore Early Development

One or more older sibling(s) has condition	ASD (738)		DD (1186)		POP (1039)		p-value ^d ASD vs. POP	p-value ^d DD vs. POP	p-value ^d ASD vs. DD
	N	%	N	%	N	%			
Developmental Diagnoses of Siblings									
Autism spectrum disorder ^b	104	(14.1)	89	(7.5)	44	(4.2)	< 0.001	0.001	< 0.001
Developmental delay	82	(11.1)	98	(8.3)	45	(4.3)	< 0.001	< 0.001	0.037
ADHD	124	(16.8)	217	(18.3)	124	(11.9)	0.004	< 0.001	0.404
Intellectual disability	13	(1.8)	16	(1.4)	5	(0.5)	0.008	0.035	0.470
Sensory integration disorder	42	(5.7)	48	(4.1)	22	(2.1)	< 0.001	0.009	0.097
Learning disabilities	56	(7.6)	106	(8.9)	52	(5.0)	0.025	< 0.001	0.300
Speech/language delays	147	(19.9)	206	(17.4)	107	(10.3)	< 0.001	< 0.001	0.160
Movement or coordination problems, or motor delays	26	(3.5)	43	(3.6)	26	(2.5)	0.208	0.127	0.906
Psychiatric Diagnoses									
Anxiety or obsessive-compulsive disorder or bipolar disorder, or depression, or mood disorder NOS ^c	32	(4.3)	37	(3.1)	27	(2.6)	0.044	0.463	0.163
Neurologic Diagnoses									
Epilepsy or seizure disorder	19	(2.6)	21	(1.8)	15	(1.4)	0.086	0.542	0.230
Vision problems (uncorrectable)	15	(2.0)	26	(2.2)	15	(1.4)	0.342	0.190	0.814
Hearing problems	19	(2.6)	45	(3.8)	33	(3.2)	0.458	0.429	0.147
ANY									
Any condition above	290	(39.3)	447	(37.7)	285	(27.4)	< 0.001	< 0.001	0.481

Abbreviations ASD, autism spectrum disorder group; DD, other developmental disabilities group; POP, population control group; ADHD, attention-deficit/hyperactivity disorder; NOS, not otherwise specified

^aSibling diagnoses from Maternal Interview, only includes older siblings of index children (excluded younger siblings)

^bAutism spectrum disorder category is Asperger syndrome, autism spectrum disorder, and pervasive developmental disorder combined

^cThis category combines the listed diagnoses that were asked about individually in the Maternal Interview

^dp-values were derived from a chi-square test for comparing between study groups