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Shared Familial Transmission of Autism Spectrum and Attention-Deficit/Hyperactivity Disorders

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Abstract

Background—To determine whether familial transmission is shared between autism spectrum disorders and attention-deficit/hyperactivity disorder, we assessed the prevalence, rates of comorbidity, and familial transmission of both disorders in a large population-based sample of children during a recent seven year period.

Methods—Study participants included all children born to parents with the Kaiser Permanente Northwest (KPNW) Health Plan between January 1, 1998 and December 31, 2004 ($n = 35,073$). Children and mothers with physician-identified autism spectrum disorders (ASD) and/or attention-deficit/hyperactivity disorder (ADHD) were identified via electronic medical records maintained for all KPNW members.

Results—Among children aged 6-12 years, prevalence was 2.0% for ADHD and 0.8% for ASD; within those groups, 0.2% of the full sample (19% of the ASD sample and 9.6% of the ADHD sample) had co-occurring ASD and ADHD, when all children were included. When mothers had a diagnosis of ADHD, first born offspring were at 6-fold risk of ADHD alone ($OR=5.02$, $p<0.0001$) and at 2.5-fold risk of ASD alone ($OR=2.52$, $p<0.01$). Results were not accounted for by maternal age, child gestational age, child gender, and child race.

Conclusions—ASD shares familial transmission with ADHD. ADHD and ASD have a partially overlapping diathesis.

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Supporting Information

Additional Supporting Information is provided along with the online version of this article.

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Keywords

attention-deficit/hyperactivity disorder; autism spectrum disorder; shared familial transmission

Introduction

Attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorders (ASD) are the two most common neurodevelopmental disorders observed in children (APA, 2013), with overall, estimated prevalence rates of 3-8% and 0.9-1.1%, respectively (Akinbami, Liu, Pastor, & Reuben, 2011; Boyle et al., 2011; Kogan et al., 2009), although a recent Bayesian analysis of worldwide ADHD prevalence taking into account method artifact put the prevalence at about 2% (Erskine et al., 2013). The Diagnostic and Statistical Manual of Mental Disorders 4th Edition (DSM-IV; American Psychological Association [APA], 2000) did not permit comorbid diagnosis of ADHD and ASD, yet 30-50% of children with an ASD display problematic levels of *symptoms* of ADHD (Frazier et al., 2001; Lee & Ousley, 2006; Leyfer et al., 2006; Rowlandson & Smith, 2009; Simonoff et al., 2008; Sinzig, Walter, & Doepfner, 2009), and as many as 20% of children with ADHD display notable *symptoms* of ASD (Clark, Feehan, Tinline, & Vostanis, 1999; Reiersen, Constantino, Volk, & Todd, 2007; Santosh & Mijovic, 2004). Partly as a result of these findings, DSM-5 (APA, 2013) permits co-diagnosis of ASD and ADHD.

Heritability of each of these disorders is substantial (Freitag, 2007; Pamploma et al., 2009; Reiersen, Constantino, Gimmer, Martin, & Todd, 2008), and evidence for shared liability, shared heritability, and shared familial transmission is intriguing. Specifically, twin (Lichtenstein, Carlstrom, Rastam, Gillberg, & Anckarsater, 2010; Nijmeijer et al., 2009; Reiersen et al., 2007; Reiersen et al., 2008; Rommelse, Franke, Geurts, Hartman, & Buitelaar, 2010; Ronald, Simonoff, Kuntsi, Asherson, & Plomin, 2008; Smalley, 1997) and small, family-based studies (Mulligan et al., 2009; van Steijn et al., 2013) have suggested shared genetic overlap, while genome wide association studies have identified both unique and overlapping candidate regions (Bakker et al., 2003; Rommelse et al., 2010; Smalley, 1997; Weiss, 2009). Further, ADHD and ASD have yielded some overlapping findings in regard to brain (MRI) and cognitive correlates (Brieber, Neufang, Bruning, Kamp-Becker, Remschmidt, Herpertz-Dahlmann, et al., 2007; Nyden, Niklasson, Stahlberg, Anckarsater, Wentz, Rastam, et al., 2010; Rommelse, Guerts, Franke, Buitelaar, & Hartman, 2011). A critical test of shared etiology has classically been shared familial transmission (Cantwell, 1988); yet no large, population-based studies of the familial transmission of these disorders from mothers to offspring have been conducted.

The current study sought to test this basic hypothesis by evaluating the shared familial transmission of ASD and ADHD from mothers with ADHD to their offspring in a large, population-based sample (the number of mothers with ASD were too few to include). We begin with an analysis based on one child per family to avoid confounds of family size and birth order. We then repeat the analysis with inclusion of siblings, and also evaluate whether transmission rates increase when a relaxed definition of ASD is used (testing the idea of transmission of a spectrum).

Methods

Study participants included all children born to parents with the Kaiser Permanente Northwest (KPNW) Health Plan between January 1, 1998 and December 31, 2004 (n = 46,030). KPNW is an integrated, group model, nonprofit health plan, which serves more than 480,000 members in Oregon and Washington. The membership is demographically representative of the service area, and is about 80% white. The institutional review board of Oregon Health & Science University (OHSU) released oversight to the KPNW Center for Health Research institutional review board, which approved this study.

Of the 46,030 children served by KPNW during the specified time period, 34.9% (n = 16,058) were singletons, while 65.1% (n = 29,972) were from families with multiple children. For the first analyses, to avoid non-independent confounding and birth order effects, the first-born child from each family was selected for analysis, yielding n = 28,646 children. In follow-up sensitivity analyses, analysis was repeated for (a) all singletons (n = 16,058) combined with (b) one child selected at random from families with multiple children (n = 12,588), for a combined n = 28,646 children. For the second analyses, we examine siblings, first asking if rates of transmission exceed chance, and then finally we ask whether rates are higher if a relaxed definition of ASD is allowed, as a proxy for a test of a spectrum. For families with multiple children, the average number of children per mother was 2.45 (SD=1.08).

Children with clinician-identified autism spectrum disorders (ASD) and/or attention-deficit/hyperactivity disorder (ADHD) were identified from electronic medical records maintained for all KPNW members. Clinicians at KPNW record diagnosis in children when it is among the problems they are treating. For ADHD, the practice has instituted a share algorithm that physicians follow based on both parent and teacher report. For ASD, the practice completes a universal screening for all children aged 18 to 24 months, and children complete a multidisciplinary evaluation upon screening positively. This database contains all diagnoses recorded at each outpatient medical visit for all KPNW members. Children with a diagnosis of ADHD (attention-deficit/hyperactivity disorder: *International Classification of Diseases, 9th Edition, Clinical Modification [ICD-9-CM]* codes 314.00 or 314.01) recorded at least twice were included as ADHD cases, to further reduce false positives. Children with a diagnosis of autism spectrum disorder (ASD: *ICD-9-CM* code 299.00, as well as Asperger's syndrome or pervasive developmental disorder-not otherwise specific, PDD-NOS: *ICD-9-CM* code 299.80 or 299.81, respectively) recorded at least twice were included as ASD cases. Children with two recorded diagnoses of both ASD *and* ADHD were counted as comorbid cases¹. All other participants were included as control cases. That is, patients were included as control cases if they had zero or onetime diagnosis of both or either an ASD and/or ADHD. This was done to be as conservative as possible for case inclusion (and could lead to slight underestimation of effects). As a sensitivity analysis, analyses were checked both with comorbid children classified as ASD and as non-ASD (i.e., ADHD). In a

¹As a secondary check, we asked whether defining ASD by as present with at least a single time point diagnosis (perhaps a mild spectrum case rather than a misdiagnosis) increased the relative magnitude of its preferential appearance in offspring of mothers with ADHD. It did not change any result in a meaningful way. These data are available from the first author.

secondary analysis, we allowed ASD with only one instance of diagnosis to test the spectrum transmission question.

Relevant maternal records with demographic information and maternal diagnoses of ASD or ADHD were also obtained, such that maternal diagnosis was generated by a physician (generally because the physician is treating for this problem, although information on physician diagnostic procedures was not available). Mothers were included as ASD, ADHD, comorbid, or control cases based on the same criteria applied to children, that is, 2 times points of confirmed diagnosis counted as a case. However, there were no mothers with only 1 time point of ADHD diagnosis, so this decision was immaterial to results. Paternal demographic and diagnostic information was not available (discussed below).

Data were extracted from KPNW electronic medical records on May 17, 2010, when all study children were between 6 and 12 years of age, and included maternal age, maternal and child race and ethnicity, maternal and child ASD or ADHD diagnosis, birth order, gestational age, child gender, and birth weight.

Data Analysis

Descriptive data across groups were evaluated by either ANOVA (maternal age at child birth, child's gestational age at birth, and child's birth weight according to child group status) or chi-square (race, sex, percentage of children born to mothers over 35 years of age, born pre- and post-term).

To evaluate the primary hypotheses, a series of 2×2 χ^2 analyses were used to examine group differences in the percentage of children with ADHD, ASD, or both who were born to mothers with and without ADHD. Logistic regression was used to examine the association between maternal diagnosis and child diagnosis while covarying for variables which differed significantly among the child diagnostic groups. SEM with a clustering function was used to ensure results held when all children in all families were included.

This same approach was utilized in additional data checks. Most notably, age was examined, because age of diagnosis for ADHD is generally between 7 and 8 years of age (Akinbami, Liu, Pastor, & Reuben, 2011), it may be that there are more false negatives for ADHD than ASD because some younger children in the sample classified as controls will go on to receive a diagnosis of ADHD. Although this would have minimal effect on our primary question about ASD offspring of mothers with ADHD, we nonetheless accounted for it by repeating analyses were repeated for children age 9 years and older with no change in conclusions; those details are made available in an online supplement (Table S1, Table S2, Table S3). In a second set of analyses we explored whether a single time point diagnosis might function as a part of an ASD spectrum and increase familiarity by being elevated in offspring of mothers with ADHD. In a final set of analyses, we examine familiarity of ASD and ADHD by asking whether rates of multiplex ASD families (multiples siblings with diagnoses) are more common among mothers with than without ADHD.

Results

Study Participant Groups

The first analysis looked only at first born children to avoid any effects that could be attributed to birth order or family size. Here, of the 28,646 first born children, 876 (3.1%) were designated as cases, that is, as ASD (0.7%), ADHD (2.1%), or both (0.2%). Of the 28,646 mothers in the sample, 9 were diagnosed as ASD (0.03%) and 516 as ADHD (1.8%). As noted earlier, the 9 mothers who had an ASD diagnosis and their offspring were excluded as they were too few to permit meaningful analysis.

The next analysis selected singletons plus one child at random from multi-child families to create an alternative analysis to ensure that effects were not unique to first born children. In that case, of 28,646 children, 1,053 (3.7%) were designated as cases, that is, they were classified as ASD (0.8%), ADHD (2.6%), or both (0.2%).

In the third set of analyses, when all children were included (i.e., all singletons and all siblings), 1,458 (3.2%) were designated as cases, that is, they were classified as ASD (0.7%), ADHD (2.3%), or both (0.2%). The remaining 44,572 (96.8%) children were designated as controls.

Study Participant Demographic Characteristics

Table 1 presents demographic characteristics of the sample when we selected the first-born children. Because these features were nearly identical when we selected at random or selected all siblings, we do not present further demographic information. Those details are available upon request from the first author. Maternal age at gestation ranged from 12 to 55 years (mean 27.4, SD = 6.1 years). At gestation, mothers of children with ASD (mean age 30.2 yr, SD = 6.0 yr) were older than mothers of control children ($\bar{m}=27.4$, SD = 6.1; $p<0.001$) and children with ADHD ($\bar{m}=26.6$, SD = 6.0; $p<0.001$); mothers of control children were older than mothers of children with ADHD ($p=0.005$; Table 1). Children with any disorder were more likely than children with no disorder to be male and to be a racial minority ($\chi^2(3)=209.98$, $p<0.001$ and $\chi^2(3)=229.91$, $p<0.001$, respectively).

Preliminary Data Check: Co-diagnosis of ADHD and ASD disorders

As summarized in **Table 2a**, when examining first born children, ASD and ADHD children were more likely than chance to have the other disorder co-occur ($\chi^2(1)=464.90$, $p<0.001$). 22.3% of the children with ASD also had ADHD (versus an expected rate of 2.3%), and 8.8% of the children with ADHD also had ASD (versus an expected rate of 0.93%). Overall, the relevant odds ratio for a second diagnosis, given an initial diagnosis of either ADHD or ASD was 13.02 (CI: 9.64-17.58), $z=16.75$, $p<0.001$.

When examining a child selected randomly from each family, these results reproduced closely: ASD and ADHD children were more likely than chance to have the other disorder co-occur ($\chi^2(1)=370.11$, $p<0.001$). 21.5% of the children with ASD also had ADHD (versus an expected rate of 2.8%), and 7.8% of the children with ADHD also had ASD (versus an expected rate of 1.03%; **Table 2b**). Overall, the relevant odds ratio for a second diagnosis,

given an initial diagnosis of either ADHD or ASD was 10.03 (CI: 7.53-13.34), $z=15.80$, $p<0.001$. First analysis: ADHD and ASD in offspring of mothers with ADHD

We first examined ADHD in offspring; results are displayed in Tables 3 & 4. As expected, ADHD was familial among first-born children, regardless of whether the analysis treated only non-comorbid cases of ADHD ($\chi^2(1)=124.35$, $p<0.001$; OR 5.02 [CI: 3.69-6.83], $z=10.21$, $p<0.001$) or comorbid ADHD+ASD ($\chi^2(1)=125.59$, OR=4.87 [CI: 3.61-6.58], $z=10.35$, $p<0.001$). As shown in Tables 3 & 4, results were essentially the same when children were selected at random, confirming what has been seen in many other population samples.

We therefore moved on to the more novel analysis of ASD in offspring of women with ADHD. Among first-born children, ASD occurred at a higher rate among children of mothers with ADHD than without ADHD when comorbid cases were treated as non-ASD (1.7% versus 0.70%; $\chi^2(1)=7.54$, odds ratio 2.52 [CI: 1.28-4.94], $z=2.69$, $p=0.006$); this effect was, naturally, even stronger when ASD+ADHD was allowed into the ASD group (2.3% vs 0.9%, $\chi^2(1)=10.94$, odds ratio 2.62 [CI: 1.46-4.72], $z=3.23$, $p<0.001$). Rates of transmission are again shown in Tables 3 & 4. The same story held when one child was selected at random from the multi-child families (without comorbid cases, $\chi^2(1)=5.50$, odds ratio 2.21 [CI: 1.29-4.33], $z=2.31$, $p=0.019$; with ASD+ADHD allowed into the ASD group: $\chi^2(1)=17.41$, odds ratio 2.96 [CI: 1.75-5.01], $z=4.03$, $p<0.001$; Tables 3 & 4).

Examination of covariates—Logistic regression analyses, conducted using M-Plus V6.11 (Muthen & Muthen, 2012) with bootstrapping at 1000 samples and a 95% confidence interval, examined the association between maternal diagnosis and child diagnosis while covarying maternal age at delivery, child gestational age, child gender, and child race in the sample of first-born children. Again, this was conducted separately with comorbid cases (ASD+ADHD) first classified as non-ASD (to get a minimum estimate of the effect) and then re-classified as ASD. With comorbid child cases classified as non-ASD, maternal ADHD was significantly associated with child ASD diagnosis with no covariates ($R^2=0.020$; maternal ADHD beta=0.022, $p<0.01$) and this effect remained after controlling for maternal age at child birth, child gestational age, race, and gender ($R^2=0.082$; maternal ADHD beta=0.020, $p<0.001$). With comorbid child cases classified as ASD (as they would be in DSM-5), the effect was slightly larger (base model: $R^2=0.024$; maternal ADHD beta=0.033, $p<0.001$), even after controlling for covariates ($R^2=0.084$; maternal ADHD beta=0.032, $p<0.001$).

The analysis was repeated selecting a child at random from each family with nearly identical results. With comorbid child cases classified as non-ASD, the transmission effect from maternal ADHD was significant in Step 1 ($R^2=0.023$; maternal ADHD beta=0.023, $p<0.001$) and after control of covariates ($R^2=0.088$; maternal ADHD beta=0.023, $p<0.001$). With comorbid child cases classified as ASD, the effect was slightly larger at baseline ($R^2=0.027$; maternal ADHD beta=0.031, $p<0.001$), and with covariates ($R^2=0.093$; maternal ADHD beta=0.031, $p<0.001$).

Examination of ADHD and ASD in offspring of mothers with ADHD while including siblings

Here, we asked whether transmission rates remained significant when all children were included, while handling non-independence. As described above, of the 46,030 children served by KPNW during the specified time period, 34.9% ($n = 16,058$) were singleton cases, while 65.1% ($n = 29,972$) were in families with multiple children. For families with siblings, the average number of children per mother was 2.45 ($SD=1.08$). When we examined prevalence rates of two-time point diagnoses among children aged 6-12 years, in multi-child families, while controlling for issues of non-independence, the prevalence was 2.0% for ADHD and 0.8% for ASD; within those groups, 0.2% of the full sample (19% of the ASD sample and 9.6% of the ADHD sample) had co-occurring ASD and ADHD. Here, we examined the correlation between mother diagnosis (ADHD yes/no) and child diagnosis (ASD yes/no) using an SEM model in MPLUS; we ran the model with the clustering function to designate children from the same family. This model again revealed that ASD was more common in children of mothers with ADHD than without ADHD, ($B=.39$, $p=.02$), essentially the same effect we saw in the logistic regression model above.

Next, in a separate analysis, we examined whether mothers with ADHD were more likely to have multiple children with ASD (i.e., multiplex cases) versus single children with ASD (i.e., simplex cases), compared to mothers without ADHD. After accounting for the total number of children per family, multiplex families were no more likely among mothers with ADHD than without ADHD when comorbid cases were treated as non-ASD (12.5% versus 5.1%; $\chi^2(1) = 1.633$, odds ratio 2.66 [CI: 0.560-12.675], $z=1.69$, $p=0.20$). However, it should be noted that when just examining the children with diagnosis of ASD, the number of mothers with ADHD in the sample was reduced to 16 (two of whom had multiple children with ASD), compared to 334 mothers without ADHD (17 of whom had multiple children with ASD). Thus, it may be that we were underpowered to detect these effects.

Discussion

Both the conceptualization of ADHD as a developmental disorder and suggestive evidence that ADHD and ASD have some shared liability warrant closer examination of the degree to which ADHD and ASD are transmitted in the same families. The present report provides one of the first population-based studies to investigate the degree to which ASD and ADHD are transmitted in the same families. Results confirm this supposition. Both ADHD (unsurprisingly) and ASD (our novel finding) were more likely among the offspring of mothers with ADHD than among the offspring of typically developing mothers. This was true under the sensitivity-based criteria we examined, including: (a) selecting first born children, one child at random, or fitting multi-child families in an SEM model, (b) controlling for a variety of covariates. A secondary analysis of spectrum effects mentioned in footnote 1 did not lend support to the hypothesis that a broader autism phenotype (i.e., a single diagnosis of ASD) would occur more frequently among mothers with ADHD than typically developing mothers, with only weak effects under that definition. Instead, the data suggested that the family transmission effect was stronger when analysis was restricted to clear, unambiguous cases of ASD. Additionally, a tertiary analysis of rates of multiplex families (i.e., those families with multiple children with ASD) suggested that maternal

ADHD did not influence the likelihood of having multiple children with ASD any more than the effect carried by having one child with ASD.

These finding must be interpreted in light of some unavoidable limitations. The children in this sample had all passed through the age of risk for onset of ASD, and the prevalence of ASD in this sample (0.9%) was within the range based on previous population reports of 0.9-1.1% (Boyle et al., 2011; Kogan et al., 2009). The children had not all passed the period of receiving a possible diagnosis of ADHD. Further, the physicians in the practice we sampled from followed a diagnostic algorithm that may be more conservative than in some regions. Finally, the sample had insurance, and so does not represent or generalize to populations in extreme poverty who may have higher rates of parental or child ADHD or child ASD. As a result the ADHD prevalence in this sample, at 2.4%, was lower than other population estimates (Boyle et al., 2011; Mulligan et al., 2009). However, it is similar to that suggested in a recent Bayesian meta-analysis (Erskine et al., 2013). It is lower than the CDC-reported prevalence rate in Oregon of 8.8% (CDC, 2013) although that estimate only reports children who have ever been told they had an ADHD diagnosis and may over-estimate true prevalence. However, rates of ASD identified in this sample were similar to those seen in population surveys, suggesting that our findings of ASD transmission may be generalizable.

Further, diagnoses of ADHD and ASD were by community clinicians and were not research-verified, which could result in some over- or under-identification in the sample compared to a standardized assessment. However, by requiring the clinician to have coded the diagnosis at least twice, we provided some protection against false positives. Another limitation is that we did not have diagnostic and age data for the fathers. Maternal age effects could be due to paternal age effects, as maternal and paternal age are correlated. More importantly, parent-to-child transmission rates could appear higher than estimated here if paternal diagnosis was available, depending on whether assortative mating occurred (ADHD+ADHD). Also, assortative mating of ADHD mothers with ASD fathers could create an artifactual appearance of ADHD to ASD transmission, although we are aware of no evidence of such assortment.

The small number of ASD diagnoses among the mothers in this study, while not addressed a priori, also warrants further discussion. ASD identification rates have increased dramatically over the past several decades (CDC, 2013), which may impact the overall prevalence of ASD observed among the mothers in this sample. Specifically, the prevalence of ASD among the mothers in this sample was 0.03%, which is between the estimated prevalence in the 1980s (0.01%, Fombonne, 2005) and the 1990s (0.04%, Fombonne, 2005). In addition to the comparative rarity of ASD, the reduced romantic relationship rates observed among individuals with ASD versus general population are obstacles to determining whether ADHD and ASD share family genetic characteristics (Farley et al., 2009). With these limitations in mind, results were clearly consistent with shared transmission of ADHD and ASD from mothers with ADHD. The rate of transmission of ASD was about three times that in the general population, and about 1/3 the size of the ADHD transmission rate.

While this is the first large population-based study (using physician-based diagnoses) to investigate the degree to which ASD and ADHD are transmitted in the same families, both

genetic and smaller family-risk studies (typically using standardized assessment instruments for diagnostic purposes) have suggested shared genetic overlap among these disorders. While population-based, genetic, and family-risk studies, as well as physician- and standardized assessment-based diagnoses, are each associated with unique limitations, the fact that the results of the present study are consistent with these lines of prior research suggests the etiological overlap between the two disorders is fairly robust across diverse research methodologies.

With respect to comorbidity, rates were consistent with previous research, as approximately 19% of children with a diagnosis of ASD also had a diagnosis of ADHD, while prior estimates suggest that as many as 40-50% of children with an ASD display problematic levels of *symptoms* of ADHD (Frazier et al., 2001; Lee & Ousley, 2006; Leyfer et al., 2006; Rowlandson & Smith, 2009; Simonoff et al., 2008; Sinzig, Walter, & Doepfner, 2009). As clinicians were using ICD-10, they may have chosen not to co-diagnose ADHD when ASD was present due to diagnostic guidelines in both the DSM-IV and ICD-10, which discouraged co-diagnosis. In contrast, DSM-5 (APA, 2013) permits co-diagnosis of ADHD and ASD. The results of this study along with others showing high comorbidity rates between ADHD and ASD provide additional empirical support for this change to the diagnostic criteria.

Also consistent with prior studies, mothers of children with ASD were older than mothers of children with ADHD or non-disordered children (Sandino et al., 2012) and both ADHD and ASD children were more likely to be male at rates consistent with other studies (Gaub & Carlson, 1996; Gershon, 2002; Stone et al., 2004), although neither of these facts accounted for the results. The convergence of our data with others in these respects lends some additional confidence to the findings.

Other strengths of this study included a large, population-derived sample. Full medical record access to all ASD and ADHD diagnoses, providing a unique opportunity to explore the maternal familial transmission of ADHD and ASD without the need for self-report or diagnostician bias related to study hypotheses.

Conclusion

ADHD and ASD co-segregate in families, consistent with possible shared genetic diatheses (Lichtenstein et al., 2010; Nijmeijer et al., 2009; Reiersen et al., 2007; Reiersen et al., 2008; Rommelse et al., 2010; Ronald et al., 2008; Smalley, 1997). The co-occurrence of these disorders supports the conceptualization of ADHD as a neurodevelopmental disorder, and suggests value in continued efforts to identify shared and distinct etiological inputs to ADHD and ASD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

ADHD	attention-deficit/hyperactivity disorder
ASD	autism spectrum disorder
CI	confidence interval
ICD-9-CM	International Classification of Diseases-9 th Edition-Clinical Modification
KPNW	Kaiser Permanente Northwest
OHSU	Oregon Health & Science University
PDD-NOS	pervasive developmental disorder-not otherwise specified

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Key Points

- Prior data suggest an etiological association of ASD and ADHD. Population-based studies of family transmission are needed to fully test this hypothesis.
- ASD and ADHD are the most common neurodevelopmental disorders of childhood. We show, in a population-based sample, these disorders share familial transmission risk.
- Mothers with ADHD are more likely to have children with ADHD and/or ASD than typically developing mothers.

Table 1

Demographic characteristics of child groups in first born child sample

Characteristic N	Control 27770	ASD 213	ADHD 609	Comorbid 54
Maternal Age	27.4 (6.0) ^a	30.2 (6.0) ^b	26.6 (6.1) ^c	29.5 (6.1) ^{a,b}
Maternal Age 35	13.2% ^a	24.4% ^b	12.0% ^a	24.1% ^{a,b}
Number of Siblings	1.6 (1.0)	1.6 (1.3)	1.6 (1.0)	1.5 (0.7)
Child Gest. Age, wks	39.4 (1.8)	39.3 (2.1)	39.3 (2.0)	39.2 (2.0)
Child Born Preterm	3.9%	6.0%	3.8%	7.4%
Child Born Post-term	1.9%	3.2%	2.3%	1.9%
Child Gender (% Male)	50.9% ^a	81.0% ^b	72.6% ^b	83.3% ^b
Child Birth Weight, kg	3.4 (0.6)	3.5 (0.6)	3.5 (0.6)	3.4 (0.6)
Child Race (% White)	57.1% ^a	33.8% ^b	37.4% ^b	38.9% ^b

Note. Differing superscripts indicate pairwise comparisons that were significant after a modified Bonferroni correction for multiple groups ($\alpha=0.012$) for continuous variables, including: maternal birth age, child's gestational age at birth, and child's birth weight; and Chi-square comparisons for categorical variables, including: maternal birth age >35 years, child born pre- or post-term, gender, and race.

Table 2a

Co-Occurrence: Rate of ADHD and ASD in the first-born child sample (i.e., counts and percentage of total).

	Child not ADHD	Child ADHD	Child Total
Child not ASD	27770 96.9% (control)	611 2.2% (ADHD)	28381 99.1%
Child ASD	206 0.7% (ASD)	59 0.2% (comorbid)	265 0.9%
Child Total	27976 97.6%	770 2.4%	28646 100.0%

Note: 22.3% of the children with ASD also had ADHD (versus an expected rate of 2.3%), and 8.8% of the children with ADHD also had ASD (versus an expected rate of 0.93%; $\chi^2(1)=464.90$, $p<0.001$). Overall, the odds ratio for a second diagnosis, given an initial diagnosis of either ADHD or ASD was 13.02 (CI: 9.64-17.58), $z=16.75$, $p<0.001$.

Table 2b

Co-Occurrence: Rate of ADHD and ASD in the randomly selected child sample (i.e., counts and percentage of total).

	Child not ADHD	Child ADHD	Child Total
Child not ASD	27593 96.4% (control)	756 2.6% (ADHD)	28349 99.0%
Child ASD	233 0.8% (ASD)	64 0.2% (comorbid)	297 1.0%
Child Total	27826 97.2%	820 2.8%	28646 100.0%

Note: 21.5% of the children with ASD also had ADHD (versus an expected rate of 2.8%), and 7.8% of the children with ADHD also had ASD (versus an expected rate of 1.03%; $\chi^2(1) = 370.11$, $p < 0.001$). Overall, the odds ratio for a second diagnosis, given an initial diagnosis of either ADHD or ASD was 10.03 (CI: 7.53-13.34), $z = 15.80$, $p < 0.001$.

Table 3

Rates (observed %) of mothers (no disorder and ADHD) with first-born children with no disorder, ADHD, ASD, or comorbid diagnosis and with randomly selected children with no disorder, ADHD, ASD, or comorbid diagnosis

	<u>Mother Status</u>	
	Control N=28103	ADHD N=516
FIRST BORN:		
Child no disorder (obs. %)	97.10%	88.38%
Child ADHD	2.00%	9.30%
Child ASD	0.70%	1.74%
Child ADHD+ASD	0.20%	0.58%
Total	100.00%	100.00%
RANDOMLY SELECTED:		
Child no disorder (obs. %)	96.49%	86.83%
Child ADHD	2.50%	10.27%
Child ASD	0.80%	1.74%
Child ADHD+ASD	0.21%	1.16%
Total	100.00%	100.00%

Note: Among first born children ASD more common in mothers with ADHD versus without (odds ratio 2.52 [CI: 1.28-4.94], $z=2.69$, $p<0.007$; ADHD more common in mothers with ADHD versus without (odds ratio 5.02 [CI: 3.69-6.83], $z=10.21$, $p<0.001$); comorbid diagnosis of ASD and ADHD not 0.97-9.39], $z=1.81$, $p=0.073$). Among randomly selected children from multi-child families, ASD more common in mothers with ADHD versus without (odds ratio 2.21 [CI: 1.29-4.33], $z=2.32$, $p<0.01$); ADHD more common in mothers with ADHD versus without (odds ratio 4.47 [CI: 3.33-5.99], $z=9.98$, $p<0.001$); comorbid diagnosis of ASD and ADHD more likely in ADHD than non-ADHD mothers (odds ratio 5.69 [CI: 2.44-13.25], $z=4.03$, $p<0.001$).

Table 4

Chi-square results of different models examining first-born child disorder stratified by presence/absence of maternal ADHD.

	First Born Children			Randomly Selected Children		
	<i>Chi2</i>	<i>df</i>	<i>p-value</i>	<i>Chi2</i>	<i>df</i>	<i>p-value</i>
Model 1 ^a	142.43	3	1.0*10 ⁻²⁹	145.14	3	1.0*10 ⁻³⁰
Model 2 ^b	140.19	2	1.0*10 ⁻³⁰	143.27	2	1.0*10 ⁻³¹
Model 3 ^c	141.95	2	1.0*10 ⁻³¹	135.29	2	1.0*10 ⁻²⁹
Model 4 ^d	133.18	1	1.0*10 ⁻³⁰	132.44	1	1.0*10 ⁻²⁹
Model 5 ^e	132.06	1	1.0*10 ⁻³⁰	113.89	1	1.0*10 ⁻²⁵
Model 6 ^f	7.43	1	0.007	5.50	1	0.019
Model 7 ^g	10.77	1	0.001	17.41	1	1.0*10 ⁻⁴

Note: Individual Chi² models fit for the following individual models:

^a Model 1: 2×4 Mother ADHD (yes/no) × child no disorder, ASD, ADHD, ADHD+ASD

^b Model 2: 2×3 Mother ADHD (yes/no) × child no disorder, ADHD, ASD, comorbid as ADHD

^c Model 3: 2×3 Mother ADHD (yes/no) × child no disorder, ADHD, ASD, comorbid as ASD

^d Model 4: 2×2 Mother ADHD (yes/no) × child ADHD (yes/no), (comorbid=ADHD)

^e Model 5: 2×2 Mother ADHD (yes/no) × child ADHD (yes/no), (comorbid=not ADHD)

^f Model 6: 2×2 Mother ADHD (yes/no) × child ASD (yes/no), (comorbid= not ASD)

^g Model 7: 2×2 Mother ADHD (yes/no) × child ASD (yes/no), (comorbid=ASD)