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A study of the genetic architecture of social responsiveness in families with parental schizophrenia or bipolar disorder and population-based controls

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ABSTRACT

Twin-studies of social responsiveness have reported moderate to high heritabilities, but studies using parent-child data are lacking. Additionally, social impairments have been suggested as a vulnerability marker for schizophrenia and bipolar disorder, but the heritability of social responsiveness in this context is unknown. This study is part of the Danish High Risk and Resilience Study – VIA, comprising families with one parent with schizophrenia (n = 202) or bipolar disorder (n = 120) and population-based controls (PBC, n = 200). Social responsiveness was assessed with The Social Responsiveness Scale, Second Edition (SRS-2). Heritability was estimated from variance components, and a polygenic risk score (PRS) for autism spectrum disorder (ASD) was calculated to assess the genetic relationship between ASD and SRS-2. SRS-2 heritability was moderate to high and significantly different from zero in all groups when the children were rated by the primary caregiver. With teacher ratings, the heritability was lower and only significant in the full cohort and PBC. We found no significant association between SRS-2 and PRS for ASD. Our study confirms that social responsiveness is heritable, but that heritability estimates are affected by the child-respondent relation and familial risk of mental illness. This has implications for clinical practice and research using SRS-2 and provides insight on the familial transmission of mental illness.

1. Introduction

Social responsiveness, also referred to as social reciprocity, involves understanding and engaging in social interactions with other people in an appropriate way. More specifically, it involves processing social information, understanding the message being conveyed, responding appropriately, and being motivated to engage in interpersonal interactions (Constantino et al., 2000). Social responsiveness, typically assessed with the Social Responsiveness Scale, Second Edition (SRS-2), is typically linked to and has been used as an endophenotype for autism spectrum disorder (ASD) (Duvall et al., 2007; Lowe et al., 2015), as it was originally designed to identify the presence and severity of social
impairments associated with ASD (Constantino et al., 2003; Constantino and Gruber, 2012). Following this, the scale has been validated and widely used in various populations (Boyle et al., 2008; Chan et al., 2017; Gau et al., 2013; Takei et al., 2014; Wigham et al., 2012), as it is a relevant measure when characterizing behavior or impairments falling below the threshold for a diagnosis of ASD, but which nonetheless may indicate a need for help or support (Constantino, 2011; Constantino et al., 2000). ASD is a complex and heterogeneous disorder characterized by impairments in social communication and interaction as well as restricted, repetitive patterns of behavior, interests, or activities (Mast et al., 2017). The underlying genetic risk factors of ASD are known to include common genetic variants, rare genetic variants, copy number variants, and larger chromosomal abnormalities (Abrahams and Geschwind, 2008). Genetic studies using SRS-2 or the previous version of the questionnaire have been published (Lowe et al., 2015; Piven et al., 2013), including our previous study, where we identified a genome-wide significant parent-of-origin effect for social responsiveness (Nudel et al., 2022). However, studies investigating the genetic relationship between social responsiveness and ASD are lacking.

Although not part of the diagnostic criteria for these disorders, schizophrenia and bipolar disorder are also associated with clinically significant social impairments (Gillissie et al., 2022; Savla et al., 2013). Both schizophrenia and bipolar disorder are severe mental disorders with high heritability estimates, and family history of these illnesses remains the single strongest predictor for developing a mental disorder (Sandstrom et al., 2019). In relation to this, social impairment has been suggested as a potential vulnerability marker for both schizophrenia and bipolar disorder (Bora and Pantelis, 2013; Bora and Ozserdem, 2017; Lavoie et al., 2013), for which reason it is highly relevant to consider the heritability of social functioning in families with parental schizophrenia or bipolar disorder. Previously, we have shown that children born to parents with schizophrenia or bipolar disorder exhibit poorer social responsiveness than population-based controls (PBC), both at age 7 and at age 11 (Christiani et al., 2019; Veddum et al., 2022). Yet, to the best of our knowledge, the heritability of such traits has not been investigated in familial high-risk populations. However, studies of the general population have found strong associations between parental and offspring social responsiveness (Constantino and Todd, 2003; Lyall et al., 2014). This suggests that social responsiveness may be a heritable trait. Nevertheless, due to shared environmental effects and mutual influence, associations or correlations of a trait between parents and their children do not necessarily entail familial transmission or high heritability a priori.

Heritability is defined as the proportion of variation in a trait attributable to genetic variation in a given population (Mayhew and Meyre, 2017). Mathematically, it is defined as the ratio of the genetic variance (Vg) to the total phenotypic variance (Vp), where a phenotypic value (P) is composed of the genotypic value (G) and an environmental deviation (E). Hence, the respective variances of these terms are Vp = Vg + Ve (unless G and E are correlated, in which case their covariance will influence Ve, or if they interact) (Falconer and Mackay, 1996). Thus, heritability as described above, called the broad-sense heritability (h2) is defined as Vg/Vp. When the genetic variance is in relation only to additive effects (A), i.e., the effects which account for parent-offspring resemblance, the heritability is the narrow-sense heritability (h2 = VA/VA), where VA refers to the additive component of the genetic variance (Falconer and Mackay, 1996). Twin-studies of the general population have reported moderate to high heritability estimates for social responsiveness (Constantino and Todd, 2000, 2003), which is in accordance with a twin-study in which at least one co-twin was diagnosed with ASD (Deng et al., 2015). Similar results were found in a family-based study of adults, which included various types of family relations (Taylor et al., 2021). However, it should be noted that the heritability of a trait is dynamic and can differ in different populations or within the same population but across different groups, including different age groups. For instance, the heritability of height (a classic example of a heritable trait) differs across populations (Silventoinen et al., 2003) and across age groups (Jelenkovic et al., 2016). Therefore, studies attempting to estimate the heritability of social responsiveness in complementary ways and in different populations, e.g., using parent-child data and including investigation of potential contributing factors such as age and mental illness, are warranted. Additionally, such studies may provide insight into the familial transmission of social functioning in families with parental mental illness.

The main aims of the current study were to elucidate the genetic architecture of social responsiveness in families with parental schizophrenia or bipolar disorder and PBC families using pedigree-based heritability estimation, and to study the genetic relationship between social responsiveness and ASD; while social responsiveness is a heritable trait (Constantino and Todd, 2003) and used as an endophenotype of ASD (Lowe et al., 2015), a direct investigation of the prediction ability of ASD genetic risk on social responsiveness has not been previously reported. To this end, we use polygenic risk scores (PRS) for ASD and examine their association with SRS-2. Regarding the former aim, we focused on the impact of the child’s age, family history of severe mental illness, and the child-respondent relation. Moreover, in addition to the global score, we investigated the two behavioral domains that can be assessed with SRS-2.

2. Methods and materials

2.1. Sample

The current study is part of The Danish High Risk and Resilience Study – VIA, which is a longitudinal population-based study of 522 children at familial high-risk of schizophrenia (FHR-SZ, n = 202), bipolar disorder (FHR-BP, n = 120), or neither of these two disorders (n = 200) (Thorup et al., 2018, 2015). Currently, the children and their parents have been examined twice, first when the children were 7 years old (the VIA 7 study) and again at age 11 (the VIA 11 study). Of the initial cohort, a total of 465 families participated at follow-up at age 11 (FHR-SZ, n = 179; FHR-BP, n = 105; PBC, n = 181), equaling a retention rate of 89%. The PBC children were matched to the FHR-SZ children based on age, sex, and municipality. The FHR-BP children were a non-matched sample, but comparable to the two other groups in terms of age and sex. The VIA 7 study was conducted from January 1st, 2013, to January 1st, 2016, and the VIA 11 study took place from March 1st, 2017, to June 30th, 2020.

The index parent was defined as the parent registered with a diagnosis of schizophrenia or bipolar disorder. Index PBC parents were matched to an index schizophrenia parent based on sex. The non-index parent was defined as the other parent without a diagnosis of schizophrenia or bipolar disorder. PBC parents and non-index parents could have any other mental disorders than schizophrenia or bipolar disorder.

2.2. Procedures

Participants were identified through The Danish Civil Registration System and The Danish Psychiatric Central Research Register (Mors et al., 2011; Pedersen et al., 2006). The study was approved by the Danish Data Protection Agency and The National Committee on Health Research Ethics (ref. H16043682). All participants received written and verbal information about the study and written informed consent was obtained from the legal guardians of the child and the participating parents themselves.

2.3. Social responsiveness

Social responsiveness was assessed with SRS-2, which is a well-validated 65-item rating scale providing a global score ranging from 0 to 195, where higher scores indicate more severe impairment (Constantino et al., 2003; Constantino and Gruber, 2012). The scale can be
divided into two well-validated, DSM-5-compatible, and highly correlated subscales – namely the Social Communication and Interaction (SCI) subscale and the Restricted Interests and Repetitive Behavior (RIRB) subscale (Frazier et al., 2014). At age 7, the SRS-2 School-Age Form was completed by the teacher who knew the child best in school settings, and at age 11 the questionnaire was completed both by a teacher and the primary caregiver. The primary caregiver was in most cases a parent, as the role was defined as an adult living with, taking care of and knowing the child the best. Both biological parents were asked to complete the SRS-2 Adult Self-report Form if participating in the VIA 11 study.

2.4. Genetic data and polygenic risk score for autism spectrum disorders

At baseline, participants provided DNA samples (parents provided blood samples and children provided saliva samples). The samples were genotyped on the Illumina PsychChip array. Quality control (QC) for the genetic data is described in detail elsewhere (Nudel et al., 2020a, 2020b). Following this QC, the data were prepared for imputation and additional markers were imputed on the Michigan Imputation Server (Das et al., 2016). The imputation and imputation QC have been described in detail elsewhere (Jefsen et al., 2022).

The summary statistics for the PRS for ASD were from an ASD GWAS which used European individuals (Grove et al., 2019). As this study included Danish individuals, some of them could potentially overlap with some of the parents in the current study. However, we expect the number of overlapping samples to be negligible as the parents in the current study were not ascertained for ASD, and the population prevalence of ASD is quite low (Baird et al., 2006). The ASD phenotype in the discovery meta-analysis GWAS was based either on ICD-10 criteria (diagnostic codes F84.0, F84.1, F84.5, F84.8, F84.9), in the largest cohort, or diagnostic tools such as the Autism Diagnostic Observation Schedule or the Autism Diagnostic Interview-Revised in the smaller cohorts.

The PRS for ASD was generated using PRSice v2.2.3 (Choi and O’Reilly, 2019) with the following parameters: clumping window of 250 kb and $r^2$ of 0.1 (the default parameters); scoring method: score sum; otherwise, the default parameters were used. The p-value threshold employed in our analyses was $p_T = 1$. The choice of $p_T$ was based on the following:

1 Prior studies of both empirical and simulated data have shown that a $p_T = 1$ typically leads to better prediction (Dudbridge, 2013; Erin B Ware et al., 2017). This has also been demonstrated for schizophrenia, where $p_T = 1$ had the best prediction ability or close to the best prediction ability, depending on the target cohort (Ripke et al., 2014).

2 Only one genome-wide significant locus from the discovery GWAS overlapped with our QCed marker dataset, which, after the clumping procedure, would contribute very little to the PRS; we also confirmed in a post hoc analysis that none of the genome-wide significant markers from this locus were associated with social responsiveness in our sample.

3 Given the sample size of the VIA cohort, we wanted to avoid having to correct for testing multiple thresholds.

2.5. Data analysis

Demographic characteristics (age and sex) were analyzed using one-way ANOVA or chi-square tests, followed by pairwise comparisons, when relevant. As advised in the manual, missing items on SRS-2 were assigned with the particular item’s median score with a maximum of six missing answers for each respondent (Constantino and Gruber, 2012).

We used QTDT v2.6.1 (Abecasis et al., 2000) to estimate the variance components of the social responsiveness phenotype using SRS-2 outcomes for children (teacher or primary caregiver ratings) and parents (self-report). In the null model, we estimated the non-shared environment variance component (Ve), whereas both the non-shared environment and the polygenic variance components (Vg) were estimated in the full model, without modeling association. As described previously (Kaplan et al., 2002), the narrow-sense heritability ($h^2$) was calculated as $h^2 = Vg/(Ve + Vg)$ from the estimates in the full model (while the additive and the shared environment variance components may be conflated in family-based designs, it has been shown that it is mostly the non-shared environment variance component that is responsible for environmental variation relevant to psychological traits (Blokland et al., 2017)). The p-value for the heritability is calculated by QTDT using the $\chi^2$ distribution with 1 degree of freedom, whereby the test statistic equals twice the difference between the log-likelihoods of the two models (i.e., a likelihood ratio test). This approach was used with various subsets of the sample based on familial high-risk status, children’s SRS-2 outcome at age 7 or 11, and children’s SRS-2 outcome at age 11 with the primary caregiver or teacher as respondent.

The association between social responsiveness and PRS for ASD was ascertained using linear regression models with SRS-2 outcome as the dependent variable and PRS for ASD as the independent variable. Using multiple linear regression analyses, we examined the interaction effect of familial high-risk status on all associations. In the event of a non-significant interaction, the interaction term was removed, and the models were subsequently adjusted for familial high-risk status. Analyses regarding demographic characteristics and the association between social responsiveness and PRS for ASD were conducted using Stata IC software, version 16.1 (StataCorp., 2019).

For post hoc analyses, we used PLINK v1.90b6.26 (Purcell et al., 2007) to test for association between social responsiveness and the top GWAS risk variance of ASD. For the latter, we examined genome-wide significant markers from the ASD GWAS summary statistics described above, which were available in our QCed dataset. We used the family-based association test (qfam-parents with 1,000,000 permutations) and examined the empirical p-values for association. Post hoc analyses of the association between any lifetime ASD diagnosis at age 11 and PRS for ASD were tested with a logistic regression analysis with ASD diagnosis (yes/no) as the dependent variable and PRS for ASD as the independent variable. Additionally, the association between social responsiveness and PRS for ASD in children with or without any lifetime diagnosis of ASD until age 11 was explored using multiple linear regression analysis with SRS-2 outcome as the dependent variable and PRS for ASD as the independent variable, including an interaction term of any lifetime ASD diagnosis. The presence of any lifetime ASD diagnosis was ascertained with the Kiddie Schedule for Afffective Disorders and Schizophrenia for School-Age Children – Present and Lifetime Version (Gregersen et al., 2022; Kaufman et al., 1997).

All analyses were repeated both for the SRS-2 global score as well as the two subscale scores. In case of siblings, we only included data from the first participating sibling. Alpha level was set to 0.05 for all analyses. We corrected for multiple comparisons using the Benjamini-Hochberg correction procedure with the false discovery rate set to 5% (Benjamini and Hochberg, 1995).

3. Results

Across the two assessments, a total of 495 children (FHR-SZ, $n = 187$; FHR-BP, $n = 112$; PBC, $n = 196$), 363 index parents (FHR-SZ, $n = 117$; FHR-BP, $n = 85$; PBC, $n = 161$), and 325 non-index parents (FHR-SZ, $n = 117$; FHR-BP, $n = 74$; PBC, $n = 161$) participated in the current study. The children in the three groups did not differ significantly with regard to age or sex at any time point. Both index and non-index schizophrenia parents were younger than the parents in the two other groups, and more schizophrenia index parents and index PBC parents were females compared with index bipolar parents. Additionally, more index PBC
parents were primary caregivers compared with index schizophrenia parents and index bipolar parents (Table 1). We excluded 14 children due to sibling participation (FHR-SZ, n = 8, FHR-BP, n = 5, PBC, n = 1). Cross-sectional as well as longitudinal comparisons of the children’s social responsiveness in the current cohort have already been presented elsewhere (Christiani et al., 2019; Veddem et al., 2022).

3.1. Heritability of social responsiveness

Results based on teacher ratings at age 7 revealed a significant heritability estimation for the SRS-2 global score and the SCI subscale score in the full cohort and the PBC group. Likewise, based on teacher ratings at age 11, the heritability estimation was significant for the SRS-2 global score and the SCI subscale score in the full cohort, but only for the SCI subscale in the PBC group. When the children were rated by the primary caregiver at age 11, the heritability estimation was significant for the SRS-2 global score and the SCI subscale score both in the full cohort as well as in all three groups. The results revealed no significant heritability estimation for the RIRB subscale score (Table 2).

3.2. Associations between social responsiveness and polygenic risk for autism spectrum disorder

We found no significant interaction effect of familial high-risk status on the association between social responsiveness and PRS for ASD for index parents, non-index parents or children when rated by a teacher. However, when the children were rated by the primary caregiver, results revealed a significant interaction effect of familial high-risk status for the SRS-2 global score (F(2, 339) = 3.17, p = 0.04324) and the RIRB subscale score (F(2, 339) = 3.57, p = 0.02922) (Table S1). In relation to this, we only found a significant positive association between social responsiveness and PRS for ASD for children at FHR-SZ when rated by the primary caregiver, suggesting that higher SRS-2 global scores were associated with higher PRS for ASD in this group. However, this association did not remain significant after correction for multiple comparisons (Table 3). The associations between social responsiveness and PRS for ASD were non-significant for index parents and non-index parents as well as for the children when rated by a teacher (Table 4).

Results from post hoc analyses of the top GWAS risk variance of ASD did not reveal even nominally significant associations with social responsiveness (data not shown). Results from post hoc analyses revealed no significant association between lifetime ASD diagnosis at age 11 and PRS for ASD (OR = 1.13, p = 0.498, 95% CI: 0.79–1.62). However, we found a significant interaction effect of having a lifetime diagnosis of ASD on the association between social responsiveness and PRS for ASD. However, group-specific results revealed that the association between social responsiveness and PRS for ASD was non-significant both in children with and without any lifetime diagnosis of ASD (Table S2).

4. Discussion

In this study, we investigated the genetic architecture of social responsiveness in families with parental schizophrenia or bipolar disorder and PBC families using parent-child data. The results revealed that social responsiveness is heritable, but that the heritability estimates vary depending on whether the child has been assessed by a teacher or by the primary caregiver. In relation to this, we only identified a significant heritability estimate in the two familial high-risk groups when the children were assessed by the primary caregiver, and, overall, the heritability was lower in the two familial high-risk groups than in the PBC group, in contrast to results for related traits in a previous study (Blokland et al., 2017), although the heritability of social responsiveness was not compared between schizophrenia and control families in that study. The heritability estimation based on teacher ratings did not differ notably between age 7 and 11, irrespective of familial high-risk status. There were no significant associations between social responsiveness and PRS for ASD.

Previous studies have established narrow-sense heritability estimates of 0.40–0.76 for social responsiveness (Constantino and Todd, 2000; Deng et al., 2015; Taylor et al., 2021), which is in line with the results from the current study, when the heritability estimation was based on primary caregiver ratings. However, important differences between previous studies and our study should be taken into consideration. Firstly, in contrast to previous studies, all included children in the current study had the same age at both assessments diminishing potential age-related and developmental effects. Moreover, the follow-up design allowed us to compare the heritability estimates based on

Table 1
Demographic characteristics of the participating children and their biological parents.

<table>
<thead>
<tr>
<th></th>
<th>FHR-SZ</th>
<th>FHR-BP</th>
<th>PBC</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>n</td>
<td>n</td>
<td>p-value</td>
<td>p-value</td>
<td></td>
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<tr>
<td>Children, age 7, N</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Female, N (%)</td>
<td>162</td>
<td>99</td>
<td>167</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Age, mean (SD)</td>
<td>7.85(0.20)</td>
<td>7.85(0.21)</td>
<td>7.83(0.19)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Children, age 11, N</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Female, N (%)</td>
<td>167</td>
<td>98</td>
<td>178</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, mean (SD)</td>
<td>11.96(0.25)</td>
<td>11.94(0.22)</td>
<td>11.94(0.22)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Index parents a, N</td>
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<td>80</td>
<td>143</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female, N (%)</td>
<td>86(76.11)</td>
<td>45(56.25)</td>
<td>99(69.23)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at inclusion, mean (SD)</td>
<td>41.30(6.07)</td>
<td>44.88(6.45)</td>
<td>44.60(4.71)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary caregiver, N (%)</td>
<td>73(64.60)</td>
<td>51(63.75)</td>
<td>111(77.62)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: Familial high-risk of schizophrenia (FHR-SZ); Familial high-risk of bipolar disorder (FHR-BP); Population-based controls (PBC), Social Responsiveness Scale, Second Edition (SRS-2).

a Index parent refer to the biological parent registered with a diagnosis of schizophrenia or bipolar disorder. The PBC parents are matched to the schizophrenia index parents based on sex.

b Non-index parent is the biological parent not registered with a diagnosis of schizophrenia or bipolar disorder.

c DSM-5-compatible subscales.

d One-way ANOVA, significance level p<0.05.

e Chi-square test, significance level p<0.05.
different ages using the same children and parents. That said, our results suggest that child age may not affect the heritability of social responsi-

Table 2
Heritability estimation for social responsiveness in families with parental schizophrenia or bipolar disorder and population-based controls, calculated from child and parent scores on The Social Responsiveness Scale, Second edition.

| Abbreviations: Familial high-risk of schizophrenia (FHR-SZ), Familial high-risk of bipolar disorder (FHR-BP), Population-based controls (PBC), Social Responsiveness Scale, Second Edition (SRS-2), p-value < 0.022 after correction according to the Benjamini-Hochberg procedure. E followed by a number n in a p-value column denotes ×10^-n e.g., 1E-016 denotes 1 × 10^-16.

Table 3
Associations between children’s social responsiveness and polygenic risk for autism spectrum disorders.

<table>
<thead>
<tr>
<th>Unadjusted model</th>
<th>Adjusted modela</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coefficient</td>
<td>95% CI</td>
</tr>
<tr>
<td>Teacher, age 7b</td>
<td></td>
</tr>
<tr>
<td>SRS-2 Global Score</td>
<td>-1.11</td>
</tr>
<tr>
<td>Social Communication and Interaction (SCI)b</td>
<td>-0.87</td>
</tr>
<tr>
<td>Restricted Interests and Repetitive Behavior (RIRB)b</td>
<td>-0.24</td>
</tr>
<tr>
<td>Social Communication and Interaction (SCI)b</td>
<td>-1.09</td>
</tr>
<tr>
<td>Restricted Interests and Repetitive Behavior (RIRB)b</td>
<td>-0.34</td>
</tr>
<tr>
<td>Primary caregiver, age 11b</td>
<td></td>
</tr>
<tr>
<td>SRS-2 Global Score</td>
<td>1.77</td>
</tr>
<tr>
<td>Social Communication and Interaction (SCI)b</td>
<td>-</td>
</tr>
<tr>
<td>Restricted Interests and Repetitive Behavior (RIRB)b</td>
<td>-</td>
</tr>
<tr>
<td>Social Communication and Interaction (SCI)b</td>
<td>1.50</td>
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<tr>
<td>Restricted Interests and Repetitive Behavior (RIRB)b</td>
<td>0.27</td>
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<tr>
<td>Social Communication and Interaction (SCI)b</td>
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</tr>
<tr>
<td>Restricted Interests and Repetitive Behavior (RIRB)b</td>
<td>-</td>
</tr>
<tr>
<td>FHR-SZ</td>
<td>-</td>
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<tr>
<td>FHR-BP</td>
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<td>PBC</td>
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</table>

Abbreviations: The Social Responsiveness Scale, Second Edition (SRS-2), Familial high-risk of schizophrenia (FHR-SZ), Familial high-risk of bipolar disorder (FHR-BP), Population-based controls (PBC), p-value = significance level p < 0.002 after correction according to the Benjamini-Hochberg procedure.

a These analyses are based on data from 336 children (FHR-SZ, n = 122; FHR-BP, n = 81; PBC, n = 133).

b These analyses are based on data from 308 children (FHR-SZ, n = 109; FHR-BP, n = 71; PBC, n = 128).

c These analyses are based on data from 345 children (FHR-SZ, n = 123; FHR-BP, n = 79; PBC, n = 143).

d DSM-5-compatible subscales.

Model adjusted for familial high-risk status.

Group-specific coefficients reported due to a significant interaction effect of familial high-risk status.
impairment may constitute a vulnerability marker for developing a severe mental disorder (Bora and Pantelis, 2013; Bora and Ozerdem, 2017; Lavoie et al., 2013). In keeping with this, we have recently shown that the children at FHR-SZ or FHR-BP exhibit poorer social responsiveness compared with PBC children, both at age 7 and 11 (Christiani et al., 2019; Veddum et al., 2022).

Results from heritability analyses of the two SRS-2 subscales revealed an interesting difference as the heritability estimation for the RIRB subscale was non-significant in all cases, whereas significant heritability estimates were obtained for the SCI subscale. In fact, results for the SCI subscale and the SRS-2 global score were very similar. This is likely related to the way in which the subscales are derived from the total scale, where the SCI subscale is based on 53 questions, while the RIRB subscale is based on only 12 questions (Frazier et al., 2014). Additionally, the RIRB subscale reflects highly autistic-like behaviors and as described earlier, the incidence of ASD in our cohort is relatively low (Ellersgaard et al., 2018; Gregersen et al., 2022). Consequently, the variation in the participants’ results on the RIRB subscale may be small and, therefore, our study may be underpowered to detect a significant and precise heritability estimate. Of note, another family-based study of adults with a high degree of autistic traits did actually identify significant and moderate heritability for the RIRB subscale (Taylor et al., 2021).

Our results regarding heritability of social responsiveness are important in the context of GWAS studies of ASD since the heritability of a trait influences the power to detect genetic associations (Melo et al., 2016). Here, we were not able to detect any significant associations between social responsiveness and PRS for ASD, neither for children nor parents. Similarly, we did not find significant associations in the post hoc analyses of specific genome-wide significant markers for ASD. One possible explanation is that we examined a continuous scale as the outcome measure, whereas PRS for ASD may be predictive only for a binary ASD phenotype. In this respect, it is important to keep in mind that, while our post hoc analysis revealed no significant association between having a diagnosis of ASD at age 11 and PRS for ASD, this could be due to the small sample size in VIA (only a very small group of the children included in this study had any lifetime diagnosis of ASD at age 11 (n = 22 of the children with teacher ratings; n = 25 of the children with primary caregiver ratings) or due to differences in how ASD was assessed between the target and discovery samples, namely K-SADS (where the ASD diagnosis is based on DSM) in VIA and ICD-10, the Autism Diagnostic Observation Schedule, or the Autism Diagnostic Interview-Revised in the discovery GWAS on which the PRS is based (Anney et al., 2017; Grove et al., 2019). K-SADS is a broad screening tool, and a recent study found that it could miss some autism cases, as it was weighted more towards behavioral deficits compared to social interaction deficits (Jarbin et al., 2017).

Furthermore, the largest of the ASD cohorts in the discovery GWAS had different numbers of ASD subtype cases (e.g. childhood autism, Asperger’s syndrome and so on), which could potentially have genetic differences and, therefore, this might reduce the prediction ability of the

**Table 4** Associations between parents’ social responsiveness and polygenic risk for autism spectrum disorders.

<table>
<thead>
<tr>
<th>Index parent</th>
<th>Unadjusted model</th>
<th>Adjusted model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Coefficient</td>
<td>95% CI</td>
</tr>
<tr>
<td>SRS-2 Global Score</td>
<td>0.51</td>
<td>−1.52 to 2.53</td>
</tr>
<tr>
<td>Social Communication and Interaction (SCI)</td>
<td>0.39</td>
<td>−1.43 to 2.21</td>
</tr>
<tr>
<td>Restricted Interests and Repetitive Behavior (RIRB)</td>
<td>0.12</td>
<td>−0.24 to 0.48</td>
</tr>
</tbody>
</table>

Abbreviations: Familial high-risk of schizophrenia (FHR-SZ), Familial high-risk of bipolar disorder (FHR-BP), Population-based controls (PBC).

* Index parent refers to the biological parent with a registered with schizophrenia or bipolar disorder. The PBC parents are matched to the schizophrenia index parents based on sex. These analyses involved 261 index parents (FHR-SZ, n = 80; FHR-BP, n = 65; PBC, n = 117).
* Non-index parent is the biological co-parent not diagnosed with schizophrenia or bipolar disorder. These analyses involved 215 non-index parents (FHR-SZ, n = 83; FHR-BP, n = 51; PBC, n = 83).
PRS in the VIA sample, if the ASD cases differed in the subtype distributions. Nonetheless, the direction of association was positive, as the ASD PRS had OR>1 on having a diagnosis of ASD at age 11. We did not identify any significant associations between social responsiveness and PRS for ASD in children with or without any lifetime diagnosis of ASD either.

The current study has several strengths. To the best of our knowledge, it is the first to explore the effects of age, child-responder relation, and parental mental illness on the heritability of social responsiveness, and also the first study to investigate the relationship between social responsiveness and genetic risk of ASD specifically. Moreover, our cohort was population-based and consisted of same-aged children rated by multiple informants. Nevertheless, the results should be interpreted in light of some potential limitations. Firstly, while larger than the typical sample size in pedigree-based heritability analyses, the sample size may be too small for analyses using molecular genetic data, which may have an impact regarding the lack of significant association between social responsiveness and PRS for ASD. Secondly, the sample was not an ASD sample, which could potentially contribute to lower phenotypic variance in the sense that most children would score in the average range of the SRS-2. Thirdly, non-index parents and PBC parents could have any other mental disorders than schizophrenia or bipolar disorder, potentially presenting with social responsiveness and thus affecting our results. Lastly, the SRS-2 data were not perfectly normally distributed, which could influence the estimation of the variance components.

In conclusion, social responsiveness isheritable, but narrow-sense heritability estimation may be affected by factors such as child-responder relation and familial risk of severe mental illness. These findings have implications for clinical practices as well as research applying SRS-2 and provide further insights into the familial transmission of severe mental disorders.

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**CRediT authorship contribution statement**

Lotte Vedum: Conceptualization, Formal analysis, Investigation, Writing – original draft, Writing – review & editing. Aja Neergaard Greve: Conceptualization, Investigation, Writing – review & editing, Project administration. Maja Gregersen: Investigation, Writing – review & editing. Anna Krogh Andreassen: Investigation, Writing – review & editing. Christina Brun Knudsen: Investigation, Writing – review & editing. Julie Marie Brandt: Investigation, Writing – review & editing. Mette Falkenberg Krantz: Investigation, Writing – review & editing. Anne Søndergaard: Investigation, Writing – review & editing. Birgitte Klee Burton: Investigation, Writing – review & editing. Jens Richard Mallegaard Jepsen: Writing – review & editing. Nicoline Hemager: Investigation, Writing – review & editing, Project administration. Thomas Werge: Writing – review & editing, Project administration. Anne Amalie Elgaard Thorup: Writing – review & editing, Project administration. Merete Nordentoft: Writing – review & editing, Project administration, Funding acquisition. Ole Mors: Writing – review & editing, Project administration, Funding acquisition. Ron Nudel: Conceptualization, Methodology, Formal analysis, Writing – original draft, Writing – review & editing, Project administration, Supervision.

**Declaration of Competing Interest**

All authors declare no conflicts of interest, but TW states that he has acted as a lecturer and scientific counselor to H. Lundbeck A/S.

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**Supplementary materials**


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