IMPORTANCE  Although autism spectrum disorder (ASD) is known to be heritable, patterns of inheritance of subclinical autistic traits in nonclinical samples are poorly understood.

OBJECTIVE  To examine the familiality of Social Responsiveness Scale (SRS) scores of individuals with and without ASD.

DESIGN, SETTING, AND PARTICIPANTS  We performed a nested case-control study (pilot study: July 1, 2007, through June 30, 2009; full-scale study: September 15, 2008, through September 14, 2012) within a population-based longitudinal cohort. Participants were drawn from the Nurses’ Health Study II, a cohort of 116,430 female nurses recruited in 1989. Case participants were index children with reported ASD; control participants were frequency matched by year of birth of case participants among those not reporting ASD. Of 3161 eligible participants, 2144 nurses (67.8%) returned SRS forms for a child and at least 1 parent and were included in these analyses.

EXPOSURE  The SRS scores, as reported by nurse mothers and their spouses, were examined in association with risk of ASD using crude and adjusted logistic regression analyses. The SRS scores of the children were examined in association with SRS scores of the parents using crude and adjusted linear regression analyses stratified by case status.

MAIN OUTCOMES AND MEASURES  Autism spectrum disorder, assessed by maternal report, validated in a subgroup with the Autism Diagnostic Interview–Revised.

RESULTS  A total of 1649 individuals were included in these analyses, including 256 ASD case participants, 1393 control participants, 1233 mothers, and 1614 fathers. Risk of ASD was increased by 85.0% among children whose parents had concordantly elevated SRS scores (odds ratio [OR], 1.85; 95% CI, 1.08-3.16) and by 52.0% when the score of either parent was elevated (OR, 1.52; 95% CI, 1.11-2.06). Elevated scores of the father significantly increased the risk of ASD in the child (OR, 1.94; 95% CI, 1.38-2.71), but no association was seen with elevated scores of the mother. Elevated parent scores significantly increased child scores in controls, corresponding to an increase in 23 points (P < .001).

CONCLUSIONS AND RELEVANCE  These findings support the role of additive genetic influences in concentrating inherited ASD susceptibility in successive generations and the potential role of preferential mating, and suggest that typical variation in parental social functioning can produce clinically significant differences in offspring social traits.
Genetic factors are known to be involved in autism spectrum disorders (ASDs); however, the cause of ASD is currently not well understood. Wide phenotypic variability exists in the severity of affected individuals. In addition, evidence suggests that variation in social functioning exists in the general population in a continuum of autistic-like traits, referred to as the broader autism phenotype or quantitative autistic traits (QATs). Studies have reported inter-generational transmission of QATs, but patterns of familial transmission are not well understood, and large-scale epidemiologic investigations of families affected and unaffected by ASD are lacking.

The Social Responsiveness Scale (SRS) is a validated, widely used questionnaire that assesses behavioral and social-communicative traits, yielding a single score that has been justified in factor analyses. Established thresholds reliably distinguish children with ASD from children without ASD and those with other psychiatric and developmental conditions. The SRS scores have been reported to be continuously distributed, reproducible, unrelated to intelligence or age, and highly valid compared with the Autism Diagnostic Interview-Revised (ADI-R; r = 0.7).

Family studies that used the SRS have provided some evidence of heritability of QATs by reporting familial aggregation of elevated scores. However, prior studies have had relatively small sample sizes, limiting the ability to fully examine associations. Previous studies have also focused on simplex (1 child with ASD) vs multiplex (≥1 affected child) families and/or used clinic-referred populations or twin pairs or families with twins. However, patterns of inheritance may differ in these populations because of the differences in comorbidity and severity levels. Large studies drawn from the general population are needed to better understand the transmission of subthreshold autistic traits to learn more about the inheritance of ASD and QATs. The purpose of this study was to examine familiarity of SRS scores of individuals with and without ASD drawn from a nonclinical sample. In particular, we sought to examine whether higher parent scores were associated with (1) increased risk of ASD and (2) higher child scores.

**Methods**

**Study Population**

Participants were part of a nested case-control study (pilot study: July 1, 2007, through June 30, 2009; full-scale study: September 15, 2008, through September 14, 2012) drawn from the Nurses’ Health Study (NHS) II, a prospective cohort of 116,430 female nurses aged 25 to 42 years when recruited in 1989. Since that time, women have completed mailed questionnaires every 2 years. The Partners Health Care Institutional Review Board approved this study; completion and return of questionnaires constituted implied informed written consent. Additional details of the cohort have been previously reported. The NHS II questionnaires are available online (http://www.channing.harvard.edu/nhs/?page_id=246). In 2005, participants were asked whether any of their children had autism, Asperger syndrome, or another condition on the autism spectrum. In 2007, a nested case-control study (hereafter referred to as the follow-up study) was initiated, the details of which have been previously described. Briefly, 756 case participants and 3000 control participants frequency matched by year of birth were included. A total of 3383 women responded to the case-control follow-up study mailings (636 case participants; mean response rate, 90.1% [study mailed to 3756 individuals, with 3383 responses]).

**Measures**

Child (SRS) and adult (SRS-A) versions of the SRS were mailed to participants as part of the nested case-control study to examine QATs. The SRS raw scores were created according to publisher criteria. T scores (with scoring by child’s sex) and cutoff ranges (normative: T score, ≤59; mild ASD: T score, 60–75; severe ASD: T score, ≥76) were calculated from all forms for children to examine the validity of maternal report of ASD according to SRS scores.

For 50 randomly selected case participants, ASD diagnosis was validated by a trained professional who administered the ADI-R (the criterion standard diagnostic instrument) over the telephone. Of these, 43 case participants (86.0%) met the cut-off scores in all domains for an ADI-R diagnosis of autism; of the remaining individuals, 6 missed the diagnostic cutoff by 1 point on 1 domain, and all met the age-at-onset criterion and at least 1 domain cut-off, indicating the presence of autistic spectrum behaviors. In the subgroup of case participants who completed the SRS and ADI-R (n = 49), agreement was high (93.0% met criteria on both). Although the ADI-R was designed for in-person use, telephone administration has been validated, with results indicating no significant difference between the 2 methods.

**Statistical Analysis**

We used t tests to compare mean raw scores between case and control participants for index children and parents. Within-family correlation of SRS scores was examined by calculating Pearson and intraclass correlation coefficients (ICCs) for mother–father, mother–child, and father–child groups by case status and by examining scatterplots. Raw scores, rather than T scores, were used in all family analyses because this approach has been conducted in previous studies of familiarity of SRS scores and because of shifts in the distribution of parental scores inherent in ascertainment of this nurse-selected population.
We examined case status in association with elevated parent scores via the \( \chi^2 \) test and crude and multivariate adjusted logistic regression analysis. Elevated SRS parent scores were defined as the top 20.0% of the score distribution of the mothers’ and fathers’ distributions separately; the remaining 80.0% of these distributions were used as reference groups. We also examined associations with ASD when either parent had an elevated score and when both parents had elevated scores (concordantly elevated). In analyses that used quintiles of parent scores, tests of trend were conducted.

Next, we examined whether the distribution of child scores was shifted according to elevated parent scores by using \( t \) tests and crude and adjusted multivariate linear regression stratified by case status. Continuous parent scores, the binary variable for elevated parent scores, and quintiles of parent scores were examined for these analyses.

For all analyses, mother and father scores were examined separately to assess whether transmission of risk of ASD traits might have parent-of-origin effects. Secondary analyses stratified by child sex were conducted to examine the potential for sex-specific transmission. Because of suggested associations or correlations with SRS scores\(^{15,27-28} \) and a priori knowledge of associations with ASD and QATs, we tested adjustment for the following in all multivariate models: child sex (when not defining strata), child year of birth, birth order, maternal and paternal age at index birth, household income level, race (binary indicator for white or other), maternal prepregnancy obesity (according to self-reported height and weight), and maternal history of depression (binary variable for report of diagnosed depression). Maternal race/ethnicity (with options defined by study investigators), depression, income, and obesity were collected on previous NHS II questionnaires; other variables were collected from the nested case-control follow-up study.\(^{24} \) We also tested adjustment for divorce status (collected through NHS II questionnaires), depression in the child, and attention-deficit/hyperactivity disorder in the child (reported as binary yes or no variables on the follow-up questionnaire), given the potential influence of these factors on rating SRS forms. Models assessing the scores of the mothers and fathers also examined the effect of adjusting for the other parent’s score.

### Sensitivity Analyses

Analyses were also conducted within the subgroup of complete trios (mother, father, and index child; 72.7% of the study population). Multiple imputation\(^{29,30} \) analyses of missing parent scores were conducted using Proc MI/MIANALYZE in SAS statistical software (SAS Institute Inc) to examine potential bias due to a missing parent form.

### Results

Characteristics of the study population are provided in Table 1. The study group is representative of the NHS II as a whole in terms of income and race. Individuals from the follow-up study\(^{24} \) who did not return SRS forms but were otherwise eligible did not significantly differ from those included in these analyses on demographic characteristics and other factors, such as divorce, smoking status, and low birth weight of the child.

All SRS forms for the index children and fathers were completed by the nurse participants, whereas forms for the mothers were completed by the nurse’s spouse/child’s father or a close relative. Raw scores by group are provided in eTable 1 in
the Supplement. As expected, the SRS scores of the index children were significantly higher than the scores of the control participants ($P < .001$), and $93.2\%$ of case participants were within the range consistent with clinical ASD according to previously established SRS score cut-offs (T score, ≥60) compared with only $6.5\%$ of control participants. Overall, mean raw scores were slightly higher for male than female index children, but scores did not differ by sex for case children. The SRS scores of the index children were not associated with age or, for case participants, with age at diagnosis (mean, 7.8 years; mean year of birth of the child, 1990).

**Family Correlations**
The correlation of scores between mothers and fathers was moderate for both case and control participants (case participants: $r = 0.25$, ICC = 0.14; control participants: $r = 0.34$, ICC = 0.39). Other within-family correlations were low for case participants (mother-child pairs: $r = 0.02$, ICC = 0.0; father-child pairs: $r = 0.13$, ICC = 0.0) and moderate for control participants (mother-child pairs: $r = 0.30$, ICC = 0.31; father-child pairs: $r = 0.42$, ICC = 0.33). Examination of scatterplots did not reveal any nonlinear patterns.

**Association of Parent Scores With ASD**
Mean parent scores were significantly higher among case participants than control participants (mother scores: $P = .03$; father scores: $P < .001$). The distribution of scores of the case fathers was shifted noticeably higher compared with scores of the control fathers (Figure 1). Case participants were significantly more likely to have a parent with an elevated SRS-A score: $41.0\%$ of case participants and $27.9\%$ of control participants had at least one parent with an elevated score ($P < .001$), and $12.4\%$ of case participants and $6.0\%$ of control participants had parents with concordantly elevated scores ($P < .001$). The scores of case fathers but not case mothers ($P = .40$) were significantly higher than the scores of control parents ($32.6\%$ of case fathers had elevated scores vs $18.1\%$ of control parents; $P < .001$). These associations remained significant in adjusted analyses (Table 2); risk of ASD was increased by $85.0\%$ among children with parents with concordantly elevated scores (odds ratio [OR], 1.85; 95% CI, 1.08-3.16) and by $52.0\%$ when either parent’s score was elevated (OR, 1.52; 95% CI, 1.11-2.06). Elevated scores of the father significantly increased the risk of ASD (OR, 1.94; 95% CI, 1.38-2.71), but no association was seen for elevated scores of the mother. Associations were somewhat stronger in male children (Table 2), although there were fewer female children. When using quintiles of parent scores, results were similar.

**Association of Parent Scores With Child Scores**
The distribution of child scores was shifted toward higher scores when parent scores were in the top $20\%$ of their respective (mother or father) distributions (Figure 2), particularly for control participants. Differences in child scores according to elevations in parent scores were only statistically significant in control participants (eTable 2 in the Supplement). The strongest mean increases in child scores occurred with concordantly elevated scores of control parents (23 points, $P < .001$). Examination of quintiles revealed similar results (Figure 3), and tests of trend for quintiles in mothers and fathers were significant ($P < .001$). Among case participants, no significant associations were seen in quintile analyses, although child scores increased slightly as the father’s quintile increased. Stratified by child sex (eTable 2 in the Supplement), increases in child score according to parent score were slightly greater among male control participants than among female control participants but were overall similar. Among case participants, a greater increase in the scores of female children according to score increases in parents was suggested, although small numbers led to unstable estimates.

**Sensitivity Analyses**
Results were materially unchanged in the subgroup with complete trio data. In analyses that used imputed missing values, results were also similar and yielded the same conclusions.

**Discussion**
To our knowledge, this is the first large intergenerational epidemiologic sample demonstrating that parental QAT elevations predict risk of ASD among offspring. We found evidence that parents of children with ASD had greater social impairment than control parents as measured by the SRS and that concordantly elevated SRS scores in parents significantly increased the risk of ASD in the child. Further, the heritability of broader autism traits was also supported through significant increases in child scores according to elevated parent scores among individuals without ASD.

The finding that the risk of ASD in children increased significantly when parental SRS scores were in the top $20\%$ of the distribution supports the vast literature that suggests the strong heritability of ASD. We also noted slight differences in risk according to whether the elevated score was that of the father, mother, either parent, or both parents. In particular, concordantly elevated parent scores were found far more often than expected by chance in case participants compared with control participants and nearly doubled the risk of ASD.
The absence of correlation between SRS scores among case parents and children has been previously observed and is expected from restriction in the range of scores when limiting analysis to affected individuals. The fact that the scores of the control children increased significantly with increases in the scores of the control parents supports the familial transmission of QATs in the general population, suggested in other studies as well. These findings provide evidence that sons and daughters of affected parents are more likely to develop autism, even when the parents themselves have only mild symptoms.

Although the stronger prediction from paternal scores may suggest a parent-of-origin effect, there are also other potential explanations for these results, including the possibility that the phenotypic expression of inherited susceptibility to ASD is reduced in females. Two recent studies found strong evidence of transmission through unaffected mothers. Robinson et al. found that a higher level of familial loading was required to bring females to the threshold of clinical affectation in a general population sample. In contrast, there was no evidence of increased recurrence of clinical autistic syndromes among siblings of female vs male probands in a Danish population–based sample of approximately 1.5 million. Similar to the current study, Virkud et al. found higher SRS scores of unaffected brothers and fathers of multiplex probands. A more detailed discussion of this topic is included in the article by Constantino and Charman. The absence of correlation between SRS scores among case parents and children has been previously observed and is expected from restriction in the range of scores when limiting analysis to affected individuals. The fact that the scores of the control children increased significantly with increases in the scores of the control parents supports the familial transmission of QATs in the general population, suggested in other studies as well.
Parental Social Responsiveness and Offspring Autism

This study has a number of unique strengths, including the ability to adjust for multiple potential confounders, use of case participants and control participants from a large existing cohort drawn from the general population, and the ability to examine familial transmission in a relatively large number of individuals affected and unaffected by ASD. However, some limitations should be noted. The NHS II population is not ethnically or racially diverse, so if impairments in social functioning are related to these factors, results may not generalize to all groups. Case status, as well as information on other conditions in children, was primarily determined through maternal report. We therefore cannot rule out outcomes misclassification, inclusion of milder cases, or other diagnoses. However, although we did not have other clinical measures, SRS scores and our ADI-R validation subgroup suggest a high degree of validity of maternal report of ASD in this medically trained population. We also did not have complete information on potential confounding by paternal conditions, such as depression. Residual confounding by divorce, which was reported in 2001 rather than at SRS administration, is also possible; however, our analyses that adjusted for divorce status according to available information were materially unchanged, suggesting little effect of divorce.

Although reporter bias is another possible limitation given that mothers completed SRS forms for the father and child, a number of factors within our own data and from outside sources suggest this is unlikely to affect our results. First, our results demonstrated an equal proportion of elevated scores of control mothers and fathers. We also found similar associations with the risk of ASD according to concordantly elevated parent scores and elevated father scores and the strongest increase in child scores when the scores of both parents were elevated. If reporter bias alone were accounting for the findings, one might expect effects on child risk and scores according to scores of fathers only. Second, results from other studies in which multiple raters were used suggest a high interrater reliability ($r = 0.75-0.91^6$), particularly between mother and father SRS ratings of the child ($r = 0.91-0.92^6,7^9$). In addition, a previous study$^7$ that examined potential models to explain patterns in familial SRS data found evidence that a rater-bias model fit the data poorest, whereas an assortative mating model fit the data best. Of note, this previous study found patterns of transmission of QATs similar to ours. Our data also suggested evidence of assortative mating through the moderate spousal correlation. Although it is possible that parents of children with ASD may be more attuned to social deficits, therefore potentially influencing ratings, the observation of significant associations in the unaffected controls argues against such bias driving results.

A final question is whether broader psychiatric behaviors and symptoms might mediate the association between SRS scores in parents and children. In considering this possibility, we examined whether SRS scores in parents predicted attention-deficit/hyperactivity disorder in children and found that there was no significant association when adjusting for SRS scores in children. These and other previous results$^7$ have suggested that QATs exacerbate comorbid general psychopathologic symptoms when present rather than vice versa.

Conclusions

The results of this study demonstrate the strong familiality of SRS scores, as well as, more broadly, of ASD and subclinical ASD traits, in families unaffected and affected by ASD. Our work was conducted within a nonclinical group, with participants drawn from a well-established cohort from the US population. Our findings suggest that typical variation in parental social functioning and autistic traits is correlated in spousal pairs, predicts differences among offspring for these same traits, and at higher levels elevates risk of clinical autistic syndromes in children.
Author Contributions: Dr Lyall had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Lyall, Weisskopf, Ascherio, Santangelo. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: Lyall, Weisskopf. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: Lyall, Constantino, Weisskopf, Roberts, Santangelo. Obtained funding: Lyall, Weisskopf, Ascherio, Santangelo. Study supervision: Ascherio, Santangelo.

Conflict of Interest Disclosures: Dr Constantino reported having received royalties from Western Psychological Services from the distribution of the SRS. No other disclosures were reported.

Funding/Support: This work was supported by grants CA50385, HD062171, and HD042541 from the National Institutes of Health, grants 1788 and 464-472 from the US Army Medical Research and Material Command.

Role of the Sponsor: The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

REFERENCES


17. Robinson EB, Koenen KC, McCormick MC, et al. Evidence that autistic traits show the same etiology in the general population and at the quantitative extremes (5%, 2.5%, and 1%). Arch Gen Psychiatry. 2011;68(11):1113-1121.


