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Familial and genetic associations between autism spectrum disorder and other neurodevelopmental and psychiatric disorders

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Background: Familial and genetic associations between autism spectrum disorder (ASD) and other neurodevelopmental and psychiatric disorders have been reported, sometimes with conflicting results. We estimated familial and genetic associations between ASD and nine disorder groups, and explored differences in these associations for ASD in the context of intellectual disability, epilepsy, chromosomal abnormalities, and congenital malformations. **Methods:** Individuals born between 1985 and 2009 living in Sweden on their seventh birthday were linked to their biological parents in order to identify different types of relatives. We retrieved information on all the disorders considered from the National Patient Register. Logistic regression was used to estimate the familial association between ASD and other neurodevelopmental and psychiatric disorders in the different groups of relatives. Structural equation modeling was used to estimate phenotypic (r_p) and genetic associations (r_g), as well as the contribution of genetic influences to r_p. **Results:** The study included 2,398,608 individuals. Among relatives of individuals diagnosed with ASD, there was an increased risk of the disorders considered, compared to relatives of individuals who were not diagnosed with ASD. Stronger associations were detected for ASD without any additional diagnosis of intellectual disability, epilepsy, chromosomal abnormalities, and congenital malformations. The strongest genetic correlation was estimated between ASD and other neurodevelopmental disorders (r_g = 0.73; 95% CI = 0.66–0.79). Moderate genetic correlations were estimated for anxiety disorders (r_g = 0.47; 95% CI = 0.33–0.61), depression (r_g = 0.52; 95% CI = 0.37–0.66), and intentional self-harm (r_g = 0.54; 95% CI = 0.36–0.71). **Conclusions:** ASD shows familial and genetic association not only with other neurodevelopmental disorders, but also with other psychiatric disorders, such as anxiety, depression, and intentional self-harm. Family history of ASD comorbid with intellectual disability, epilepsy, congenital malformations, or chromosomal abnormalities is less related to other psychiatric disorders, potentially suggesting a different etiology for this subgroup of patients. **Keywords:** Autism spectrum disorder; neurodevelopmental disorders; family based study; genetic association.

Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder that emerges early in childhood and is characterized by difficulties with social communication and by the presence of restricted and repetitive behaviors and interests (APA, 2013). ASD presents heterogeneously in terms of specific symptoms, level of impairment, and presence of other disorders, which range from other neurodevelopmental disorders, such as ADHD, to social anxiety disorder, oppositional defiant disorder, and obsessive-compulsive disorder (Lundström et al., 2015; Simonoff et al., 2008).

The clinical complexity of ASD is mirrored by a complex etiological architecture (Lord et al., 2020). ASD is highly heritable, with heritability estimates around 50%–90% (Bai et al., 2019; Tick, Bolton, Happe, Rutter, & Rijsdijk, 2016). Different types of genetic variants have been implicated, including relatively common genetic variants with smaller effects and rare mutations with individually larger effect sizes (Grove et al., 2019; Lord et al., 2020). In addition, a number of early environmental risk factors have been consistently associated with ASD (Carlsson, Molander, Taylor, Jonsson, & Bölte, 2020).

ASD may also be diagnosed in the context of congenital malformations or chromosomal abnormalities, such as fragile X syndrome (Sztainberg & Zoghbi, 2016). These conditions may also cause intellectual disability and epilepsy. Therefore, when ASD symptoms appear in the context of a diagnosis of congenital malformations, chromosomal abnormalities, intellectual disability, or epilepsy, the implicated etiological mechanisms may differ from ASD without these comorbidities. There is some

Conflict of interest statement: See Acknowledgements for full disclosures.

evidence to support this notion, by showing that heritability of ASD is lower among those with comorbid intellectual disability vs. those who do not have intellectual disability (Xie et al., 2020). In addition, although de-novo mutations (that is, not inherited) have been implicated in the etiology of ASD across the whole distribution of intelligence, a higher burden of these types of mutations is associated with lower intelligence quotient (Sanders et al., 2015). Therefore, possible etiological heterogeneity of ASD may be related to the presence of congenital malformations, chromosomal abnormalities, intellectual disability, and epilepsy.

Several twin studies have found shared genetic risks between ASD traits and traits related to other neurodevelopmental disorders (Lundstrom et al., 2011; Pinto, Rijsdijk, Ronald, Asherson, & Kuntsi, 2016; Polderman, Hoekstra, Posthuma, & Larsson, 2014; Polderman et al., 2013; Reiersen, Constantino, Grimmer, Martin, & Todd, 2008; Ronald, Larsson, Anckarsater, & Lichtenstein, 2014; Ronald, Simonoff, Kuntsi, Asherson, & Plomin, 2008; Taylor et al., 2013; Taylor, Charman, & Ronald, 2015; Tick, Colvert, et al., 2016). Fewer studies have focused on other psychiatric disorders. One study reported moderate genetic correlations between ASD traits and traits related to anxiety (Lundstrom et al., 2011) and depression (Lundstrom et al., 2011) both in children (for anxiety $r_g = 0.53$) and in adults (for anxiety $r_g = 0.51$ and for depression $r_g = 0.53$), while other studies have found somewhat lower genetic correlations, with the strongest estimates in the range of 0.2–0.3 (Hallett, Ronald, & Happé, 2009; Hallett, Ronald, Rijsdijk, & Happé, 2012). However, these studies focused on measures of traits related to the disorders, rather than clinical diagnoses.

Family studies with information on clinical diagnoses have found support for genetic association between ASD and affective and anxiety disorders (Jokiranta-Olkoniemi et al., 2016), bipolar disorder (Song et al., 2015), schizophrenia (Sullivan et al., 2012), and obsessive-compulsive disorder (Huang et al., 2020; Meier et al., 2015). The latest cross-disorder analysis from the Psychiatric Genomics Consortium (PGC), including data from genome-wide association studies (GWAS) of several neurodevelopmental and psychiatric disorders, found a moderate genetic correlation between ASD and another neurodevelopmental disorder, ADHD ($r_g = 0.44$). In addition, a correlation of similar magnitude was found between ASD and depression ($r_g = 0.45$). Lower correlations were estimated between ASD and schizophrenia and bipolar disorder (in the range of 0.2–0.3), and even lower (and not statistically significant) correlations (in the range of 0.1–0.2) were reported with Tourette syndrome, anorexia, and obsessive-compulsive disorder (Lee et al., 2019).

The discrepancy between some of the results from the GWAS and those from family studies based on large population-based datasets may be due to issues with lower statistical power, stricter inclusion criteria for the study participants and possible ascertainment bias in GWAS. In addition, genetic correlations estimated from GWAS mainly capture the contribution of common genetic variants with additive effects, whereas genetic effects estimated from twin and family studies include rare and non-additive genetic influences, such as dominance and epistasis.

Another interesting aspect about the association between ASD and other psychiatric disorders is the role of comorbidities such as congenital malformations, chromosomal abnormalities, intellectual disability, and epilepsy, which may indicate a different etiology. There is some evidence from family studies of ASD comorbid with intellectual disability and its relationship with neurodevelopmental and psychiatric disorders, but the results are conflicting (Ghirardi et al., 2018; Jokiranta-Olkoniemi et al., 2016).

The aim of this study was to estimate the familial and genetic associations between ASD and other neurodevelopmental and psychiatric disorders identified through nationwide registers, covering the whole population of Sweden and reflecting specialist psychiatric care practice. We hypothesized that the association with neurodevelopmental disorders will be stronger than with other psychiatric disorders. In addition, we explored if comorbidity with intellectual disability, epilepsy, chromosomal abnormalities, and congenital malformations influenced the pattern of familial associations, an aspect that cannot be studied in other samples that exclude patients with these comorbidities. We expected that the familial associations between ASD and the disorders under study will be different between individuals with and without these comorbidities.

Methods

The study was approved by the Regional Ethics Review Board in Stockholm, Sweden. Informed consent was waived because the study was register-based and individuals included in the study were not identifiable.

Study population

We retrieved information from the Total Population Register (Ludvigsson et al., 2016) on all individuals born in Sweden between 1985 and 2009. We excluded individuals with no information on biological mother or father, those who were adopted away, and those who died or migrated outside Sweden before their seventh birthday. By linking each person to their biological parents, we identified the following groups of relatives: monozygotic twins, dizygotic twins, full siblings, maternal and paternal half siblings, full cousins, and half cousins.

Definition of ASD

We identified individuals with a diagnosis of ASD from the National Patient Register according to the International Classification of Diseases, Ninth Revision (ICD-9; 1987–1996) and

ICD-10 (1997–2013; Ludvigsson et al., 2011). The register covers all inpatient care in Sweden since 1987 (national coverage) and outpatient visits since 2001. For ICD-9 we used the code 299A and for ICD-10 we used the codes F84.0, F84.1, F84.5, F84.8. We only considered recorded diagnoses from age three onwards.

Definition of other neurodevelopmental and psychiatric disorders

Similar to the definition of ASD, we used ICD-9 and ICD-10 codes from the National Patient Register to identify the following nine categories of disorders: neurodevelopmental disorders other than ASD (i.e. intellectual disability, ADHD, communication, learning, and motor disorders, and other/unspecified neurodevelopmental disorders); anxiety disorders; obsessive compulsive disorder; eating disorders; depression; intentional self-harm, psychotic disorders, bipolar disorder, and borderline personality disorder. All the corresponding ICD-9 and ICD-10 codes and youngest age at diagnosis included are reported in Table S1. Of note, for borderline personality disorder we only used information from ICD-10, as the diagnosis is not captured by diagnostic codes in ICD-9.

Covariates and other variables

We used information on sex and year of birth from the Total population register (Ludvigsson et al., 2016). Year of birth was used as a categorical variable with four levels: 1985–1990; 1991–1995; 1996–2000; 2001–2009. We used the National patient register (Ludvigsson et al., 2011) to identify diagnoses of intellectual disability from age three (ICD-9: 317–319; ICD-10: F7), epilepsy (ICD-9: 345; ICD-10: G40, G41), and chromosomal abnormalities and congenital malformations (ICD-9: 740–759; ICD-10: Q00–Q99). These diagnoses were used for the stratified analyses on familial association between ASD with and without these comorbidities and other neurodevelopmental and psychiatric disorders.

Statistical analyses

In order to estimate familial associations between ASD and other neurodevelopmental and psychiatric disorders in the different groups of relatives, we first performed a series of logistic regressions and calculated the odds ratios (ORs) with two-sided 95% confidence intervals (CIs), adjusting for sex and year of birth, which may influence the prevalence of the disorders considered. The CIs were adjusted for non-independence of the observations from the same family (that is, same parents for twins and siblings, and same grandparents for cousins) using cluster-robust variance estimation. In each group of relatives, we estimated the OR of being diagnosed with other neurodevelopmental and psychiatric disorders in individuals whose relative(s) had been diagnosed with ASD compared with individuals whose relative(s) had not been diagnosed with ASD. The same set of analyses were repeated separately for the following subgroups: males and females, presence or absence of comorbidity with intellectual disability, epilepsy, congenital malformations, or chromosomal abnormalities (that is, no comorbidity subgroup vs any comorbidity subgroup). The subgroup analyses were performed only in the largest groups of relatives, that is, full siblings and full cousins, to ensure sufficient power. All the analyses were performed using Stata 15 (StataCorp, 2017).

The rationale behind the estimation of the association for each relative group is to compare the strength of the familial association across the different types of relatives, who are assumed to share familial factors, including genetic and environmental factors, to a varying extent.

In order to estimate the genetic correlations between ASD and other neurodevelopmental and psychiatric disorders, we performed structural equation modeling (SEM). In this analysis, we also evaluated the genetic association between ASD and ADHD, in order to compare it with results from GWAS. In addition, we estimated the influence of genetic factors, including additive genetic and dominant genetic, on the phenotypic correlation (r_p) between ASD and other neurodevelopmental and psychiatric disorders.

In this framework, the diagnostic status of each individual (that is, the diagnosis being either present or absent) is assumed to represent the measurement of an underlying liability to the disorder that is normally distributed in the population. When considering the correlation between two disorders, this is assumed to represent the correlation between the liabilities to the two disorders and a joint distribution of the liabilities for the disorders under study is assumed to follow a multivariate normal distribution (Rijsdijk & Sham, 2002).

For SEM we used the following relative groups: monozygotic twins, dizygotic twins, full siblings, maternal half siblings, and paternal half siblings. More details on the assumptions on the types of relatives are reported in Table S2. We restricted the analysis to a birth cohort with better coverage of diagnoses in order facilitate models' optimization. The birth cohort included individuals born between 1988 and 2005. Due to lower prevalence of some of the disorders considered, for this analysis we grouped together obsessive-compulsive disorder with other anxiety disorders. In addition, we could not perform this analysis on eating disorders, psychotic disorders, bipolar disorder, and borderline personality disorder because of the low prevalence in this cohort.

SEM was performed using OpenMx package (Neale et al., 2016) in R software (RCoreTeam, 2013).

Results

The study sample included 2,398,608 individuals. Among them, the prevalence of ASD was 1.38%. The prevalence of each of the nine categories of disorders in the study population, overall and by sex, is reported in Table 1. As expected, ASD, other neurodevelopmental disorders, and psychotic disorders were more common among males than females. All other disorders considered were more prevalent among females.

Among individuals diagnosed with ASD, 32.62% had at least one additional diagnosis of intellectual disability (18.39%), epilepsy (8.54%), or any congenital malformation or chromosomal abnormalities (17.29%). An additional diagnosis of intellectual disability and epilepsy was more common among females with ASD compared to males, while congenital malformation or chromosomal abnormalities were more common among males with ASD compared to females.

As illustrated in Figure 1, all disorder categories were more common among relatives of individuals diagnosed with ASD than among relatives of individuals who were not diagnosed with ASD. In addition, the magnitude of the association was larger among relatives who are more genetically similar than among relatives who are less genetically similar. For virtually all the disorder categories examined, the association with ASD was positive and statistically significant even among cousins and half

Table 1 Prevalence of disorders considered in the study population

	Whole study population		Males		Females	
	N = 2,398,608		*N* = 1,232,306		*N* = 1,166,302	
	Frequency	Percentage	Frequency	Percentage	Frequency	Percentage
ASD	33,014	1.38	22,949	1.86	10,065	0.86
Neurodevelopmental disorders[a]	106,480	4.44	70,248	5.7	36,232	3.11
Anxiety disorders	70,770	2.95	25,280	2.05	45,490	3.9
Obsessive-compulsive disorder	10,828	0.45	4,788	0.39	6,040	0.52
Eating disorders	17,872	0.75	1,311	0.11	16,561	1.42
Depression	66,055	2.75	24,141	1.96	41,914	3.59
Intentional self-harm	23,264	0.97	7,357	0.6	15,907	1.36
Psychotic disorders	5,266	0.22	3,041	0.25	2,225	0.19
Bipolar disorder	8,291	0.35	2,557	0.21	5,734	0.49
Borderline personality disorder[b]	5,750	0.24	604	0.05	5,146	0.44
ASD comorbidities[c]						
ASD + any comorbidity[d]	10,769	32.62	7,527	32.80	3,242	32.21
ASD + intellectual disability	6,070	18.39	4,141	18.04	1,929	19.17
ASD + epilepsy	2,818	8.54	1,800	7.84	1,018	10.11
ASD + CMCA	5,707	17.29	4,078	17.77	1,629	16.18

ASD, autism spectrum disorder; CMCA, congenital malformations and chromosomal abnormalities.
[a]This group does not include ASD.
[b]Only ICD-10 code was used for borderline personality disorder.
[c]The percentages for these groups indicate the prevalence of each comorbidity among individuals with ASD.
[d]This group include anyone having ASD in comorbidity any of the following: intellectual disability, epilepsy and CMCA.

cousins, who share, on average, 12.5% and 6.25% of their DNA, but probably share very little in terms of (early) environmental influences, suggesting the importance of genetic influences.

Stratified familial associations are reported in Figures 2 and 3. When examining the familial association stratifying by sex (Figure 2), we did not find evidence of a different risk of neurodevelopmental and psychiatric disorders among relatives of males compared to females with ASD. The point estimates for obsessive-compulsive disorder, eating disorders, depression, and psychotic disorders may suggest a higher risk conferred by having a female sibling with ASD compared to having a male sibling with ASD, but the overlap between CIs does not exclude the possibility that this may be due to chance.

When comparing the familial association stratifying by any comorbidity with intellectual disability, epilepsy, congenital malformations, and/or chromosomal abnormalities, we found differences in the estimates (Figure 3). Having a sibling with ASD without any of these comorbidities conferred higher risk of neurodevelopmental and psychiatric disorders compared to having a sibling with ASD with any of these comorbidities. The only exception was for psychotic disorders, where the CIs for the two estimates largely overlapped. For several disorders, such as neurodevelopmental disorders, anxiety disorders, and depression, a similar pattern was observed also when comparing the estimates from cousins.

Estimates of familial associations illustrated in Figures 1–3 are also reported in Tables S3–S5, respectively.

Phenotypic correlations, contribution of genetic influences to the correlations, and genetic correlations are reported in Table 2. The strongest phenotypic (r_p = 0.73; 95% CI = 0.73–0.74) and genetic (r_g = 0.73; 95% CI = 0.66–0.79) correlations were estimated for the category including all neurodevelopmental disorders. Genetic influences, including additive and dominant effects, accounted for 82% of the phenotypic correlation (95% CI = 72–91). When we focused on ADHD, the most common diagnosis within the category of neurodevelopment disorders, we found a strong phenotypic (r_p = 0.66; 95% CI = 0.65–0.66) and genetic correlation (r_g = 0.61; 95% CI = 0.53–0.68), with 79% of the phenotypic correlation being accounted for by genetic influences (95% CI = 68–91). Moderate phenotypic and genetic correlations with ASD were estimated for anxiety disorders, including obsessive-compulsive disorder (r_p = 0.49; 95% CI = 0.48–0.50; r_g = 0.47; 95% CI = 0.33–0.61), depression (r_p = 0.47; 95% CI = 0.46–0.48; r_g = 0.52; 95% CI = 0.37–0.66), and intentional self-harm (r_p = 0.34; 95% CI = 0.33–0.36; r_g = 0.54; 95% CI = 0.36–0.71). Genetic influences accounted for most of the phenotypic correlation between ASD and these disorders. All the estimates of the parameters from the structural equation modeling are reported in Table S6.

Discussion

In this study, we found evidence of familial and genetic overlap between clinically ascertained ASD and other neurodevelopmental and psychiatric disorders. As expected, the associations were stronger for neurodevelopmental disorders than for other

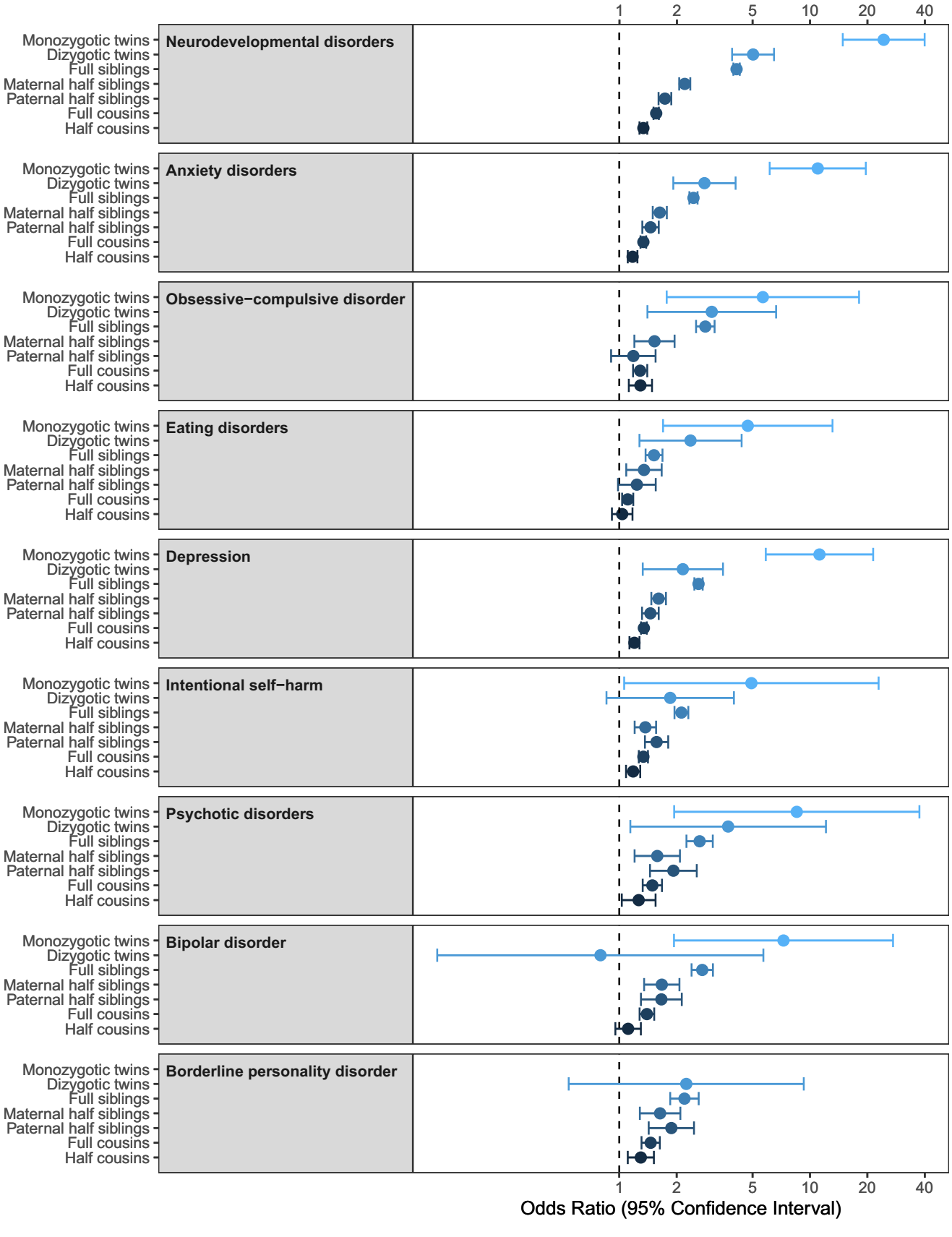

Figure 1 Familial associations between ASD and other neurodevelopmental and psychiatric disorders

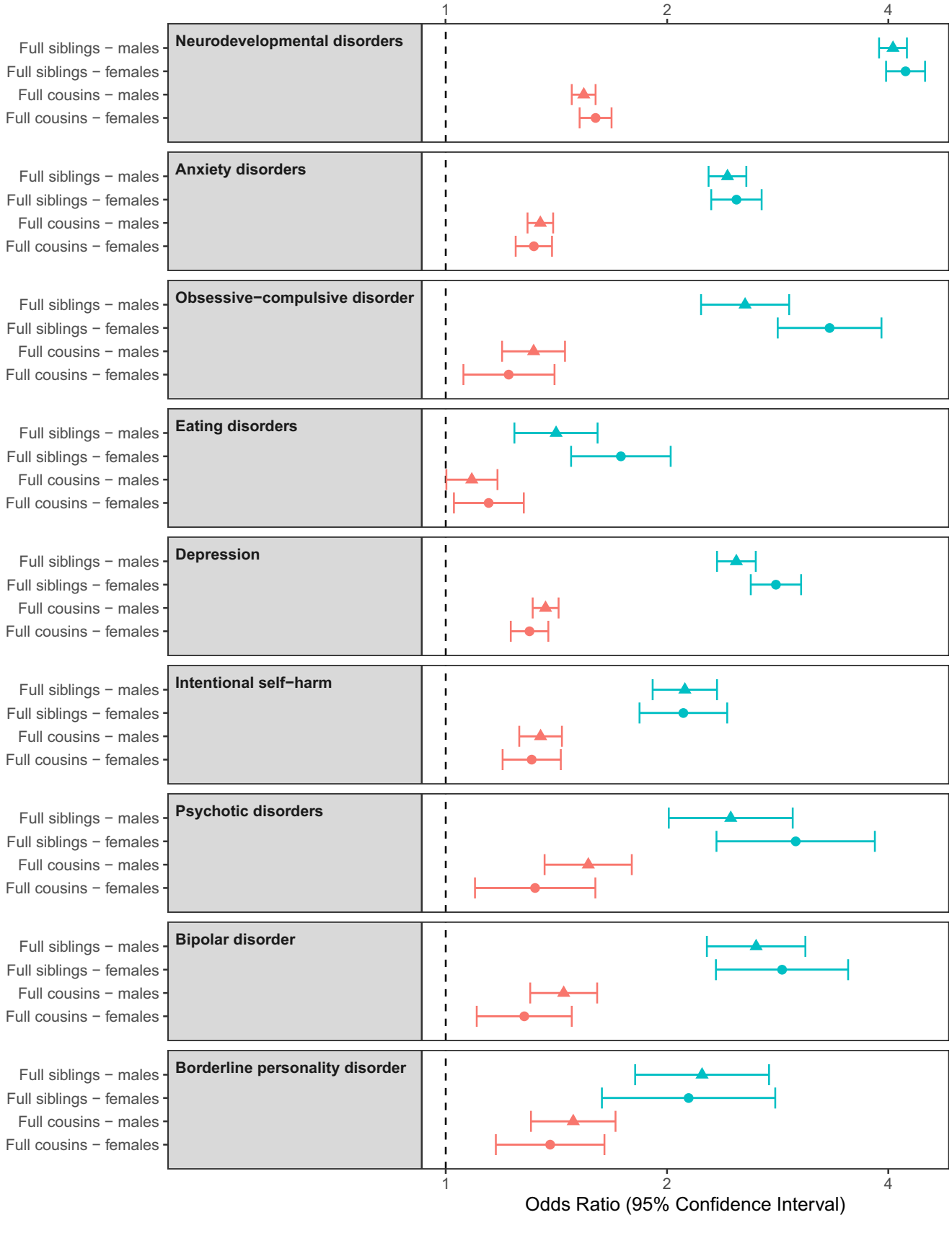

Figure 2 Stratified familial associations between ASD and other neurodevelopmental and psychiatric disorders by sex. Legend: Light blue = full siblings; light red = full cousins; triangle = males; circle = females

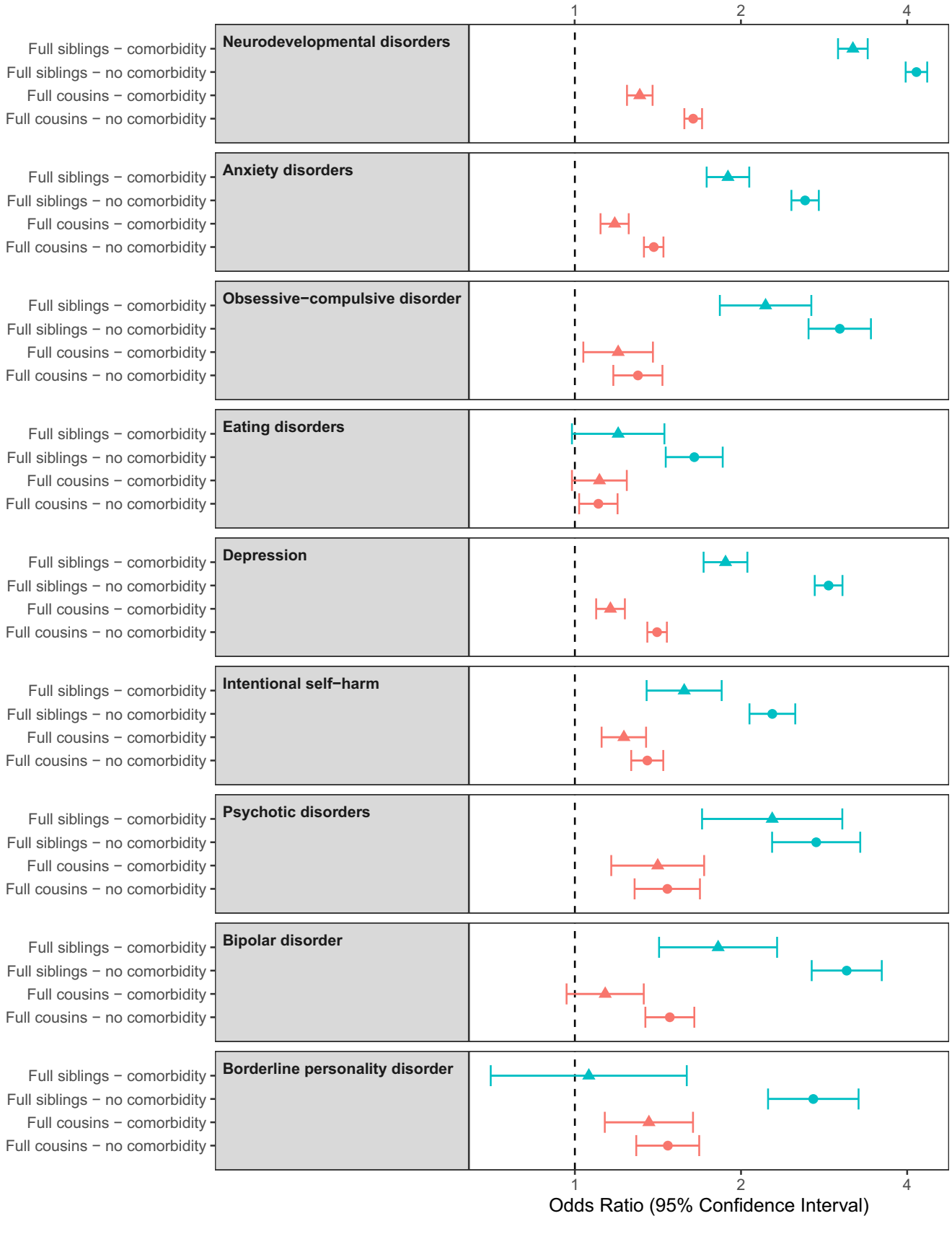

Figure 3 Stratified familial associations between ASD and other neurodevelopmental and psychiatric disorders by comorbidity. Legend: Light blue = full siblings; light red = full cousins; triangle = comorbidity (intellectual disability, epilepsy, congenital malformations, or chromosomal abnormalities); circle = no comorbidity

Table 2 Phenotypic correlations, contribution of genetic influences, and genetic correlations

	Phenotypic correlations	Contribution of genetic influences to the phenotypic correlation	Genetic correlation
ADHD	0.66 (0.65–0.66)	79% (68–91)	0.61 (0.53–0.68)
Neurodevelopmental disorders[a]	0.73 (0.73–0.74)	82% (72–91)	0.73 (0.66–0.79)
Anxiety disorders[b]	0.49 (0.48–0.50)	65% (45–84)	0.47 (0.33–0.61)
Depression	0.47 (0.46–0.48)	71% (51–92)	0.52 (0.37–0.66)
Intentional self-harm	0.34 (0.33–0.36)	110% (81–137)	0.54 (0.36–0.71)

[a]This group does not include ASD.
[b]Anxiety disorders including obsessive-compulsive disorder; in parentheses are reported confidence intervals.

psychiatric disorders. Previous studies have found evidence for familial and genetic association between ASD and ADHD (Ghirardi et al., 2018; Jokiranta-Olkoniemi et al., 2016; Lee et al., 2019), affective and anxiety disorders (Jokiranta-Olkoniemi et al., 2016), depression (Lee et al., 2019), bipolar disorder (Song et al., 2015), schizophrenia (Jokiranta-Olkoniemi et al., 2016; Sullivan et al., 2012), and obsessive-compulsive disorder (Huang et al., 2020; Meier et al., 2015). In this study, we confirmed these findings and expanded previous knowledge by providing additional evidence supporting familial association between ASD and anxiety disorders (separating obsessive-compulsive disorder from other disorders), eating disorders, intentional self-harm, and borderline personality disorder. These results confirm that family history, even across different diagnoses, is a strong predictor of risk of neurodevelopmental and psychiatric disorders. Therefore, this information should be assessed and used in the clinical setting and for research purposes. In addition, the pattern of decreasing magnitude of the association as the degree of genetic relatedness diminishes highlights the importance of genetic influences in the association between these disorders.

In the stratified analyses, we did not find evidence for sex differences in familial associations, but we found clear differences in the magnitude of the associations when considering ASD with or without at least one additional diagnosis of either intellectual disability, epilepsy, congenital malformations, and/or chromosomal abnormalities. When ASD is not comorbid with any of these disorders, it shows a stronger familial association with other neurodevelopmental and psychiatric disorders. Of note, intellectual disability was included among the neurodevelopmental disorders in the stratified analyses. Therefore, one might have expected a stronger association with neurodevelopmental disorders among those with ASD and comorbid intellectual disability than among those with ASD without intellectual disability, because intellectual disability also runs in families. Similarly, because epilepsy and some congenital malformations and chromosomal abnormalities are associated with mental health problems, stronger associations among those with ASD and any of these comorbidities might have been expected. However, that was not the case, suggesting that these comorbidities do not explain the observed associations. These results are in line with one previous study that focused on familial association between ASD and ADHD in different types of relatives (Ghirardi et al., 2018), but in conflict with another study that explored the association between ASD with or without intellectual disability and several neurodevelopmental and psychiatric disorders in siblings (Jokiranta-Olkoniemi et al., 2016). In this study, we included other comorbidities (that is, epilepsy, congenital malformations, and/or chromosomal abnormalities) that may indicate a form of ASD with a different etiology, which may be less genetically related to other neurodevelopmental and psychiatric disorders. This highlights the importance for future genetic studies (e.g. common variant GWAS and studies of rare variations) to consider within-disorder clinical heterogeneity even when studying cross-disorder overlap, in order to understand ASD's complex genetics and biology. Genetic studies of ASD already regularly take into consideration comorbid intellectual disability (e.g. Sanders et al., 2015); additional phenotypes, such as epilepsy, information on symptom dimensions and severity, age at onset, and medication status and response, may help identifying sub-groups of patients with different pathophysiological profiles.

We also estimated genetic correlations, using information on degree of genetic and environmental similarity across different types of relatives, between ASD and other neurodevelopmental disorders, anxiety disorders and obsessive-compulsive disorders (considered together), depression, and self-harm. As expected, we found the strongest phenotypic and genetic correlation with neurodevelopmental disorders as a group and when focusing on ADHD specifically. The magnitude of the association was larger than what reported in the latest cross-disorder analysis from the PGC on ASD and ADHD (Lee et al., 2019). The genetic correlation estimated between ASD and depression and self-harm was in line with the association in the cross-disorder analysis from the PGC on ASD and depression (Lee et al., 2019). We reported for the first time a genetic correlation for clinically ascertained anxiety disorders (including obsessive-compulsive disorder) and for intentional

self-harm of moderate magnitude, very similar to the correlation for depression. Estimation of genetic correlations does represent one important step in understanding why some traits and disorders overlap. Other studies may be able to identify underlying mechanisms, for example, whether (and to what extent) there are biological pathways common to several psychiatric disorders or causal relationships between them.

Several strengths and limitations should be considered when interpreting the results of the study. Estimates of familial and genetic associations are based on nationwide healthcare registers, which cover individuals living in Sweden and reflect specialist psychiatric care practice. Therefore, cases identified via registers are not affected by the same recruitment biases that may be present in other epidemiological samples. This allowed us to include several diagnostic groups and explore sub-group differences. By performing familial co-aggregation analyses and structural equation modeling, the study contributes to the existing literature on familial and genetic relationships across neurodevelopmental and psychiatric disorders by providing robust and representative estimates of the association between ASD and several other groups of disorders.

However, registers used in this study only capture information on individuals seeking help and receiving specialist care. Individuals being treated only in primary care are not included. Therefore, individuals with psychiatric disorders identified in this study may represent the most severe cases, who are treated in specialist care. It should be noted that, despite the study sample including over two million individuals, for later-onset disorders, such as bipolar disorder and borderline personality disorder, as compared to ASD and other neurodevelopmental disorders, the prevalence was low due to the follow-up not being long enough for some individuals included in the study to receive a diagnosis. This has two main consequences. For familial associations, it limits the ability to exclude the possibility that some of the group differences are due chance for the smaller groups, such as twins, as the uncertainty of the estimates, illustrated by CIs, was larger for those groups. For genetic associations, estimated via SEM, there was not enough statistical power for eating, psychotic, bipolar, and borderline personality disorders. In addition, to increase the power for this analysis, we grouped together obsessive-compulsive disorder with other anxiety disorders. Future genetic studies, with longer follow-up and richer phenotypic information, may be able to expand current results on associations between different disorders and differentiate across different patient sub-groups.

Conclusion

We found evidence of familial and genetic associations between ASD and other neurodevelopmental disorders, as well as other psychiatric disorders. However, ASD comorbid with intellectual disability, epilepsy, congenital malformations or chromosomal abnormalities, shows weaker familial associations with neurodevelopmental and psychiatric disorders.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article:

Table S1. Diagnostic codes from ICD used to identify neurodevelopmental and psychiatric disorders.
Table S2. Structural equation modeling assumptions for different types of relatives.
Table S3. Familial associations illustrated in Figure 1 (whole sample).
Table S4. Familial associations illustrated in Figure 2 (stratified by sex).
Table S5. Familial associations illustrated in Figure 3 (stratified by comorbidity status).
Table S6. Results of structural equation modeling.

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Key points

- Familial and genetic association have been reported between autism spectrum disorder (ASD) and neurodevelopmental and psychiatric disorders, such as ADHD and depression, but other disorders have not been investigated.
- We found strong a genetic correlation between ASD and other neurodevelopmental disorders, modest genetic correlations between ASD and anxiety, depression, and intentional self-harm.
- We found familial associations between ASD and other neurodevelopmental and psychiatric disorders, which were lower when ASD was comorbid with either intellectual disability, epilepsy, chromosomal abnormalities, or congenital malformations.
- Family history of neurodevelopmental and psychiatric disorders should be considered in ASD assessment.
- In order to understand ASD genetics and biology, cross-disorder genetic influences, but also patients' subgroup differences, should be investigated.

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