Early manifestations of genetic risk for neurodevelopmental disorders

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Abstract

Background

Attention deficit/hyperactivity disorder (ADHD), autism spectrum disorder (autism), and schizophrenia, are highly heritable neurodevelopmental disorders, affecting the lives of many individuals. To improve prevention and treatment, it is important to increase our understanding of how the polygenic risk for neurodevelopmental disorders manifests during childhood in boys and girls.

Method

Polygenic risk scores (PRS) for ADHD, autism and schizophrenia were calculated in a sub-sample of 15 205 children from the Norwegian Mother, Father and Child Cohort Study (MoBa). Mother-reported traits of repetitive behavior, social communication, language and motor difficulties, hyperactivity and inattention were measured in children at 6 and 18 months, 3, 5 and 8 years. Linear regression models in a multi-group framework were used to investigate associations between the three PRS and dimensional trait measures in MoBa, and sex was used as a grouping variable.

Results

Before the age of 2, PRS associations were found with language difficulties, inattention and hyperactivity, mostly increasing in strength up to 8 years. PRS for autism was associated with motor difficulties as early as 6 months. By 8 years, all measured neurodevelopmental traits had shown some association with at least one neurodevelopmental PRS. In general, genetic risk manifested similarly in boys and girls. Associations were, however, stronger in girls for language difficulties and ADHD PRS at 8 years. The association between schizophrenia PRS and inattention was found in girls only at 18 months. For autism PRS, associations with social communication difficulties at 18 months, and motor difficulties at 5 years were observed in boys only.

Conclusions

Genetic risk for neurodevelopmental disorders manifests early in childhood and broadly across behavioral measures of neurodevelopment. Manifestations may be sex specific in some domains, but these findings need to be replicated.

Keywords: Polygenic risk score, neurodevelopmental disorders, ADHD, autism, schizophrenia, repetitive behavior, social communication, language and motor difficulties, hyperactivity, inattention, MoBa

Abbreviations: PRS – polygenic risk score

Introduction

Neurodevelopmental disorders (NDDs) are characterized by childhood-onset impairments in developmental domains such as language, motor skills, communication and social interaction, behavioral flexibility, and regulation of attention, activity and impulses (Association, 2013; Thapar, Cooper, & Rutter, 2017). Common neurodevelopmental disorders include attention deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (autism) (Thapar et al., 2017). Schizophrenia, although typically diagnosed in adolescence or early adulthood, is commonly associated with developmental difficulties in childhood and therefore also considered to be a neurodevelopmental disorder (Riglin et al., 2017).

ADHD, characterized by inattention and/or hyperactivity-impulsivity, is the most common behavioral disorder in childhood, affecting approximately 4-5% of children worldwide and usually diagnosed around age 6 years (Kessler et al., 2007; G. Polanczyk, De Lima, Horta, Biederman, & Rohde, 2007; G. V. Polanczyk, Willcutt, Salum, Kieling, & Rohde, 2014; Visser et al., 2014). Autism, characterized by communication and social interaction impairments along with restricted and repetitive behavior (Grove et al., 2019; Sullivan, Daly, & O'donovan, 2012) affects about 1.5% of children in high-income countries (Lyall et al., 2017), and is diagnosed at a median age of 4 years (Baio et al., 2018). Schizophrenia, characterized by long-standing delusions and hallucinations, disorganized speech or behavior (Sullivan et al., 2012), affects about 1% of the population in adulthood (Segal, 2010). ADHD and autism are more prevalent in males compared to females (Surén et al., 2012; Willcutt, 2012). For schizophrenia, although the prevalence is similar, males have an earlier onset than females (Li, Ma, Wang, Yang, & Wang, 2016). Mechanisms underlying sex differences are largely unknown, and recognition and diagnosis might be biased towards male manifestations (May, Adesina, McGillivray, & Rinehart, 2019). Although ADHD, autism and schizophrenia are categorically defined for clinical

purposes, they can also be viewed as the extremes of continuous trait dimensions found in the general population (Rössler, 2013).

Neurodevelopmental disorders like ADHD, autism and schizophrenia are highly heritable (70-90%) and etiologically complex, involving a large number of potentially overlapping genetic and environmental risk factors (Burmeister, McInnis, & Zöllner, 2008; Faraone & Larsson, 2019; Homberg et al., 2016; Mulligan et al., 2009; Sullivan et al., 2018; Sullivan et al., 2012).

The genetic influence on neurodevelopmental disorders includes both common (present in >1% of the population) and rare variants. Genome wide association studies (GWAS) indicate that a substantial part of the genetic liability to neurodevelopmental disorders are conferred by common single nucleotide polymorphisms (SNPs) distributed across the genome (Grove et al., 2019; Sullivan et al., 2012). Common SNPs have individually low impact, but together explain a substantial proportion of the risk.

Genetic risk for neurodevelopmental disorders might manifest in sub-clinical symptoms in the general population. Prospective and longitudinal general population cohorts, like the Norwegian Mother, Father and Child Cohort Study (MoBa), represent a unique framework for studying manifestations of genetic risk (Robinson, Shaver, & Wrightsman, 2013).

Only a few studies have used PRS to examine manifestations of genetic risk for neurodevelopmental disorders in early childhood (Jansen et al., 2018; Martin, Hamshere, Stergiakouli, O'Donovan, & Thapar, 2014; Nivard et al., 2017; Riglin et al., 2017). In the Avon longitudinal study of parents and children cohort (ALSPAC), PRS for schizophrenia predicted impairments of language and social communication at age 7-9 years (Riglin et al., 2017), and PRS for ADHD were associated with hyperactivity and inattention at 7-9 years (Martin et al., 2014). A lack of measures of

neurodevelopmental traits prior to the age of four years has been a limitation for multiple studies. Inclusion of earlier measures is needed to increase our understanding of when, during development, genetic risk for various neurodevelopmental disorders is expressed in observable traits. To improve prevention and treatment, the knowledge gap on developmental influences on the phenotypic manifestations of genetic risk for psychiatric disorders is important to address (Sullivan et al., 2018).

Previous studies have focused on the genetic risk of specific disorders (Burmeister et al., 2008; Faraone & Larsson, 2019; Homberg et al., 2016; Sullivan et al., 2018; Sullivan et al., 2012) often using diagnostic measures in older children as outcomes. Where trait measures of neurodevelopment have been studied, they have rarely been measured in children younger than 4 years old. We examined when and how genetic risk for ADHD, autism and schizophrenia is expressed in neurodevelopmental traits (repetitive behavior, social communication difficulties, language and motor difficulties, hyperactivity and inattention) from 6 months up to 8 years, and if they are expressed differently between boys and girls.

Methods

Sample

We used children from the Norwegian Mother, Father and Child Cohort Study (MoBa) as our sample. MoBa is a longitudinal pregnancy cohort including about 114 500 children, their mothers and fathers (Magnus et al., 2016; Magnus et al., 2006). Blood samples were collected from the children's umbilical cord at birth (Paltiel et al., 2014). The genotyping, imputation and quality control is described in the supplementary material. Genotype data was available for a sub-sample of 15 205 of the children (48.9% girls). In MoBa, pregnant women were recruited from 1999 to 2008. The women consented to participation in 40.6% of the pregnancies. Written informed consent was obtained from all participants upon recruitment. The initial data collection was based on a license from the Norwegian Data Protection Agency and approval from The Regional Committee for Medical Research

Ethics. The MoBa cohort is currently regulated by the Norwegian Health Registry Act. The current study was approved by the Regional Committees for Medical and Health Research Ethics (2016/1702) and has undergone a Data Protection Impact Assessment.

Measures

Mother-reported questionnaire data was available from when children were aged 6 and 18 months, 3, 5, and 8 years. The questionnaires included several dimensional measures of traits related to neurodevelopment. Version 12 of the quality assured MoBa data files were used to conduct the analyses.

Social communication difficulties and *repetitive behavior* were measured using items from the Ages and Stages Communication scale at 6 months (only social communication) (Richter & Janson, 2007), the Modified Checklist for Autism in Toddlers (M-CHAT) (Baron-Cohen, Allen, & Gillberg, 1992; Robins, Fein, Barton, Green, & disorders, 2001) at 18 months and the Social Communication Questionnaire (SCQ) (Rutter, Bailey, & Lord, 2003) at 3 and 8 years. When the children were 5 years old, the mothers reported on a short version (Ronald, Happé, Plomin, & Psychiatry, 2008) of the Childhood Autism Spectrum Test (CAST; formerly named Childhood Asperger Syndrome Test) (Scott, Baron-Cohen, Bolton, & Brayne, 2002), which includes items similar to the SCQ and M-CHAT.

Inattention and hyperactivity/impulsivity were assessed using the Diagnostic and Statistical Manual of Mental Disorders (DSM)-oriented ADHD problems scale of the Child Behavior Check List (CBCL) (Achenbach, Dumenci, & Rescorla, 2001) at 18 months and 3 years, the revised Conner's Parent Rating Scale (CPRS-R) (Kumar & Steer, 2003) at 5 years, and the full Parent/Teacher Rating Scale for Disruptive Behavior Disorders (RS-DBD) (Silva et al., 2005) at 8 years.

Language difficulties were measured at 18 months, 3 and 5 years using the Ages and Stages Questionnaire (ASQ). The ASQ has been found to be an effective screening tool for developmental

difficulties (Richter & Janson, 2007). At 8 years, the Children's Communication Checklist-2 (CCC-2) (Bishop, 2003) was used to identify language difficulties. *Motor difficulties* were measured at 6 and 18 months, and 3 years using ASQ, and at 5 years using Children's Development Inventory (CDI) (Ireton, 1992).

Statistical analyses

Polygenic risk scores (PRS) were generated, using PRSice2 (Choi & O'Reilly, 2019), for each child in our analytic sample, based on summary statistics from European samples from the most recent Psychiatric Genomic Consortium (PGC) GWAS for each disorder; ADHD (20 183 cases and 35 191 controls) (Demontis et al., 2019); autism (18 381 cases and 27 969 controls) (Grove et al., 2019), and schizophrenia (36 989 cases and 113 075 controls) (Ripke et al., 2014). PRS combines the effects of common SNPs observed in large-scale GWAS to capture the cumulative effect of risk alleles in an individual (Wray et al., 2014). All summary statistics from PGC were subject to quality control including filtering for minor allele frequencies (MAF>1%) and INFO threshold>0.8. We used PRS built on a range of p value thresholds (*<5e-8, <1e-6, <1e-4, <0.001, <0.01, <0.05, <0.1., <0.2, <0.5.* and *1*) for inclusion of SNPs with progressively weaker associations with the disorders in the original GWAS, and assessed the consistency of results across thresholds as part of sensitivity checking. In our main figures and tables, we present results of PRS made at the p-value threshold <0.05, in line with other studies (Riglin et al., 2017), but results at all thresholds are presented in the supplementary material as well as tables of which p-value threshold that explained most variance in the outcome (see supplementary table S3, S5 and S7).

R version 3.4.4 was used for linear regression models in the *lavaan*-package (Rosseel, 2012) to assess associations between the PRS for the three neurodevelopmental disorders and dimensional measures of development at all ages (for one PRS at the time). The correlations between PRS (calculated at the p <0.05 threshold) were 0.17 between ADHD and autism PRS (95% CIs: 0.16-0.19); 0.07 between ADHD and schizophrenia (95% CIs: 0.05-0.08); and 0.01 between autism and

schizophrenia (95% CIs: -0.01-0.03). PRS and outcome measures were standardized to zero mean and unit variance prior to analyses. Sex differences were investigated by including sex as a grouping variable in a multi-group framework.

In order to account for multiple testing, we corrected the critical p-value threshold for the number of effective tests run (Bonferroni correction). To determine the number of effective tests, we ran a principal component analysis on all the 25 outcome measures (Leppert et al., 2019). The number of tests was defined as the number of principal components explaining 80% variance, which was 16. A p-value of 0.05 will therefore be represented by a corrected p-value of 0.0031 (0.05/16).

Results

Descriptive statistics for the neurodevelopmental trait scales are presented in **Table 1.** For information not divided by sex, including Cronbach's alpha for each scale, see supplementary. For each PRS, associations with the 6 developmental traits are shown in figures 1-3.

Table 1

Polygenic risk score for ADHD

The associations between ADHD PRS and neurodevelopmental traits at different time points and in boys and girls are shown in Figure 1. There was a general pattern of increasing associations with age, and most of the associations did not differ across the sexes. Genetic risk for ADHD showed a pattern of positive association with repetitive behavior across age, although strong evidence of association was only observed at 3 years (β = 0.024, CI = 0.003-0.045). There was also strong evidence of a positive association with language difficulties at 5 years for both sexes (β = 0.047, CI = 0.022-0.071) and at 8 years for girls (β = 0.061, CI = 0.028-0.093). We did not observe any robust evidence of

association with motor difficulties. Genetic risk for ADHD was also robustly associated with increased hyperactivity and inattention across development, as expected, except in 18 month old girls.

Figure 1

Polygenic risk score for autism

The associations between autism PRS and neurodevelopmental traits across age and sex are shown in Figure 2. There is a general pattern of positive association with neurodevelopmental difficulties, meaning that those with more autism-associated SNPs tended to have higher scores on these traits. The autism PRS was positively associated with repetitive behavior in both sexes at 8 years (β = 0.028, CI = 0.002-0.054). PRS for autism showed a positive association with social communication difficulties in boys at 18 months (β = 0.035, CI = 0.011-0.061), and in both sexes at 5 years (β = 0.052, CI = 0.014-0.089). PRS for autism also showed a consistent association with language and motor difficulties, although strong evidence of associations with motor difficulties was only observed in boys at age 5 years (β = 0.052, CI = 0.020-0.084). PRS for autism was associated with hyperactivity at 5(β = 0.028, CI = 0.003-0.052) and 8 years (β = 0.037, CI = 0.012-0.062), and inattention at 8 years (β = 0.055, CI = 0.030-0.080).

Figure2

Polygenic risk score for schizophrenia

The associations between schizophrenia PRS and neurodevelopmental traits across age and sex are shown in Figure 3. We observed no strong evidence of associations between the schizophrenia PRS and neurodevelopmental difficulties from infancy to mid-childhood in MoBa. However, there was weaker evidence for association with repetitive behavior at 18 months (β = 0.019, CI = 0.001-0.038)

and 3 years (β = 0.027, CI = 0.006-0.047), language difficulties at 3 years (β = 0.025, CI = 0.003-0.048) and 8 years (β = 0.030, CI = 0.006-0.054), and inattention at 18 months for girls (β = 0.033, CI = 0.007-0.059).

Figure3

Supplementary Online tables S2-S4 show the explained variance on the p-value threshold 0.05 for both males and females on all neurodevelopmental traits. Supplementary Online Figure S1 shows the correlation between neurodevelopmental traits. Supplementary Online Figures S2-S10 display the associations of the 6 developmental traits of repetitive behavior, social communication difficulties, language and motor difficulties, hyperactivity and inattention at 10 different p-value thresholds for the PRS.

Discussion

Our aim was to identify early manifestations of polygenic risk for ADHD, autism, and schizophrenia in children between 6 months and 8 years in the general population. This is important so potential mediators and moderators of risk can be examined, and to determine the usefulness of polygenic risk scores for prediction of neurodevelopmental difficulties. We found that polygenic risk was associated with developmental traits as early as 6 months. Previous studies have not been able to investigate such associations at this young age. Before the age of two each PRS showed an association with at least one of the neurodevelopmental traits, and the autism PRS did show an association with all neurodevelopmental traits at least once between the age of 6 months to 8 years. It is important to note that, due to limited number of available measures, these analyses are specific for given time points, and not analyzed as developmental trajectories. The main pattern seems to be that the polygenic risk manifest similarly in boys and girls, but we did observe some sex differences, particularly a stronger association between language difficulties and ADHD PRS in girls than in boys,

and a stronger association between hyperactivity and inattention and ADHD PRS, and motor difficulties and autism PRS in boys as compared to girls.

To our knowledge, this is the first study showing that ADHD PRS may be associated with repetitive behavior in early childhood. However, observational studies suggest that children with an ADHD diagnosis score higher on measures of repetitive behavior (Cooper, Martin, Langley, Hamshere, & Thapar, 2014), especially at younger ages (Martin et al., 2014). Although the ADHD PRS associations with repetitive behavior were relatively weak, they appeared consistent across age and sensitivity analyses with varied SNP inclusion criteria.

Our results suggest that risk alleles for ADHD may contribute to language difficulties in girls at 8 years. This is in line with previous studies (Martin et al., 2014) where they found an associaction between ADHD PRS and pragmatic language, but they did not investigate sex differences.

Our results suggest that associations between ADHD polygenic risk and hyperactivity and inattention in the general population are robust as early as age 18 months and persist and strengthen with age to mid-childhood. This supports and extends previous findings from other cohorts (Martin et al., 2014). The only identified sex difference was at 18 months, with boys showing a positive association with both hyperactivity and inattention. There are more boys being diagnosed with ADHD than girls, and these traits are core diagnostic criteria for this disorder.

We found some evidence of an association between autism PRS and repetitive behavior at age 8, which is a core feature of autism (APA, 2013). We also found some evidence of associations between polygenic risk for autism and social communication difficulties in the general population, which is in line with previous studies in mid-childhood (age 8: St Pourcain et al. (2018); age 6: Takahashi et al. (2020)). We were able to examine the association at younger ages and found an association for boys

at 18 months between autism PRS and social communication difficulties, and at 5 years for both sexes, supporting St Pourcain et al. (2018) study that social communication difficulties may manifest at an early age.

We identified an association between autism PRS and language difficulties across all ages, which indicates that polygenic risk for autism contributes to language difficulties across early and mid-childhood development.

For schizophrenia PRS, we observed only weak evidence of association with repetitive behavior at 18 months and 3 years, language difficulties at age 3 and 8 years, and attention problems at age 18 months for girls. A number of possible explanations exist for why we did not identify strong evidence of associations between the schizophrenia PRS and childhood neurodevelopmental measures. First, we examined trait associations at younger ages than most previous studies. Since schizophrenia has a late onset, signs of polygenc risk for schizophrenia may manifest at a later stage. Associations found in other cohorts from mid-childhood (e.g., Nivard et al. (2017); Riglin et al. (2017); St Pourcain et al. (2018)) have been of small magnitude, although increasing somewhat in strength with age. Thus, our power to detect earliest signs of the schizphrenia PRS manifestations might be low. Second, genetic risk for schizophrenia may be expressed in other phenotypes not captured by current measures. Genetic variants showing an association with schizophrenia may only weakly index the risk for some phenotypic measures, and may more strongly reflect genetic risk for other characteristics of the disorder, such as negative symptoms.

Limitations

The study has some limitations. Some are limitations inherent to analyses using PRS based on current GWAS including small effect sizes, GWAS sample sizes and ascertainment methods (Demontis et al., 2019; Grove et al., 2019; St Pourcain et al., 2018). Rare genetic variants are not captured by GWAS, so we are only able to examine associations with common variants. Some limitations were specific to

our study. First, we used a strict multiple testing correction which may have resulted in failure to identify some true effects. However, we saw several effects pass this strict threshold, meaning we are able to have confidence in the robustness of these findings. Second, there are demographic differences between the discovery GWAS samples and our sample. The discovery sample consists of both children and adults with a diagnosis. There is an ongoing discussion about whether childhood and adult onset ADHD is actually the same disorder (Rovira et al., 2020). If not, the PRS for ADHD would yield different results than if the discovery sample was based purely on children. Third, despite the use of one of the largest population-birth cohorts worldwide, the current subsample may not be adequately powered to identify small effects in some domains. Fourth, as with all longitudinal studies, MoBa is subject to attrition (Nilsen et al., 2013). Previous studies have shown that predictors of attrition include presence of behavioral difficulties, such as ADHD, in the study child (Wolke et al., 2009). Missing data in the cohort could lead to bias in our estimates, and selective missingness may lead to underrepresentation of participants with high genetic risk for a neurodevelopmental disorder, or an underestimation of association as it would be likely to reduce the correlation between the PRS and the neurodevelopmental traits.

Conclusions

To our knowledge, our study is the first to investigate manifestations of genetic risk for multiple neurodevelopmental disorders in a general population sample of children as young as six months of age. The results show that genetic risk for clinically diagnosed neurodevelopmental disorders is detectable in neurodevelopmental traits in the general population at an early age. It is relatively broadly expressed, and appears predominantly consistent across sex, with some exceptions that should be further investigated. Even larger population-based longitudinal studies with both genetic data and robust and consistent measures of neurodevelopmental traits are required to reliably detect how genetic risk for neurodevelopmental disorders are expressed from infancy through childhood and adulthood.

Figures and tables

Table 1. Descriptive statistics for measures of neurodevelopmental traits at all ages for children with genotype data

Age	Variable	N Boys	N Girls	Mean (SD) Boys	Mean (SD) Girls	No of items in scale
6 months	Social communication	6913	6638	5.41 (0.77)	5.38 (0.73)	5
	Motor difficulties	6915	6640	6.73 (1.23)	6.73 (1.20)	6
18 months	Repetitive behavior	5971	5644	6.36 (0.63)	6.34 (0.60)	6
	Social communication	5971	5643	15.44 (0.87)	15.36 (0.77)	15
	Language difficulties	5962	5645	4.46 (1.59)	3.91 (1.32)	3
	Motor difficulties	5971	5646	6.64 (1.27)	6.75 (1.33)	6
	Hyperactivity	5965	5634	3.50 (0.94)	3.42 (0.90)	2
	Inattention	5966	5636	3.15 (0.95)	3.06 (0.92)	2
36 months	Repetitive behavior	4818	4622	15.96 (2.53)	15.57 (2.37)	12
	Social communication	4829	4627	28.35 (1.79)	28.03 (1.55)	26
	Language difficulties	4839	4632	6.69 (1.15)	6.49 (0.86)	6
	Motor difficulties	4821	4622	5.48 (1.42)	4.80 (1.08)	4
	Hyperactivity	4826	4616	6.23 (1.59)	6.23 (1.62)	4
	Inattention	4829	4617	3.20 (0.97)	3.15 (0.94)	2
5 years	Repetitive behavior	1603	1508	5.47 (0.72)	5.36 (0.61)	5
	Social communication	1604	1510	11.71 (0.97)	11.57 (0.81)	11
	Language difficulties	3735	3579	6.73 (1.20)	6.61 (1.02)	6
	Motor difficulties	3743	3585	13.36 (1.74)	12.55 (1.10)	12
	Hyperactivity	3741	3578	4.24 (1.39)	3.99 (1.23)	3
	Inattention	3744	3585	12.60 (3.67)	11.80 (3.10)	9
8 years	Repetitive behavior	3789	3575	12.70 (1.24)	12.52 (0.95)	12
	Social communication	3773	3560	28.82 (2.51)	28.27 (2.24)	26
	Language difficulties	3776	3567	21.45 (4.87)	20.66 (4.29)	16
	Hyperactivity	3783	3572	12.93 (4.17)	11.97 (3.45)	9
	Inattention	3786	3571	14.45 (4.32)	13.15 (3.51)	9

Figure 1: ADHD PRS

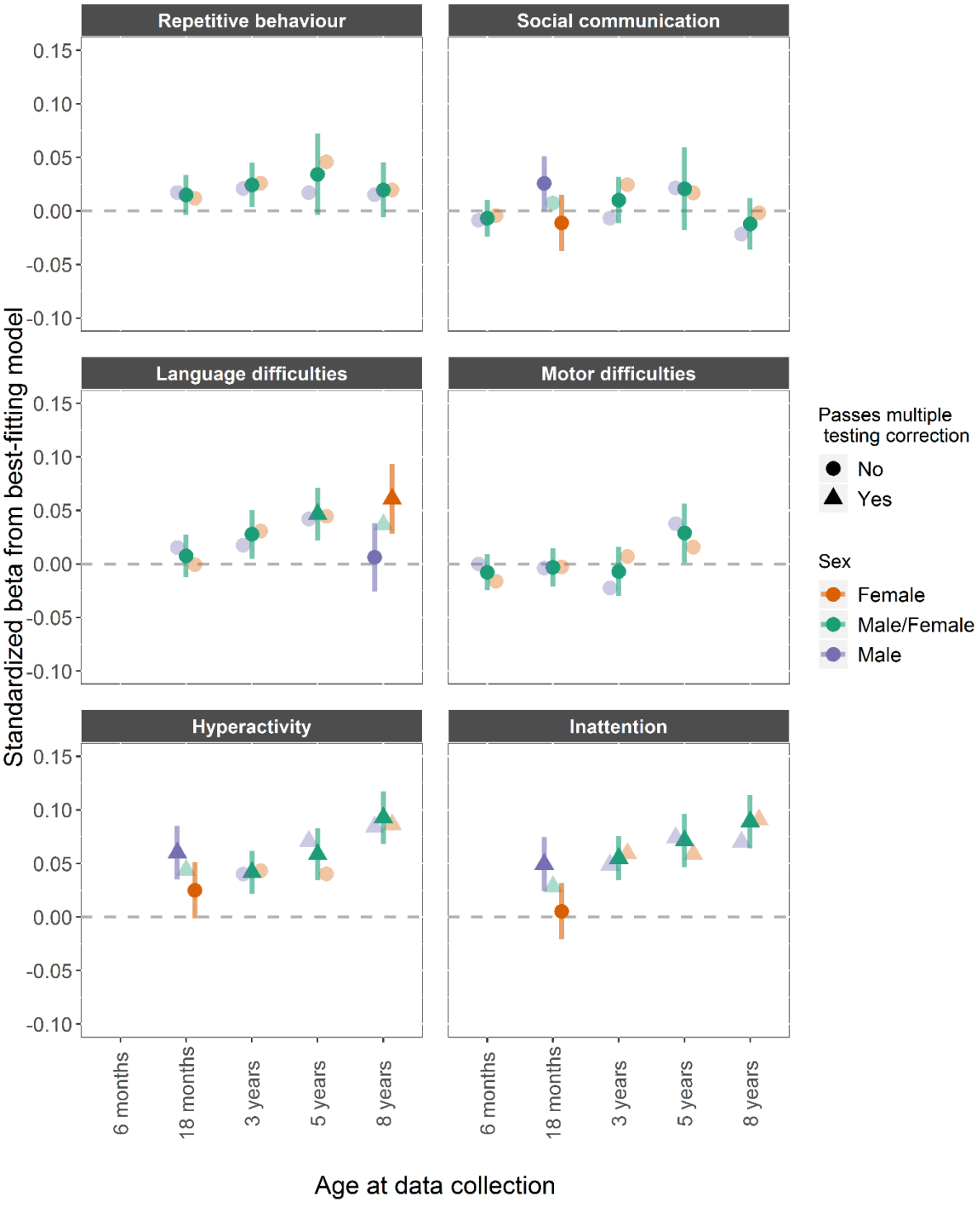


Figure2: autism PRS

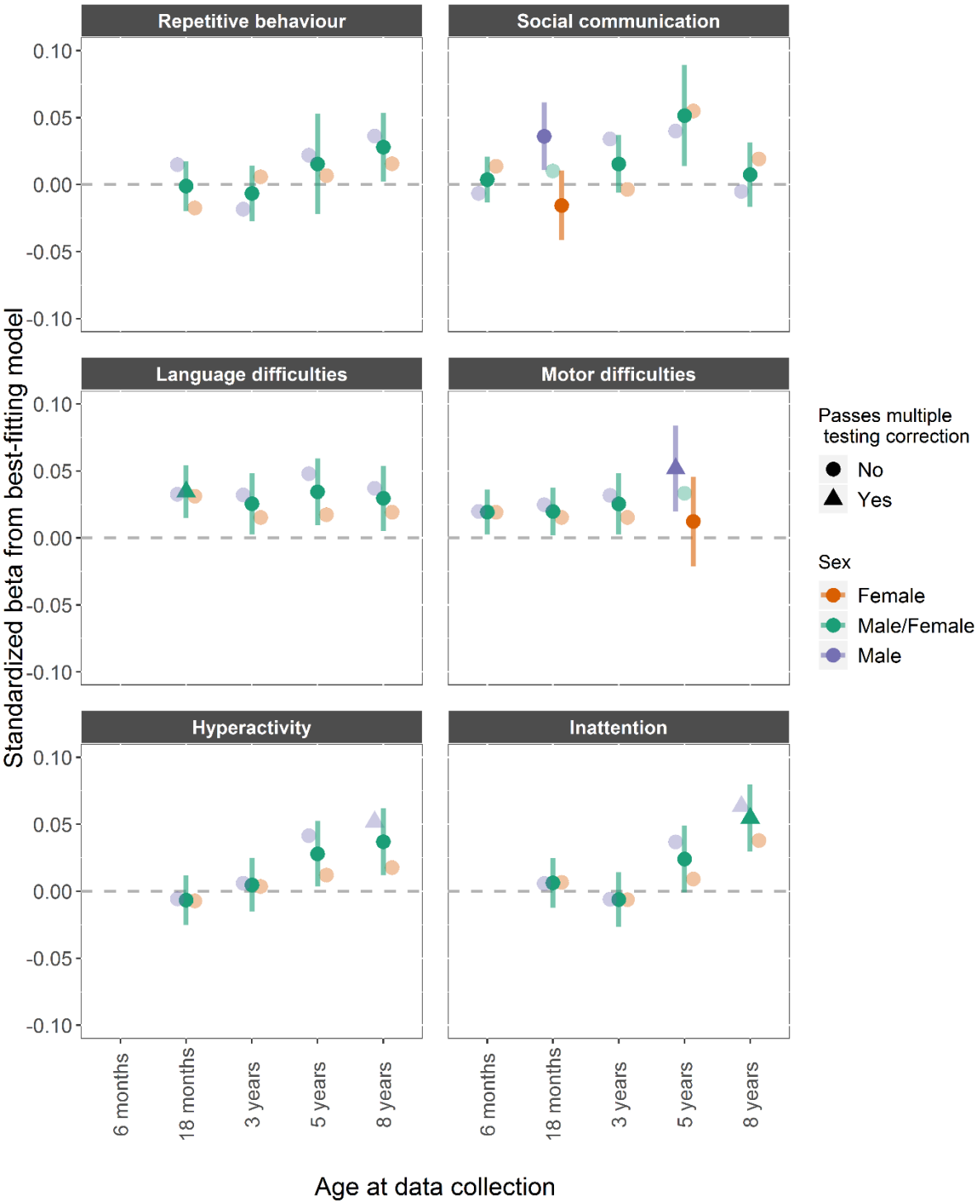
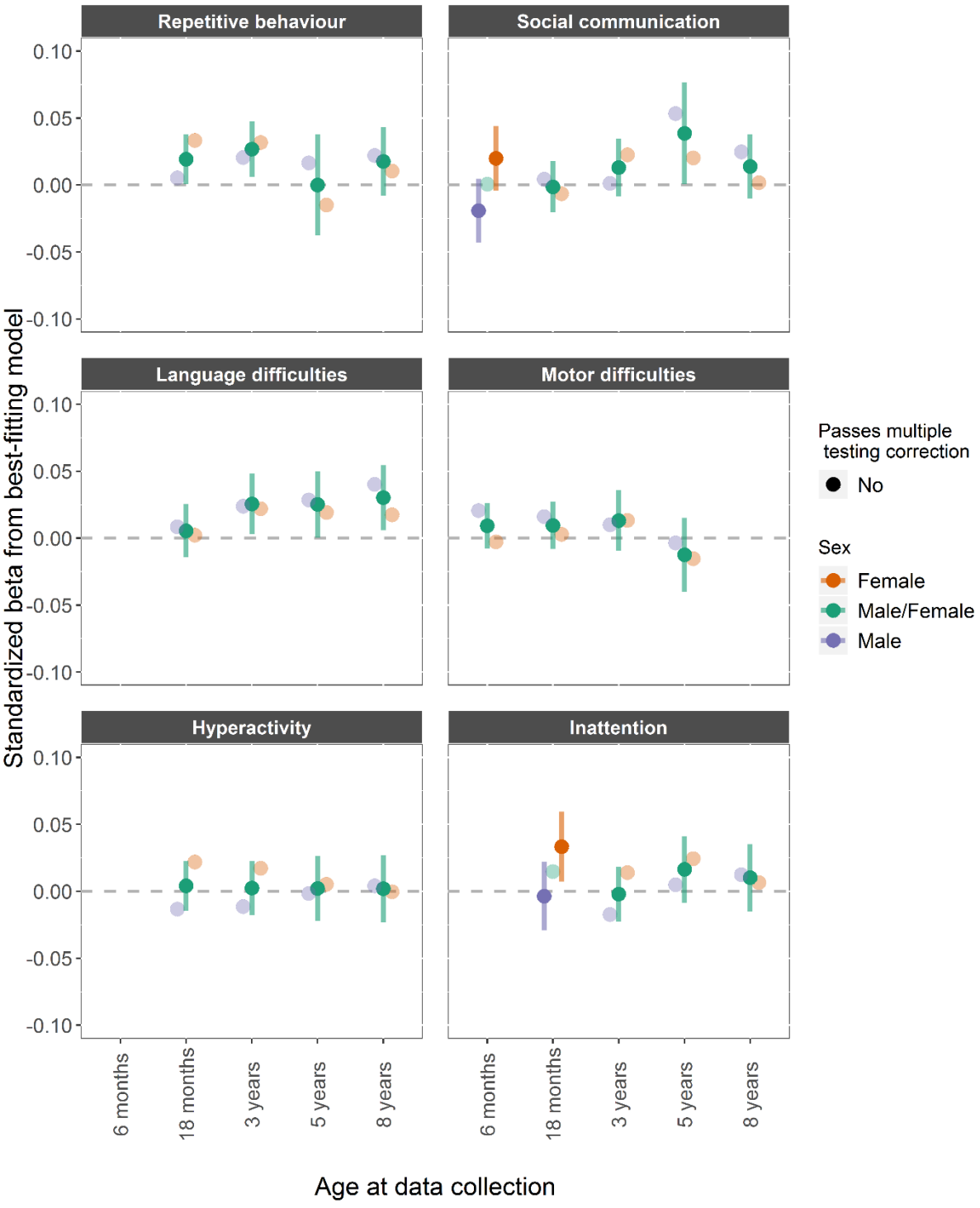


Figure3: schizophrenia PRS



Key points

- Liability to neurodevelopmental disorders is partially underpinned by incremental effects of many common genetic variants
- These variants are also associated with a range of neurodevelopmental traits in the general population across childhood and sex
- Where we found an association there is a vulnerability that needs to be attenuated by clinicians in meetings with children who show this behavior and might have a genetic risk. Our results narrow the knowledge gap on how genetic risk for neurodevelopmental disorders manifest manifests both early in development and broadly across a range of domains, with some specificity for boys and girls.
- Some behavior manifest different in boys and girls, and this should be given attention by clinicians when examining the child

Conflicts of interest

None declared.

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References

Achenbach, T. M., Dumenci, L., & Rescorla, L. A. J. B., VT: University of Vermont. (2001). Ratings of relations between DSM-IV diagnostic categories and items of the CBCL/6-18, TRF, and YSR. 1-9.

APA. (2013). *Diagnostic and statistical manual of mental disorders (DSM-5®)*: American Psychiatric Association.

Association, A. P. (2013). *Diagnostic and statistical manual of mental disorders (DSM-5®)*: American Psychiatric Pub.

Baio, J., Wiggins, L., Christensen, D. L., Maenner, M. J., Daniels, J., Warren, Z., . . . White, T. J. M. S. S. (2018). Prevalence of autism spectrum disorder among children aged 8 years—autism and developmental disabilities monitoring network, 11 sites, United States, 2014. *67*(6), 1.

Baron-Cohen, S., Allen, J., & Gillberg, C. J. B. j. o. p. (1992). Can autism be detected at 18 months? The needle, the haystack and the CHAT. *161*, 839-839.

Bishop, D. V. (2003). *The children's communication checklist: CCC-2*: Harcourt Assessment.

Burmeister, M., McInnis, M. G., & Zöllner, S. J. N. R. G. (2008). Psychiatric genetics: progress amid controversy. *9*(7), 527-540.

Choi, S. W., & O'Reilly, P. F. J. G. (2019). PRSice-2: Polygenic Risk Score software for biobank-scale data. *8*(7), giz082.

Cooper, M., Martin, J., Langley, K., Hamshere, M., & Thapar, A. (2014). Autistic traits in children with ADHD index clinical and cognitive problems. *European child & adolescent psychiatry, 23*(1), 23-34. doi:10.1007/s00787-013-0398-6

Demontis, D., Walters, R. K., Martin, J., Mattheisen, M., Als, T. D., Agerbo, E., . . . Bækvad-Hansen, M. J. N. g. (2019). Discovery of the first genome-wide significant risk loci for attention deficit/hyperactivity disorder. *51*(1), 63-75.

Faraone, S. V., & Larsson, H. J. M. p. (2019). Genetics of attention deficit hyperactivity disorder. *24*(4), 562-575.

Grove, J., Ripke, S., Als, T. D., Mattheisen, M., Walters, R. K., Won, H., . . . Anney, R. J. N. G. (2019). Identification of common genetic risk variants for autism spectrum disorder. *51*, 431-444.

Homberg, J. R., Kyzar, E. J., Scattoni, M. L., Norton, W. H., Pittman, J., Gaikwad, S., . . . Diamond, D. M. J. B. r. b. (2016). Genetic and environmental modulation of neurodevelopmental disorders: translational insights from labs to beds. *125*, 79-91.

Ireton, H. (1992). Child development inventory. In: Behavior Science Systems Minneapolis, MN.

Jansen, P. R., Polderman, T. J., Bolhuis, K., van der Ende, J., Jaddoe, V. W., Verhulst, F. C., . . . Psychiatry. (2018). Polygenic scores for schizophrenia and educational attainment are associated with behavioural problems in early childhood in the general population. *59*(1), 39-47.

Kessler, R. C., Amminger, G. P., Aguilar-Gaxiola, S., Alonso, J., Lee, S., & Ustun, T. B. J. C. o. i. p. (2007). Age of onset of mental disorders: a review of recent literature. *20*(4), 359.

Kumar, G., & Steer, R. A. J. J. o. P. a. (2003). Factorial validity of the Conners' Parent Rating Scale-revised: short form with psychiatric outpatients. *80*(3), 252-259.

Leppert, B., Havdahl, A., Riglin, L., Jones, H. J., Zheng, J., Smith, G. D., . . . Stergiakouli, E. J. J. p. (2019). Association of maternal neurodevelopmental risk alleles with early-life exposures. *76*(8), 834-842.

Li, R., Ma, X., Wang, G., Yang, J., & Wang, C. J. J. o. t. n. (2016). Why sex differences in schizophrenia? *, 1*(1), 37.

Lyall, K., Croen, L., Daniels, J., Fallin, M. D., Ladd-Acosta, C., Lee, B. K., . . . Volk, H. J. A. r. o. p. h. (2017). The changing epidemiology of autism spectrum disorders. *38*, 81-102.

Magnus, P., Birke, C., Vejrup, K., Haugan, A., Alsaker, E., Daltveit, A. K., . . . Knudsen, G. P. J. I. j. o. e. (2016). Cohort profile update: the Norwegian mother and child cohort study (MoBa). *45*(2), 382-388.

Magnus, P., Irgens, L. M., Haug, K., Nystad, W., Skjærven, R., & Stoltenberg, C. J. I. j. o. e. (2006). Cohort profile: the Norwegian mother and child cohort study (MoBa). *35*(5), 1146-1150.

Martin, J., Hamshere, M. L., Stergiakouli, E., O'Donovan, M. C., & Thapar, A. J. B. p. (2014). Genetic risk for attention-deficit/hyperactivity disorder contributes to neurodevelopmental traits in the general population. *76*(8), 664-671.

May, T., Adesina, I., McGillivray, J., & Rinehart, N. J. J. C. o. i. n. (2019). Sex differences in neurodevelopmental disorders. *32*(4), 622-626.

Mulligan, A., Anney, R. J., O'Regan, M., Chen, W., Butler, L., Fitzgerald, M., . . . disorders, d. (2009). Autism symptoms in attention-deficit/hyperactivity disorder: a familial trait which correlates with conduct, oppositional defiant, language and motor disorders. *39*(2), 197-209.

Nilsen, R. M., Surén, P., Gunnes, N., Alsaker, E. R., Bresnahan, M., Hirtz, D., . . . epidemiology, p. (2013). Analysis of self-selection bias in a population-based cohort study of autism spectrum disorders. *27*(6), 553-563.

Nivard, M. G., Gage, S. H., Hottenga, J. J., Van Beijsterveldt, C. E., Abdellaoui, A., Bartels, M., . . . Boomsma, D. I. J. S. B. (2017). Genetic overlap between schizophrenia and developmental psychopathology: longitudinal and multivariate polygenic risk prediction of common psychiatric traits during development. *43*(6), 1197-1207.

Paltiel, L., Anita, H., Skjerden, T., Harbak, K., Bækken, S., Kristin, S. N., . . . Magnus, P. J. N. e. (2014). The biobank of the Norwegian Mother and Child Cohort Study–present status. *24*(1-2).

Polanczyk, G., De Lima, M. S., Horta, B. L., Biederman, J., & Rohde, L. A. J. A. j. o. p. (2007). The worldwide prevalence of ADHD: a systematic review and metaregression analysis. *164*(6), 942-948.

Polanczyk, G. V., Willcutt, E. G., Salum, G. A., Kieling, C., & Rohde, L. A. J. I. j. o. e. (2014). ADHD prevalence estimates across three decades: an updated systematic review and meta-regression analysis. *43*(2), 434-442.

Richter, J., & Janson, H. (2007). A validation study of the Norwegian version of the Ages and Stages Questionnaires. *Acta paediatrica (Oslo, Norway : 1992), 96*, 748-752. doi:10.1111/j.1651-2227.2007.00246.x

Riglin, L., Collishaw, S., Richards, A., Thapar, A. K., Maughan, B., O'Donovan, M. C., & Thapar, A. J. T. L. P. (2017). Schizophrenia risk alleles and neurodevelopmental outcomes in childhood: a population-based cohort study. *4*(1), 57-62.

Ripke, S., Neale, B. M., Corvin, A., Walters, J. T., Farh, K.-H., Holmans, P. A., . . . Huang, H. J. N. (2014). Biological insights from 108 schizophrenia-associated genetic loci. *511*(7510), 421-427.

Robins, D. L., Fein, D., Barton, M. L., Green, J. A. J. J. o. a., & disorders, d. (2001). The Modified Checklist for Autism in Toddlers: an initial study investigating the early detection of autism and pervasive developmental disorders. *31*(2), 131-144.

Robinson, J. P., Shaver, P. R., & Wrightsman, L. S. (2013). *Measures of personality and social psychological attitudes: Measures of social psychological attitudes* (Vol. 1): Academic Press.

Ronald, A., Happé, F., Plomin, R. J. E. C., & Psychiatry, A. (2008). A twin study investigating the genetic and environmental aetiologies of parent, teacher and child ratings of autistic-like traits and their overlap. *17*(8), 473-483.

Rosseel, Y. (2012). Lavaan: An R package for structural equation modeling and more. Version 0.5–12 (BETA). *Journal of statistical software, 48*(2), 1-36.

Rovira, P., Demontis, D., Sánchez-Mora, C., Zayats, T., Klein, M., Mota, N. R., . . . Vilar-Ribó, L. J. N. (2020). Shared genetic background between children and adults with attention deficit/hyperactivity disorder. 1-10.

Rutter, M., Bailey, A., & Lord, C. J. T. S. C. Q. T., CA: Western Psychological Services. (2003). SCQ.

Rössler, W. J. F. i. p. h. (2013). What is normal? The impact of psychiatric classification on mental health practice and research. *1*, 68.

Scott, F. J., Baron-Cohen, S., Bolton, P., & Brayne, C. J. A. (2002). The CAST (Childhood Asperger Syndrome Test) Preliminary development of a UK screen for mainstream primary-school-age children. *6*(1), 9-31.

Segal, D. L. J. T. C. E. o. P. (2010). Diagnostic and statistical manual of mental disorders (DSM-IV-TR). 1-3.

Silva, R. R., Alpert, M., Pouget, E., Silva, V., Trosper, S., Reyes, K., & Dummit, S. (2005). A Rating Scale for Disruptive Behavior Disorders, Based on the DSM-IV Item Pool. *Psychiatric Quarterly, 76*(4), 327-339. doi:10.1007/s11126-005-4966-x

St Pourcain, B., Robinson, E. B., Anttila, V., Sullivan, B. B., Maller, J., Golding, J., . . . Zammit, S. J. M. p. (2018). ASD and schizophrenia show distinct developmental profiles in common genetic overlap with population-based social communication difficulties. *23*(2), 263-270.

Sullivan, P. F., Agrawal, A., Bulik, C. M., Andreassen, O. A., Børglum, A. D., Breen, G., . . . Gelernter, J. J. A. J. o. P. (2018). Psychiatric genomics: an update and an agenda. *175*(1), 15-27.

Sullivan, P. F., Daly, M. J., & O'donovan, M. J. N. R. G. (2012). Genetic architectures of psychiatric disorders: the emerging picture and its implications. *13*(8), 537-551.

Surén, P., Bakken, I. J., Aase, H., Chin, R., Gunnes, N., Lie, K. K., . . . Øyen, A.-S. J. P. (2012). Autism spectrum disorder, ADHD, epilepsy, and cerebral palsy in Norwegian children. *130*(1), e152-e158.

Takahashi, N., Harada, T., Nishimura, T., Okumura, A., Choi, D., Iwabuchi, T., . . . Takei, N. J. J. N. O. (2020). Association of genetic risks with autism spectrum disorder and early neurodevelopmental delays among children without intellectual disability. *3*(2), e1921644-e1921644.

Thapar, A., Cooper, M., & Rutter, M. J. T. L. P. (2017). Neurodevelopmental disorders. *4*(4), 339-346.

Visser, S. N., Danielson, M. L., Bitsko, R. H., Holbrook, J. R., Kogan, M. D., Ghandour, R. M., . . . Psychiatry, A. (2014). Trends in the parent-report of health care provider-diagnosed and

medicated attention-deficit/hyperactivity disorder: United States, 2003–2011. *53*(1), 34-46. e32.

Willcutt, E. G. J. N. (2012). The prevalence of DSM-IV attention-deficit/hyperactivity disorder: a meta-analytic review. *9*(3), 490-499.

Wolke, D., Waylen, A., Samara, M., Steer, C., Goodman, R., Ford, T., & Lamberts, K. J. T. B. J. o. P. (2009). Selective drop-out in longitudinal studies and non-biased prediction of behaviour disorders. *195*(3), 249-256.

Wray, N. R., Lee, S. H., Mehta, D., Vinkhuyzen, A. A., Dudbridge, F., Middeldorp, C. M. J. J. o. c. p., & psychiatry. (2014). Research review: polygenic methods and their application to psychiatric traits. *55*(10), 1068-1087.