Published in final edited form as:

J Autism Dev Disord. 2017 July ; 47(7): 1998–2009. doi:10.1007/s10803-017-3115-3.

Maternal Exposure to Childhood Abuse is Associated with Mate Selection: Implications for Autism in Offspring

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Abstract

Maternal experience of childhood abuse has been associated with offspring autism. To explore whether familial tendency towards autistic traits—presumably related to genetic predisposition—accounts for this association, we examined whether women who experienced childhood abuse were more likely to select mates with high levels of autistic traits, and whether parental autistic traits accounted for the association of maternal abuse and offspring autism in 209 autism cases and 833 controls. Maternal childhood abuse was strongly associated with high paternal autistic traits (severe abuse, OR = 3.98, 95% CI = 1.26, 8.31). Maternal and paternal autistic traits accounted for 21% of the association between maternal abuse and offspring autism. These results provide evidence that childhood abuse affects mate selection, with implications for offspring health.

Keywords

Childhood abuse; Maternal factors; Paternal factors; Genetics; Mate selection; Autism

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Author Contributions AR participated in the conception of the study, performed the statistical analysis, and drafted the manuscript; KL participated in the collection of data and coordination of the study, and in the design and interpretation of the data; MW participated in the conception of the study and its design and helped to draft the manuscript. All authors read and approved the final manuscript.

Conflict of interest The authors have no conflicts of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent The Partners Healthcare Institutional Review Board approved this research and deemed completion and return of questionnaires by US mail to constitute implied consent.

Electronic supplementary material The online version of this article (doi:10.1007/s10803-017-3115-3) contains supplementary material, which is available to authorized users.

Introduction

We previously found that women's experience of abuse in childhood was associated with autism spectrum disorder (ASD) in her offspring (Roberts et al. 2013b). One possible reason for this association could be that the experience of childhood abuse is an indicator of genetic risk for ASD. The targeting of girls with high levels of autistic traits for abuse in childhood could explain the association between maternal experience of childhood abuse and risk of ASD in offspring. We have previously shown that women with high levels of autistic traits as measured by the Social Responsiveness Scale (SRS) (Constantino et al. 2003) were more likely to have experienced childhood abuse than women with few autistic traits (Roberts et al. 2015), findings that are in keeping with research indicating that children with communication and hearing impairments (Brownlie et al. 2007; Knutson et al. 2004; Spencer et al. 2005) and cognitive and physical disabilities (Jones et al. 2012; Sullivan and Knutson 2000) are at increased risk of being targeted for abuse in childhood. This finding, together with findings from other studies that maternal autistic traits are predictors of child's ASD (Piven et al. 1994, 1997; Murphy et al. 2000; Lyall et al. 2014), and that SRS scores are highly heritable (Constantino and Todd 2000, 2005), presumably because they reflect underlying genetic predisposition for ASD, would suggest a form of confounding by maternal genetics as depicted in Fig. 1a.

Along similar lines, it is possible that higher autistic traits in women who experienced childhood abuse (Roberts et al. 2015) could lead to selection of mates with higher autistic traits. Positive assortative mating (i.e., selecting a person similar to oneself as a mate) has been identified with respect to autistic traits in this cohort and others, with correlation in autistic traits between spouses ranging from 0.25 to 0.38 (Constantino and Todd 2005; Virkud et al. 2009; Lyall et al. 2014) and with other factors such as cognitive abilities (particularly verbal ability) (Watkins and Meredith 1981), age, religiosity, and political views (Watson et al. 2004). Thus, offspring of women who experienced childhood abuse versus those who did not may have elevated risk of ASD because of factors related to the father's high levels of autistic traits, genetic predisposition again being a possibility. Fathers with high versus low levels of autistic traits are more likely to have a child with ASD (Piven et al. 1994, 1997; Murphy et al. 2000; Lyall et al. 2014). Thus, paternal factors may confound the association between maternal childhood abuse and ASD, as depicted in Fig. 1b.

It is also possible that women's experience of abuse makes them more likely to select a mate with high levels of autistic traits, independently of their own autistic traits. If so, selection of a mate with high levels of autistic traits would be a *pathway* by which women's experiences of childhood abuse cause increased risk of ASD in their offspring (Fig. 1c), although little research has directly examined whether childhood abuse affects mate selection. There is, however, precedent for this kind of phenomenon. Studies have indicated that both women and men who experienced sexual abuse are more likely to marry alcoholics (Dube et al. 2005). Research also indicates that factors that are sequelae of childhood abuse, including depression (Kirsner et al. 2003), anxiety (Hirschberger et al. 2002), emotional instability, and anxious and avoidant attachment styles (Wood and Brumbaugh 2009) influence mate selection, and autistic traits have been found to predict marrying a spouse with a history of

major depressive disorder, though this association did not reach statistical significance in the small study (Piven and Palmer 1999).

To examine the contribution of these different possibilities to the association between maternal childhood abuse and ASD in her child we explored three related questions in the present paper: (1) Are women who experienced abuse in childhood more likely to select men with high levels of autistic traits as mates compared with women who did not experience abuse? (2) If so, is the association of childhood abuse with selection of mates with high levels of autistic traits independent of women's own autistic traits? And, (3) Is the association of maternal experience of abuse in childhood and risk of ASD in offspring accounted for by maternal and paternal autistic traits?

Methods

Sample

The Nurses' Health Study II (NHSII) is a cohort of 116,430 female nurses recruited in 1989 from 14 populous US states and followed biennially. The present study uses data from the Autism Case-Control Substudy nested within the NHSII (Lyall et al. 2014; Roberts et al. 2013a). In 2005, NHSII participants were asked whether they had ever had a child with autism, Asperger syndrome, or other autism spectrum disorder. Briefly, mothers of 756 ASD cases and 3000 controls matched by year of birth were mailed follow-up questionnaires; 3383 women responded (90.1% response rate). Women who did not want to participate ($N = 164$), adopted children ($N = 15$), children with reported monogenic disorders ($N = 16$) and case mothers who later reported no child with ASD ($N = 11$) were excluded. In 2001, a supplemental Violence Questionnaire queried lifetime experiences of violence, including childhood abuse. To retain participation in the main longitudinal study, only women who have responded to the most recent biennial questionnaire are sent supplemental questionnaires. Our analytic sample includes participants who returned the measure of autistic traits (the SRS) for the mother and the father and with data on childhood abuse ($N=209$ cases, $N = 829$ controls). Maternal autistic traits were missing if their partner did not return an SRS form; paternal autistic traits were missing if the NHSII mother did not return an SRS form. Nearly all missing data on maternal childhood abuse was missing because those women were not sent the supplemental Violence Questionnaire. The Partners Healthcare Institutional Review Board approved this research and deemed completion and return of questionnaires by US mail to constitute implied consent.

Measures

We measured current autistic traits in women participating in the Autism Case-Control Substudy and their child's father (94.0% of mothers were married to the child's father) in 2007–2008 using the 65-item SRS (Constantino 2002; Constantino and Todd 2003). The SRS has been found to measure one continuously distributed underlying "autism" factor (Constantino et al. 2004). The SRS captures variation in social functioning that exists in the general population in a continuum of autistic-like traits (Constantino and Todd 2005), referred to as "the broader autism phenotype" or "quantitative autistic traits" (De la Marche et al. 2012; Virkud et al. 2009). The broader autism phenotype, as measured by the SRS, has

been found to be highly heritable in twin studies, with heritability proportion and genetic structure mirroring that of clinical autism (Constantino and Todd 2000). The SRS had high stability over time in a longitudinal study with 1–5 years of follow up (test-retest correlation = 0.90) (Constantino et al. 2009). The SRS has been validated against the Autism Diagnostic Interview-Revised (Constantino et al. 2003) and the Autism Diagnostic Observation Schedule and is widely used both in the US and internationally (Bolte et al. 2007). In previous research, maternal and paternal SRS scores in this sample have been associated with offspring ASD (Lyll et al. 2014). The NHSII woman's partner or other relative completed the SRS regarding her autistic traits; the NHSII woman completed the SRS regarding the child's father's autistic traits.

We defined SRS scores in the top 20% of fathers in our sample as indicating a high level of autistic traits (SRS score >46; SRS ranges from 0 to 168). Paternal scores in the top 20% have been associated with offspring ASD in this sample (Lyll et al. 2014). As this cutoff was somewhat arbitrary, we conducted sensitivity analyses with paternal scores as a continuous variable and with the top 10% of paternal scores considered “high” (SRS score >66; this cutoff had sensitivity = 0.85 and specificity = 0.83 distinguishing adults with ASD versus typically developing adults and adults with other mental disorders in a validation study (Bölte 2012)). To adjust for maternal SRS score in models, we evaluated maternal SRS score as a predictor of our outcomes using linear, squared and cubed terms, and in quintiles and deciles. We then coded maternal SRS score in quintiles as this coding produced the best model fit using the Akaike information criterion (AIC).

ASD case status was by maternal report, validated with the Autism Diagnostic Interview-Revised (Lord et al. 1994) in a subgroup (n = 50). As previously reported, 86% of reported cases met strict autism disorder cutoffs, another 10% only missed that cutoff by 1 point in one domain, while the remaining 4% met cutoffs in one or two domains only (Lyll et al. 2014; Roberts et al. 2013b). Additionally, over 90% of cases fell within the established range for clinically-impairing ASD symptoms according to the SRS.

Maternal exposure to childhood abuse was assessed in a supplemental questionnaire in 2001. Childhood sexual abuse occurring in two time periods was assessed, before age 12 and age 12–17 years (Moore et al. 1995). For each time period, two questions queried unwanted sexual touching by an adult or older child and forced or coerced sexual contact by an adult or older child. Response options were: “no, never”; “yes, once”; and “yes, more than once.” Sexual abuse was coded as none, mild, moderate or severe based on these responses. Childhood physical and emotional abuse before age 12 years was assessed with five questions from the Physical and Emotional Abuse Subscale of the Childhood Trauma Questionnaire (Bernstein et al. 1994) querying the frequency of people in the family: (1) hitting so hard it left bruises, (2) punishing in a way that seemed cruel, (3) insulting, (4) screaming and yelling, and (5) punishing with a belt or other hard object. For each item, response options included never, rarely, sometimes, often, or very often true. Responses were assigned values from 0 (never) to 4 (very often) and were summed following questionnaire scoring recommendations. In a validation study, the scale had good internal consistency (Cronbach's α = 0.94) and test-retest reliability (intraclass correlation = 0.82) over a 2- to 6-month interval (Bernstein et al. 1994). The resulting scale was divided

approximately into quartiles to allow for a non-linear association between abuse and the outcomes. We additionally created a variable capturing combined physical, emotional and sexual abuse by summing the measures of sexual and physical/emotional abuse. As few women were exposed to the most severe abuse, we combined the top two levels to form a measure that ranged from 0: no abuse to 5: severe abuse.

Covariates—Maternal past 2 year depression diagnosis was queried in the 2005 main cohort questionnaire, as was regular use of antidepressants during the past 2 years. Additionally, maternal phobic anxiety was measured with the 7-item Crown-Crisp Index (Crown and Crisp 1966). Paternal psychiatric diagnoses were queried in the autism case-control study. Women were asked whether any biological relatives of the child had been diagnosed with psychiatric disorders, and if so, which relative and which disorders. From these responses we created one variable indicating paternal lifetime depression diagnosis (e.g. depression, bipolar disorder) and one variable indicating paternal lifetime anxiety diagnosis (e.g., anxiety, posttraumatic stress disorder, panic disorder). Maternal childhood socioeconomic status was measured by the maximum of parents' education in childhood. Offspring sex, offspring birth year, and maternal and paternal age at the birth of the child were by maternal report.

Analyses

To ascertain whether women who experienced childhood abuse were more likely to partner with men with high autistic traits (Fig. 1b, c), we examined paternal mean SRS score by maternal exposure to childhood abuse, separately for maternal experience of sexual abuse, physical/emotional abuse and combined sexual, physical, and emotional abuse. Since our case-control study greatly oversampled women whose children had ASD, to better ascertain the relation between childhood abuse and mate selection in the general population we conducted main analyses among women whose child did not have ASD (controls). We conducted sensitivity analyses including both cases and controls.

To ascertain whether women who experienced childhood abuse were more likely to partner with men with high autistic traits independently of the woman's own autistic traits (Fig. 1c), we calculated odds ratios of high paternal SRS score associated with maternal childhood abuse, adjusted for maternal autistic traits and childhood socioeconomic status, using generalized estimating equations with a binomial distribution and a logit link (SAS PROC GENMOD). We calculated odds ratios and 95% confidence intervals (CI) of high paternal autistic traits associated with sexual and physical/emotional abuse separately and with the combined sexual, physical, and emotional abuse variable. To ascertain whether maternal or paternal anxiety or depression might be biasing assessment of autistic traits, we further adjusted this model for maternal phobic anxiety, antidepressant use, and recent depression diagnosis, and paternal lifetime anxiety and depression diagnoses. To assess whether one specific type of abuse, either sexual or physical/emotional, was responsible for a possible association between maternal childhood abuse and high paternal autistic traits, we modeled high paternal autistic traits with both sexual and physical/emotional abuse as independent variables in a single model. As above, since our case-control study greatly oversampled women whose children had ASD, to better ascertain the relation between childhood abuse

and mate selection in the general population we conducted main analyses among women whose child did not have ASD (controls) and sensitivity analyses including both cases and controls. We also examined the association of maternal childhood abuse with paternal autistic traits coded as a continuous variable.

To determine whether maternal and paternal autistic traits accounted for the association between maternal childhood abuse and offspring risk of ASD (Fig. 1a–c), we modeled offspring ASD case status as the dependent variable with maternal combined physical, emotional and sexual abuse as an independent variable adjusted in separate models for: (1) maternal autistic traits; (2) paternal autistic traits; and (3) both maternal and paternal autistic traits. To ascertain whether maternal or paternal anxiety or depression might be biasing assessment of autistic traits, we further adjusted for maternal phobic anxiety, antidepressant use, and recent depression diagnosis, and paternal lifetime anxiety and depression diagnoses. As geographic region may be associated both with maternal childhood abuse and risk of offspring ASD, we conducted sensitivity analyses adjusted for offspring region of birth, coded as: Northeast, Southeast, Midwest, Southwest, and West. We calculated odds ratios and 95% CI using generalized estimating equations with a binomial distribution and a logit link (SAS PROC GENMOD). These models adjusted for maternal childhood socioeconomic status, offspring sex and birth year and maternal age at the birth of the child.

We then calculated the percentage of the association accounted for by parental autistic traits (the joint effect of the paths depicted in Fig. 1a–c) as: % accounted for = $100 \times [1 - (\text{exposure coefficient estimate with maternal and paternal autistic traits} / \text{exposure coefficient estimate without the maternal and paternal autistic traits})]$ (Lin et al. 1997; Hertzmark et al. 2009). To determine whether perinatal factors explained the association between maternal childhood abuse and ASD, we further adjusted for perinatal factors, including birth weight, gestation length, maternal smoking, alcohol and antidepressant use, preeclampsia, gestational diabetes, and experience of intimate partner violence (Roberts et al. 2013b, 2015). We considered paternal age at offspring birth as a potential mediator of the relation between maternal childhood abuse and offspring ASD and examined the association of maternal childhood abuse with ASD further adjusted for paternal age. To examine whether results were consistent when restricted to parents with low or moderate levels of autistic traits, we conducted a sensitivity analysis excluding mothers and fathers in the top 25% of autistic traits. As some children who had received an ASD diagnosis had SRS scores below clinical cutoffs, we conducted analyses restricting autism cases to children meeting cutoffs for mild ASD (SRS t-score ≥ 60) and severe ASD (SRS t-score ≥ 77). To examine possible effects of missing maternal and paternal SRS scores and covariates, we conducted sensitivity analyses using the statistical technique of multiple imputation (Graham 2009). Among Autism Case–Control Substudy participants who returned at least one SRS form (maternal, paternal or child), we imputed all variables in 20 datasets, using logistic regression, linear regression and discriminant function methods for binomial, linear, and ordinal variables, respectively. We used auxiliary variables, including measures of maternal adulthood socioeconomic status, mental health, trauma exposure, and social support in order to reduce bias (Graham 2009; Collins et al. 2001). We conducted analyses using these 20 datasets with SAS PROC MI. Finally, as male sex is a strong risk factor for ASD, we examined the

association of maternal abuse with offspring ASD in models restricted, respectively, to male and female children.

Results

Women in the analytic sample versus those excluded were somewhat more likely to be white, to have been married at baseline (1989) and to have parents with college education or higher, and less likely to have experienced the highest level of physical/emotional abuse (all $P < 0.05$). Child ASD case status and maternal experience of childhood sexual abuse did not differ in the two groups (Table 1).

Paternal autistic traits increased with maternal childhood sexual and physical/emotional abuse and combined sexual, physical, and emotional abuse. Maternal autistic traits were lowest among women with no childhood abuse, although no dose–response relationship was apparent (Fig. 2). Results were similar in analyses including case and control parents, though as anticipated, mean paternal autistic traits were higher compared to the sample restricted to control parents (Supplemental Table 1).

Maternal childhood sexual abuse (severe, OR = 3.98, 95% confidence interval (CI) = 1.29, 12.27) and physical/emotional abuse (highest quartile, OR = 2.24, 95% CI = 1.30, 3.88) were both strong predictors of high paternal autistic traits among parents without a child with ASD (controls), adjusted for maternal autistic traits (Table 2, models 1 and 2). Combined sexual, physical and emotional abuse was also strongly associated with high paternal autistic traits (highest level, OR = 3.23, 95% CI = 1.26, 8.31), Table 2, model 3). Further adjustment for indicators of parental depression and anxiety altered associations only slightly (Table 2, model 4). In a model with both physical/emotional and sexual abuse, both types of abuse remained associated with high paternal autistic traits (severe sexual abuse, OR = 3.08, 95% CI = 0.97, 9.76; highest quartile of physical/emotional abuse, OR = 1.94, 95% CI = 1.10, 3.41).

In sensitivity analyses defining “high” paternal autistic traits as the top decile, maternal childhood sexual and combined abuse remained strongly associated with high paternal autistic traits (Supplemental Table 2). In a sensitivity analysis with paternal autistic traits coded as a continuous variable, maternal severe combined abuse was associated with 16 points higher paternal autistic trait (SRS) score ($\beta = 15.8$, 95% CI = 8.2, 23.5). In analyses including cases and controls, results were similar (Supplemental Table 3). In analyses using multiple imputation, associations of maternal childhood abuse with high paternal autistic traits were slightly attenuated, though remained strong (severe sexual abuse, OR = 3.07, 95% CI = 1.17, 8.04; severe physical/emotional abuse, OR = 2.07, 95% CI = 1.34, 3.19, Supplemental Table 4).

Maternal childhood abuse was a strong predictor of ASD case status in a monotonically increasing fashion (severe combined abuse, OR = 3.62, 95% CI = 1.80, 7.28, Table 3, model 1). Further adjustment for maternal autistic traits did not notably change this association (severe abuse, OR = 3.58, 95% CI = 1.78, 7.24, Table 3, model 2). Maternal abuse remained strongly associated with ASD in the model adjusted for both maternal and paternal autistic

traits (severe combined abuse, OR = 2.97, 95% CI = 1.45, 6.09, Table 3, model 3). Maternal and paternal autistic traits together accounted for 21.2% of the association of maternal childhood abuse with ASD in offspring. Further adjustment for maternal and paternal mental health attenuated the association of maternal childhood abuse and paternal autistic traits with offspring ASD very slightly (Table 3, model 4). Further adjustment for perinatal factors (birth weight, gestation length, maternal smoking, alcohol and antidepressant use, preeclampsia, gestational diabetes, intimate partner violence) attenuated associations very slightly (Supplemental Table 5, model 1). Results were similar in models further adjusted for paternal age at birth, in a sensitivity analysis excluding mothers and fathers in the highest 25% of autistic traits (Supplemental Table 5, models 2 and 3), and in models adjusted for geographic region. The association of maternal childhood abuse with offspring ASD remained strong in models restricting ASD cases to children with SRS scores above clinical cutoffs for mild ASD (OR_{severe abuse} = 3.06, 95% CI = 1.47, 6.36) and in models restricting ASD cases to children with SRS scores above clinical cutoffs for severe ASD (OR_{severe abuse} = 4.02, 95% CI = 1.79, 9.03, Supplemental Table 6). In analyses using multiple imputation, associations remained strong though somewhat attenuated (Supplemental Table 5, model 4). In models restricted to male children, the association between maternal abuse and ASD remained. Maternal abuse was associated with elevated risk of ASD in models restricted to female children, however, as there were only 40 ASD cases among female children, confidence intervals were wide and estimates did not reach statistical significance (Supplemental Table 5, models 5 and 6).

Discussion

We found a woman's experience of childhood abuse was strongly associated with her husband's autistic traits, even independently of her own autistic traits, but the association between maternal childhood abuse and ASD in her child was only minimally attenuated when adjusting for both parents' SRS scores. Women exposed to severe sexual abuse versus no sexual abuse in childhood were nearly four times as likely to have a husband in the top 20% of autistic traits. Similarly, women in the top quartile of physical/emotional abuse were more than twice as likely to have a husband in the top 20% of autistic traits compared with women in the lowest quartile. These results suggest that childhood abuse may affect mate selection. Although a variety of circumstances that affect mate selection have been identified, to our knowledge, only one study has examined childhood abuse, finding that adults sexually abused in childhood were 40% more likely to marry alcoholics than those not abused (Dube et al. 2005).

Related research has indicated that sequelae of childhood abuse are associated with lower mate aspiration. For example, women with depressive symptoms select less desirable mates because they underestimate their own desirability as a mate (Kirsner et al. 2003). Similarly, anxiety has been associated with selection of less attractive mates and judgement of oneself as less attractive to potential mates (Wenzel and Emerson 2009; Kirsner et al. 2009). Women with avoidant or anxious attachment style have lower preference for smiling, well-groomed men. In contrast, women with high emotional stability have heightened preference for men who are smiling and appear confident (Wood and Brumbaugh 2009). In experimental research, students primed with anxiety versus those who were not were more likely to

compromise their standards in mate selection (Hirschberger et al. 2002). Thus, these studies suggest that depression and anxiety, common sequelae of childhood abuse (Fergusson et al. 2008; Heim and Nemeroff 2001; McCauley et al. 1997), affect mate selection.

We examined parental SRS scores as an indication of familial tendency towards ASD (Constantino and Todd 2005; Constantino et al. 2003; Colvert et al. 2015). SRS scores have been estimated to reflect 0.76 genetic heritability and 0.24 non-shared environment plus error in a twin study (Constantino and Todd 2000). Our results here and in prior work showing that a woman's autistic traits are correlated with her husband's autistic traits (Lyll et al. 2014; Constantino and Todd 2005) suggest ways that parental genetics—as indexed by parental autistic traits—could possibly account for an association between maternal experience of abuse in childhood and risk of ASD in her offspring, as depicted in Fig. 1a–c. However, we also found that maternal and paternal autistic traits together explained only a small proportion of the association of maternal childhood abuse with offspring ASD. These findings suggest that inherited autistic traits alone do not account for the association of maternal childhood abuse with offspring ASD. Surprisingly, maternal childhood abuse was nearly as strong a predictor of offspring ASD as were paternal autistic traits in mutually adjusted analyses that also accounted for maternal autistic traits (which themselves were not significantly related to offspring ASD in our sample) (Lyll et al. 2014).

Our results, therefore, suggest at least two alternative possibilities. First, the experience of childhood abuse may affect women in ways that increase her risk of having a child with ASD, as depicted in Fig. 1d. Long lasting maternal inflammation, HPA-axis dysregulation (Heim and Nemeroff 2001; Heim et al. 2000, 2001), and HPG-axis dysregulation has been shown to result from these experiences. It may be that long lasting effects of childhood abuse like these put the developing fetus at increased risk of ASD. Dysregulation of the maternal HPA axis has been hypothesized to affect the fetal brain (Sandman et al. 1997; Wadhwa et al. 1996), and dysregulation of the HPA axis has been observed in children with autism (Marinovi - urin et al. 2008). Additionally, high prenatal concentrations of androgen have been associated with autistic traits (Voracek 2010; Knickmeyer et al. 2006). However, studies examining secretion of sex hormones following exposure to psychosocial stressors have had mixed findings (Lennartsson et al. 2012; Schoofs and Wolf 2011) and whether childhood abuse leads to elevated androgens in adulthood or when a woman becomes pregnant is unknown. Immune dysfunction has also been associated with exposure to childhood abuse (Danese et al. 2007, 2009; Dube et al. 2009; Flier et al. 1995; Slopen et al. 2013). Maternal inflammation affects the developing brain, and maternal inflammation and immune function (Martin et al. 2008; Wills et al. 2009; Ashwood and Van de Water 2004) have been hypothesized to be causes of autism (Licinio et al. 2002; Ashdown et al. 2006; Boksa 2010; Jonakait 2007; Onore et al. 2012; Choi et al. 2016). Immune dysfunction and inflammation, including neuroinflammation, are more prevalent in persons with autism (Dietert and Dietert 2008; Herbert 2010; Vargas et al. 2005; Jyonouchi et al. 2001, 2005; Zimmerman et al. 2005). Second, it is possible that women who experienced childhood abuse are more likely to select mates who also experienced abuse. The experience of abuse may affect men in ways that subsequently increase risk of ASD in offspring. For example, distinct paternal sperm DNA methylation patterns have been associated with offspring ASD (Feinberg et al. 2015) and paternal stress has been associated with sperm microRNA

(Rodgers et al. 2013). Sperm characteristics thus could possibly be a mechanism through which paternal experiences of abuse affect offspring ASD, though no studies have examined this possibility. Thus, several biological pathways could plausibly account for the increased risk of autism in offspring of women exposed to childhood abuse not accounted for by parental autistic traits.

A key limitation of our study is that parental autistic traits may not completely capture parental genetic loading for autism. To the extent that maternal childhood abuse is associated with additional parental genetic risk for autism not captured by the SRS, we may have underestimated the amount of the association between maternal childhood abuse and offspring ASD accounted for by genetic pathways (Fig. 1a–c). Additionally, our cohort is predominantly white and consists of professional women, therefore our results may not be generalizable to a broader population or to women of other races. However, the prevalence of childhood abuse in the NHSII is similar to that reported in other national cohorts. Among NHSII women, 33% reported any childhood sexual abuse, compared with 24% in a large HMO (Anda et al. 1999) and 17% of women in a representative survey of US adults (Roberts et al. 2013). The somewhat higher prevalence of violence victimization in NHSII may relate to participants' willingness to report: in 28 years of the NHSII, there have been no breaches of confidentiality. Finally, it is possible that sequelae of childhood abuse, including emotional dysregulation, social isolation and depressive and anxious symptoms, may have biased the measure of maternal autistic traits as well as affected maternal report of paternal autistic traits. While we were able to adjust for several indicators of maternal and paternal depression and anxiety, these were only approximate measures of parental mental health. Future studies of the relation between childhood abuse, mate selection and ASD in offspring should more comprehensively account for parental mental health.

It is important to note that our data did not suggest a threshold of abuse only above which risk for ASD is higher, but rather a steady increase in risk with abuse severity. For example, women in the second and third quartiles of physical/emotional abuse were at elevated risk of offspring ASD, though confidence intervals included 1.0 (OR, 2nd quartile = 1.48, 95% CI = 0.91, 2.40, OR 3rd quartile = 1.60, 95% CI = 1.00, 2.59). Given these associations, and as childhood abuse is highly prevalent worldwide (Fang et al. 2012; McLaughlin et al. 2010; Scott et al. 2010; Seedat et al. 2004), identifying mechanisms linking abuse with offspring ASD may aid in efforts to reduce risk among a high proportion of women. Additionally, identifying such mechanisms may provide further clues to ASD risk even among women who were not exposed to abuse, as these mechanisms could be engaged in ways other than through childhood abuse.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Funding

This study was funded by US Department of Defense (DOD) W81XWH-08-1-0499, United States Army Medical Research and Materiel Command (USAMRMC) A-14917, US National Institutes of Health (NIH)

T32MH073124-08 and P60AR047782, and Autism Speaks grants 1788 and 2210. The Nurses' Health Study II is funded in part by NIH UM1 CA176726.

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A Potential confounding of the maternal child abuse-offspring ASD association by maternal genetics **B** Potential confounding of the maternal child abuse-offspring ASD association by paternal genetics via mate selection **C** Maternal child abuse may increase risk of offspring ASD through paternal genetics via mate selection **D** Maternal child abuse may increase risk of offspring ASD through maternal biological changes **Fig. 1.**

Possibly pathways linking maternal childhood abuse with offspring autism spectrum disorder

Fig. 2.

Boxplot of maternal and paternal Social Responsiveness Scale scores by maternal experience of childhood abuse. *Boxes* indicate the interquartile range (IQR), with the *middle horizontal bar* indicating the median. *Diamonds* indicate the mean; whiskers are at $1.5 \times$ IQR or the minimum. *Circles* indicate outliers outside $1.5 \times$ IQR

Characteristics of participants in the analytic sample versus those excluded, Autism Case-Control Substudy of the Nurses' Health Study II, 2001–2009

Table 1

	Analytic sample (N = 1042)	Excluded (N = 2714)
Child is an autism case, % (N)	20.1 (209)	20.2 (547)
Maternal year of birth, median (IQR)	1957 (1954–1961)	1958 (1954–1961)
Maternal race/ethnicity		
White, non-Hispanic, % (N)	97.7 (1018)	95.1 (2582)
African-American, % (N)	0.2 (2)	1.1 (29)
Hispanic, % (N)	1.1 (11)	2.2 (60)
Asian, % (N)	1.2 (12)	1.7 (46)
Maternal childhood sexual abuse, any, % (N)	31.9 (332)	33.1 (600)
Maternal childhood physical/emotional abuse, highest quartile, % (N)	20.4 (212)	24.2 (437)
Married at baseline, 1989, % (N)	85.5 (891)	81.7 (2217)
Maternal parent's education in her infancy, college or higher, % (N)	29.3 (305)	23.2 (629)

Table 2

Odds ratios of high paternal autistic traits (top 20%) by maternal experience of childhood abuse among parents of a child without ASD (controls), adjusted for maternal autistic traits, Nurses' Health Study II, 2001–2009 (N = 833)

N controls		Odds ratio (95% confidence interval) ^a			
		Model 1	Model 2	Model 3	Model 4: model 3 further adjusted for maternal and paternal anxiety and depression
Maternal childhood sexual abuse					
None	588	1.0 [Reference]			
Mild	188	0.96 (0.58, 1.59)			
Moderate	41	2.70 (1.27, 5.78) **			
Severe	16	3.98 (1.29, 12.27) **			
Maternal childhood physical/emotional abuse					
Lowest quartile	327		1.0 [Reference]		
Second quartile	190		1.18 (0.66, 2.10)		
Third quartile	170		1.56 (0.91, 2.70)		
Highest quartile	146		2.24 (1.30, 3.88) **		
Maternal combined childhood sexual, physical and emotional abuse					
0: No abuse	249			1.0 [Reference]	1.0 [Reference]
1	207			0.80 (0.42, 1.54)	0.81 (0.42, 1.58)
2	162			1.65 (0.92, 2.96)	1.71 (0.95, 3.09)
3	141			1.92 (1.05, 3.51) *	1.88 (1.02, 3.46) *
4	45			2.48 (1.08, 5.68) *	2.31 (0.99, 5.42)
5: Severe abuse	29			3.23 (1.26, 8.31) *	3.30 (1.27, 8.53) *
Maternal mental health					
Depression dx, yes	13				1.11 (0.30, 4.08)
Antidepressant use, yes	146				1.20 (0.72, 2.00)
Phobic anxiety scale	833				0.58 (0.26, 1.26)
Paternal mental health					
Lifetime anxiety, yes	26				2.83 (1.05, 7.67) *
Lifetime depression, yes	56				0.90 (0.41, 1.99)

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^a All models adjusted for maternal autistic traits in quintiles and maternal childhood socioeconomic status, defined as the maximum of maternal parents' education in infancy. Odds ratios estimated using generalized estimating equations with a logit link and a binomial distribution. Maternal anxiety measured by the Crown-Crisp index. Maternal depression indicated by recent antidepressant use and recent depression diagnosis. Lifetime paternal anxiety and depressive disorder diagnoses by maternal report

Wald Chi square
* p < 0.05,
** p < 0.01,
*** p < 0.001

Table 3

Odds ratios of offspring ASD by maternal childhood abuse, adjusted for maternal and paternal autistic traits, Nurses' Health Study II, 2001–2009 (N = 1038, N ASD cases = 209, N ASD controls = 829)

0	N controls	N cases	Odds ratio (95% confidence interval) ^a	Model 1	Model 2: Further adjusted for maternal autistic traits	Model 3: Further adjusted for paternal autistic traits	Model 4: Further adjusted for parental anxiety and depression
Maternal childhood sexual, physical and emotional abuse							
0: None	248	42	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]
1	206	46	1.38 (0.85, 2.22)	1.39 (0.86, 2.24)	1.36 (0.84, 2.21)	1.31 (0.80, 2.15)	1.31 (0.80, 2.15)
2	162	38	1.39 (0.84, 2.30)	1.35 (0.81, 2.23)	1.22 (0.73, 2.04)	1.18 (0.71, 2.00)	1.18 (0.71, 2.00)
3	139	38	1.54 (0.92, 2.56)	1.51 (0.90, 2.53)	1.36 (0.81, 2.30)	1.23 (0.71, 2.09)	1.23 (0.71, 2.09)
4	45	25	3.47 (1.86, 6.52) ***	3.36 (1.78, 6.33) ***	2.90 (1.53, 5.51) **	2.73 (1.43, 5.21) **	2.73 (1.43, 5.21) **
5: Most severe	29	20	3.63 (1.80, 7.28) ***	3.58 (1.78, 7.24) ***	2.97 (1.45, 6.09) **	2.78 (1.34, 5.78) **	2.78 (1.34, 5.78) **
Maternal autistic traits							
Lowest quintile	171	35	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]
Second quintile	180	39	0.98 (0.58, 1.67)	0.98 (0.58, 1.67)	0.79 (0.46, 1.38)	0.75 (0.43, 1.32)	0.75 (0.43, 1.32)
Third quintile	164	46	1.29 (0.77, 2.17)	1.29 (0.77, 2.17)	0.97 (0.56, 1.67)	0.92 (0.53, 1.60)	0.92 (0.53, 1.60)
Fourth quintile	158	44	1.23 (0.73, 2.10)	1.23 (0.73, 2.10)	0.91 (0.52, 1.59)	0.87 (0.49, 1.53)	0.87 (0.49, 1.53)
Highest quintile	156	45	1.24 (0.73, 2.10)	1.24 (0.73, 2.10)	0.79 (0.45, 1.41)	0.69 (0.38, 1.23)	0.69 (0.38, 1.23)
Paternal autistic traits							
Lowest quintile	194	27	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]
Second quintile	166	38	1.56 (0.88, 2.77)	1.56 (0.88, 2.77)	1.56 (0.88, 2.77)	1.58 (0.88, 2.82)	1.58 (0.88, 2.82)
Third quintile	185	41	1.84 (1.03, 3.30) *	1.84 (1.03, 3.30) *	1.84 (1.03, 3.30) *	1.79 (0.99, 3.22)	1.79 (0.99, 3.22)
Fourth quintile	160	42	1.92 (1.07, 3.45) *	1.92 (1.07, 3.45) *	1.92 (1.07, 3.45) *	1.78 (0.99, 3.21)	1.78 (0.99, 3.21)
Highest quintile	124	61	3.20 (1.77, 5.78) ***	3.20 (1.77, 5.78) ***	3.20 (1.77, 5.78) ***	2.95 (1.62, 5.38) ***	2.95 (1.62, 5.38) ***
Maternal mental health							
Depression, yes	13	9					2.41 (0.87, 6.66)
Antidepressant use, yes	145	55					1.20 (0.79, 1.82)
Phobic anxiety scale	829	209					0.68 (0.36, 1.28)
Paternal mental health							
Anxiety, yes	26	8					0.66 (0.25, 1.72)

0	N controls	N cases	Odds ratio (95% confidence interval) ^a	Model 1	Model 2: Further adjusted for maternal autistic traits	Model 3: Further adjusted for paternal autistic traits	Model 4: Further adjusted for parental anxiety and depression
Depression, yes	56	33					2.76 (1.60, 4.77)***

^a All models adjusted for maternal childhood socioeconomic status, defined as the maximum of maternal parents' education in childhood, offspring sex and birth year and maternal age at the birth of the child. Odds ratios estimated using generalized estimating equations with a logit link and a binomial distribution

Wald Chi square

* p < 0.05,

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p < 0.01,

p < 0.001