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Manuscript Title: Prenatal maternal stress events and phenotypic outcomes in Autism Spectrum Disorder

Authors: Kandice J. Varcin¹, PhD, Gail A. Alvares^{1,2}, PhD, Mirko Uljarević^{2,3}, PhD, Andrew J. O. Whitehouse^{1,2}, PhD

(1) Telethon Kids Institute, University of Western Australia, Perth, WA, Australia

(2) Cooperative Research Centre for Living with Autism (Autism CRC), Long Pocket, Brisbane, Queensland, Australia

(3) Olga Tennison Autism Research Centre, School of Psychology and Public Health, La Trobe University, Victoria, Australia.

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Corresponding author: Kandice J. Varcin, PhD, Telethon Kids Institute, 100 Roberts Road, Subiaco, Western Australia, 6008, Australia. Phone: +61 8 9489 7916. Email:

Kandice.varcin@telethonkids.org.au.

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Scientific Abstract

There is significant heterogeneity amongst individuals with ASD in symptom presentation and severity. An understanding of the factors that contribute to and modulate symptom severity are critical to informing prognosis, stratification and treatment decisions. Maternal prenatal stress exposure is a non-specific risk factor for a wide array of neurodevelopmental outcomes in subsequent offspring. Emerging evidence suggests that prenatal maternal stress may increase ASD risk and contribute to variability in autism-like traits in the general population. In the current study, we aimed to determine whether prenatal maternal exposure to stressful life events is associated with symptom severity amongst individuals with ASD. We performed multiple regression analyses to examine associations between retrospectively recalled maternal prenatal stressful life events and the severity of ASD-associated symptoms in 174 children with ASD (*Mean* = 9.09 years; *SD* = 3.81). ASD-related symptom severity was measured using the Social Responsiveness Scale and communication abilities were measured using the Children's Communication Checklist. Exposure to prenatal stressful life events was a significant predictor of ASD-related symptom severity ($t = 2.014$; $p = .048$) and communication abilities ($t = -2.925$; $p = .004$) amongst children with ASD, even after controlling for a range of sociodemographic and obstetric variables. Follow-up analyses demonstrated significant increases in symptom severity only in the context of multiple (two or more) prenatal stressful life events. Together, these findings indicate that ASD, in the context of prenatal maternal stress exposure, may be associated with a more severe phenotype, particularly when there are multiple prenatal exposures.

Lay Summary: There is emerging evidence that prenatal maternal stress may increase the risk for ASD and contribute to variability in autism-like traits in the general population. Here, we found that more stressful life events experienced during pregnancy was associated with more severe ASD-related symptoms and poorer communication abilities amongst children with ASD. The results from this study suggest that prenatal maternal stress exposure and its sequelae may contribute to variability in symptom severity amongst children with ASD.

Keywords: autism, maternal stress, prenatal, heterogeneity

Autism Spectrum Disorder (ASD) is a neurodevelopmental syndrome characterized by a clinical dyad of difficulties with social communication and the presence of restricted interests or repetitive patterns of behavior (DSM-5; APA, 2013). Approximately 1-2% of the population has an ASD (CDC, 2014). Amongst individuals with ASD, there is substantial phenotypic heterogeneity in the severity of core symptoms, levels of cognitive ability, language, adaptive function and comorbid medical conditions (Jeste & Geschwind, 2014). This phenotypic variability is likely subserved by substantial etiologic heterogeneity. Research into the etiological bases of ASD has unveiled a complex genetic architecture implicating hundreds of risk genes (de la Torre-Ubieta et al., 2016; Geschwind & State, 2015). Increasingly, the contribution of potential environmental influences and gene x environment interactions in ASD susceptibility are being recognized, revealing a varied and multifaceted risk profile with potential prenatal origins (Kim & Leventhal, 2015; Stoner et al., 2014). Due to the implications for prognosis, stratification, and intervention, research efforts over the past decade have focused on delineating genetic, biological, and environmental factors underlying the clinical variability in ASD.

There is a substantial body of evidence from human and animal studies suggesting that prenatal maternal stress can have significant and persistent effects on neurodevelopmental outcomes. Research, primarily from animal models, suggests that prenatal maternal stress may alter the intrauterine environment and exert effects on placental structure and function during a time of rapid organ development, leading to physiological adaptations in the developing fetus that have ongoing effects throughout postnatal development (Bronson & Bale, 2016; Padmanabhan et al., 2016; Talge et al., 2007). Prenatal maternal stress exposure in humans has been linked to a wide array of psychiatric and neurodevelopmental disorders in resultant offspring (Bronson & Bale, 2016; Talge et al., 2007), including ASD.

There is evidence suggesting that prenatal maternal stress may increase risk for ASD (Kinney et al., 2008b). Indeed, increased rates of ASD have been evidenced in the offspring of mothers who were exposed to major stressful events during their pregnancy, such as natural disasters (Kinney et al., 2008a), abuse (Roberts et al., 2016), or the death of a first-degree relative (Class et al., 2014; although see Li et al., 2009 & Rai et al., 2012a). Moreover, mothers of children with ASD report experiencing more stressful life events during their pregnancy (e.g., family conflict, financial problems, illness) than mothers of typically developing children or mothers of children with a developmental disability of a known genetic etiology (e.g., Down Syndrome; Beversdorf et al., 2005; Ward, 1990).

There is also evidence that prenatal maternal stress exposure may contribute to phenotypic variability in autism-like traits in the general population. Two independent cohort studies have reported that (prospectively and retrospectively recalled) increased maternal exposure to common stressful life events during pregnancy (e.g., financial difficulties, a residential move) is predictive of increased autism-related trait severity (measured via parent-report) in the offspring in toddlerhood (Ronald et al., 2011) and childhood (Rijlaarsdam et al., 2016). Similarly, Walder et al. (2014) found that the degree of objective as well as subjective distress experienced by mothers during a major natural disaster that occurred immediately prior to, or during their pregnancy, was associated with higher levels of autism-like traits in the offspring.

Despite these links to ASD-related trait severity in non-clinical populations, there is a dearth of research examining whether prenatal maternal stress exposure may contribute to variability in phenotypic severity amongst individuals with ASD. In the only study to date to describe phenotypic outcomes amongst individuals with ASD, Beversdorf et al. (2005) reported that children with ASD with prenatal stress exposure during mid-gestation were more likely to be non-verbal than children with ASD with no prenatal stress exposure. This is

consistent with research linking prenatal maternal stress exposure to deficits in language ability in the general population (Whitehouse et al., 2010).

In the current study, we examined whether the experience of maternal prenatal stressful life events contributes to variability in ASD-related symptom severity and communication abilities amongst children and adolescents with ASD. We hypothesized that increased exposure to prenatal stressful life events would be associated with increased severity of ASD-associated traits and communication difficulties amongst children and adolescents with ASD.

Methods

Participants

Data reported here were collected as part of a larger, ongoing study of children with ASD and their families, called the Western Australian Autism Biological Registry (WAABR; for a more detailed description of the study, see Taylor et al., 2015). Individuals in the study hold a community-based diagnosis of ASD. In Western Australia this is obtained by professional consensus following a diagnostic assessment process conducted by a multidisciplinary team comprising a pediatrician, clinical psychologist, and speech-language pathologist (Glasson et al., 2008). The Autism Diagnostic Observation Schedule (ADOS; Lord et al., 2000) was administered to children and adolescents enrolled in the study by research-reliable assessors as part of a one-off study visit at Telethon Kids Institute in Perth, Western Australia.

At the time of analysis, the total WAABR sample included 263 individuals with ASD. The WAABR study did not have any exclusion criteria. However, as our primary outcome measures for the current study are only suitable for children aged 4 to 18 years, we excluded

children younger than age 4 ($n = 34$) and young adults over the age of 18.99 years ($n = 9$).

We excluded any individuals that were missing outcome data for both primary outcome measures (the Social Responsiveness Scale and the Children's Communication Checklist; $n = 27$) or information about prenatal stress exposures provided by the biological mother ($n = 19$).

The final sample comprised 174 children with ASD (141 males) who were aged between 4.00 – 18.39 years ($M_{\text{age}} = 9.09$; $SD = 3.81$). Except for chronological age (where excluded individuals were overall younger, due to excluding children under the age of 4 years, $p < .001$), included versus excluded individuals did not differ on any of the examined sociodemographic or behavioral variables, including exposure to prenatal stressful events ($p = .210$), maternal age at conception ($p = .209$), paternal age at conception ($p = .706$), child sex ($p = .774$), maternal education ($p = .095$), gestational age ($p = .854$), maternal cigarette smoking during pregnancy ($p = .205$), maternal alcohol consumption during pregnancy ($p = .738$), or calibrated severity scores on the ADOS (a severity metric for ASD symptomatology based on raw ADOS scores; Gotham et al., 2009) ($p = .670$). In terms of comorbidities amongst the final sample (as gathered from parent-report at the time of the study visit), 16 individuals had intellectual disability (9.2%), 12 had epilepsy (6.9%), and 12 individuals had attention deficit disorder or attention deficit hyperactivity disorder (6.9%). The final sample also included one individual cerebral palsy, two with known genetic and/or chromosomal abnormalities (47,XYY, Fragile X Syndrome), and four with extreme prematurity (i.e., birth prior to 32 weeks gestation). As the exclusion of these individuals did not change the pattern of results, and these individuals all had age- and language-levels appropriate for the current study, we retained these individuals in the final set of analyses.

Procedures and measures

Approval for the study was obtained from the Princess Margaret Hospital Human Research Ethics Committee and written, informed consent was provided by all caregivers.

All of the data analyzed in the current study were collected at a single time-point. The family was mailed a questionnaire pack and asked to complete it ahead of a one-off study visit at Telethon Kids Institute (in which the ADOS was conducted). This pack included a demographic and family questionnaire booklet (which contained items regarding maternal exposure to stressful events during pregnancy [i.e., the predictor variables in the current study] and sociodemographic and obstetric information [i.e., the control variables]) as well as the Social Responsiveness Scale and the Children's Communication Checklist (i.e., the outcome variables). While the forms in the questionnaire pack may have been completed by either caregiver, only cases in which the biological mother provided information regarding maternal prenatal stress exposure were included for analyses. The questionnaires were typically completed by the same caregiver.

Predictor Variables

Prenatal Stressful Life Events. Parents completed a booklet at the time of the child's assessment that asked about the occurrence of nine typically stressful life events in the three months prior to and during the pregnancy. The nine events were separation or divorce, marital problems, problems with children, involuntary job loss, partner involuntary job loss, money problems, a residential move, death of a close friend or relative, or other stressful events. These particular items were originally selected from a broader life-stress inventory (Tennant & Andrews, 1976) and have previously been used to examine the influence of maternal prenatal stressful events on a range of developmental outcomes (Li et al., 2013; Robinson et al., 2008; Robinson et al., 2011; Whitehouse et al., 2010), including autism-

associated behaviors in the general population (Ronald et al., 2011). Moreover, these specific stressful life events have been found to be particularly salient for predicting later developmental outcomes amongst a population-cohort study (Robinson et al., 2008). The number of events experienced were summed and grouped (no stressful life events, 1 event, 2 events, 3+ events).

Outcome Variables

Social Responsiveness Scale-Parent Form (SRS; Constantino & Gruber, 2005). The SRS is a 65-item caregiver-report questionnaire designed to measure ASD-related traits in children. The total SRS score provides a measure of the severity of ASD-associated impairments, with higher scores indicating more difficulties. Here, we used the SRS Second Edition algorithm (Constantino & Gruber, 2012) to calculate the SRS Total score, normed for gender (SRS-T). The SRS Total normed score was used as the outcome in the regression models. The Social Communication/Interaction and Restricted, Repetitive Behavior subscale raw scores (which together comprise the SRS Total score; Frazier et al., 2014) were examined individually in follow-up analyses. As the SRS has not been validated in non-verbal children, we confirmed that all participants had, at minimum, single words (based on the ADOS A1-item codes).

Children's Communication Checklist Second Edition (CCC-2; Bishop, 2003). The CCC-2 is a 70-item parent-report questionnaire designed to screen for communication difficulties in children. The Global Communication Composite (GCC) is an age-normed score that provides a measure of overall communication ability across eight subscales that assess speech, syntax, semantics, coherence, inappropriate initiation, stereotyped language, the use of context, and non-verbal communication. Lower scores indicate greater communication difficulties. The

age-normed GCC score was used as the outcome in the regression models. The scaled subscale scores were examined individually in follow-up analyses. As the CCC-2 is only suitable for children who (1) are aged between 4-16.99 years and (2) have phrase speech, we excluded children who were older than 16.99 years ($n = 2$) and those that did not have phrase speech, based on the ADOS A1-item codes ($n = 4$) for the CCC analyses.

Control Variables

A range of variables known to influence behavioral and language outcomes in children were also considered. These variables included chronological age of the child, child sex, maternal age at the child's birth, paternal age at the child's birth, family income (indexed at the time of the child's participation in the study), gestational age, maternal education, and maternal cigarette smoking and alcohol consumption during pregnancy. This information was collected as part of the booklet completed by either parent at the time of their study assessment.

Statistical Analyses

We conducted one-way analyses of variance (ANOVA) to compare groups of individuals exposed to zero, one, two or three or more stressors on chronological age and gestational age. Differences in sex amongst individuals exposed to zero, one, two, or three or more stressors were investigated using Chi square analyses. Kruskal-Wallis H tests were conducted to compare groups of individuals exposed to zero, one, two or three or more stressors on ordinal outcome variables (family income, maternal education, maternal cigarette smoking during pregnancy, and maternal alcohol consumption during pregnancy). We performed two hierarchical multiple regression analyses using forced entry models to assess the effect of prenatal stressful life events on (1) the severity of ASD-associated difficulties (SRS Total

Normed Score), and (2) communication abilities (CCC-2 GCC age-normed score) in children with ASD. Both models took into account the potential influence of the child or adolescent's chronological age, maternal and paternal age at the child's birth, child sex, family income, gestational age, maternal education, and maternal cigarette smoking and alcohol consumption during pregnancy (separately) on the outcome variables. Missing data were deleted pairwise. We conducted follow-up analyses that aimed to (1) investigate the number of prenatal stressors experienced before a significant difference in outcomes are observed on the SRS and GCC, (2) examine whether particular aspects of communication are influenced by prenatal stress exposure (by examining the CCC-2 individual subscale, scaled scores), and (3) examine whether particular aspects of ASD-associated difficulties are influenced by prenatal stress exposure (by examining the SRS individual subscale raw scores). For these analyses, we compared outcomes for children of mothers who experienced one, two or three or more prenatal stressful events compared to those with zero stressors. We conducted separate Kruskal-Wallis H tests comparing group scores on the SRS, CCC-2 GCC, and the individual sub-scales of the CCC-2 and SRS with follow-up pairwise comparisons with adjusted p-values. All analyses were conducted using SPSS Version 24 (IBM Corp., Armonk, NY).

Results

Two participants did not have valid ADOS data (as they were older adolescents with only single words). Of the 172 participants with valid ADOS assessments, 83% ($n = 142$) met criteria for ASD based on the ADOS revised algorithm (Gotham, Risi, Pickles, & Lord, 2007). The average ADOS calibrated severity score for the sample was 6.11 ($SD = 2.28$). As the community-based diagnosis of ASD in the sample was based on a rigorous, multidisciplinary team consensus clinical judgment, all individuals (regardless of their ADOS

outcome) were included in the primary analyses reported in the manuscript. We repeated the analyses, however, constraining the sample to only those individuals who met criteria for ASD on the ADOS and this did not change the pattern of results.

Frequency characteristics for all variables are presented in Table 1.

Group comparisons

We considered whether groups of children exposed to zero ($n = 56, 32.18\%$), one ($n = 48, 27.59\%$), two ($n = 37, 21.26\%$), and three or more ($n = 33, 18.97\%$) stressors differed on any demographic or control variables that may contribute to group differences in SRS and GCC scores. A one-way ANOVA demonstrated that there were no significant differences in chronological age amongst the groups of individuals exposed to zero, one, two, or three or more prenatal stressors, $F(3, 170) = 1.13, p = .340$. There were also no significant differences amongst the groups exposed to zero, one, two, or three or more stressors in gestational age ($F(3, 162) = 1.31, p = .274$), maternal age at the child's birth ($F(3, 170) = 2.07, p = .106$), or paternal age at the child's birth ($F(3, 168) = 1.87, p = .137$), based on one-way ANOVAs. Groups also did not differ in their sex distribution, $X^2 = 5.15, df = 3, p = .161$. Kruskal Wallis H tests showed that there were no significant group differences in family income ($H(3) = 2.51, p = .473$), maternal education ($H(3) = 3.54, p = .315$), maternal cigarette smoking during pregnancy ($H(3) = 0.11, p = .990$), or maternal alcohol consumption during pregnancy ($H(3) = 3.25, p = .355$). Frequency characteristics for all variables by prenatal stress exposure are presented in Table 1.

[TABLE 1]

Multiple Regression Models

We used hierarchical multiple regression models to examine the associations between exposure to prenatal stressful life events and the severity of ASD-associated difficulties (Model 1), and communication abilities (Model 2) in children with ASD. In both models, all control variables were entered in the first step, and the number of prenatal maternal stress events entered in the second step (see Table 2 for a summary of the models). Multicollinearity was not a concern in either model, with Tolerance values ranging from .45 - .98 and a variance inflation factor range of 1.0 – 2.2 across all variables.

Model 1: SRS Total Normed Score. In the first step, the control variables accounted for 26.2% of the variation in SRS Total Scores, $F(9, 137) = 5.405, p < .001, R^2 = .262$. In the second step, prenatal exposure to stressful life events immediately prior to, or during, pregnancy explained an additional 2.1% of the variation in SRS Total Scores and this change in R^2 was significant, $F(1, 136) = 4.057, p = .046, \Delta R^2 = .021$. The final model accounted for 28.3% of the variation in SRS Total Scores, $F(10, 136) = 5.379, p < .001, R^2 = .283$. Increased maternal exposure to stressful life events immediately prior to, or during, pregnancy was independently associated with higher Total SRS scores in children with ASD, suggestive of increased severity of ASD-associated difficulties ($t = 2.014, p = .046$). Family income, child sex, and chronological age were also significant predictors of Total SRS scores. Lower family income was associated with higher Total SRS scores, suggesting increased rates of ASD-associated difficulties ($t = -2.712, p = .008$). Male sex was associated with higher Total SRS Scores ($t = 4.010, p < .001$). The association with chronological age suggested increasing age across childhood was associated with increased symptom severity ($t = 2.025, p = .045$). Maternal education, gestational age, maternal age at child's birth, paternal age at child's birth, and maternal cigarette smoking during pregnancy and alcohol

consumption during pregnancy did not significantly contribute to the variation in SRS Total scores (all p values $> .05$). The model summary is presented in Table 2.

Model 2: CCC-2 Global Communication Composite (GCC) Score. In the first step, the control variables accounted for 38.7% of the variation in GCC scores, $F(9, 112) = 7.855, p < .001, R^2 = .387$. In the second step, prenatal exposure to stressful life events immediately prior to, or during, pregnancy explained an additional 4.4% of the variation in GCC scores and this change in R^2 was significant, $F(1, 111) = 8.554, p = .004, \Delta R^2 = .044$. The final model accounted for 43.1% of the variation in GCC scores, $F(10, 111) = 8.402, p < .001, R^2 = .431$. Increased maternal exposure to stressful life events immediately prior to, or during, pregnancy was independently associated with lower GCC scores amongst children with ASD, suggestive of greater difficulties with communication abilities ($t = -2.925, p = .004$). Family income and chronological age were also significant predictors of communication abilities amongst children and adolescents with ASD. Lower family income was associated with poorer communication abilities amongst children with ASD ($t = 2.192, p = .030$). Increasing chronological age was associated with poorer communication abilities ($t = -6.198, p < .001$). Child sex, maternal education, gestational age, maternal age at child's birth, paternal age at child's birth, and maternal cigarette smoking during pregnancy and alcohol consumption during pregnancy did not significantly contribute to the variation in GCC scores (all p values $> .05$). The model summary is presented in Table 2.

[TABLE 2]

Follow-up Analyses: Total Scores

We next considered if there were any differences in ASD symptom severity ratings and communication abilities amongst children of mothers who experienced zero prenatal

stressful life events compared to those that experienced one, two, or three or more stressful life events in the three months prior to, or during, their pregnancy.

SRS Total Normed Score: The Kruskal Wallis H test comparing SRS-Total normed scores amongst individuals exposed to zero, one, two, and three or more prenatal stressors was significant, $H(3) = 14.09$, $p = .003$. Follow-up pairwise comparisons with adjusted p -values showed that compared to children whose mothers did not experience any of the probed stressful life events in the three months prior to, or during their pregnancy, children of mothers who experienced 2 and 3 or more stressful life events had significantly increased SRS-T scores, indicative of increased symptom severity ($p = .009$ for zero stressors versus 2 stressors comparison and $p = .018$ for zero stressors versus 3+ stressors comparison; see Figure 1A). There was a trend towards increased SRS-T scores amongst children of mothers who experienced only 1 prenatal stressful event ($p = .088$), however, no other comparisons reached statistical significance (all p values $> .05$).

CCC-2 Global Composite Score (GCC): The Kruskal Wallis H test comparing GCC scores amongst individuals exposed to zero, one, two, and three or more prenatal stressors was significant, $H(3) = 16.76$, $p = .001$. Follow-up pairwise comparisons with adjusted p -values showed that compared to children whose mothers did not experience any of the probed stressful life events immediately prior to, or during, their pregnancy, children of mothers who experienced 3 or more stressful life events had significantly reduced GCC scores, indicative of poorer communication abilities ($p = .001$; see Figure 1B). There was also a significant difference in GCC scores between children of mothers who experienced one, versus three or more, stressful life events ($p = .024$). No other comparisons reached significance (all p values $> .05$).

[FIGURE 1]

Follow-up analyses: Subscale Scores

Finally, in lieu of our findings suggesting prenatal maternal stress exposure is a significant predictor of overall communication abilities (based on the CCC-2 GCC score) and ASD-associated symptom severity (based on the SRS Total score), we examined whether particular aspects of communication or ASD symptomatology, are affected amongst children with ASD with prenatal stress exposure, by examining the individual subscales that comprise the GCC and SRS.

CCC-2 Subscales: Krusal-Wallis H tests comparing subscale scores amongst individuals exposed to zero, one, two, and three or more prenatal stressors revealed overall significant effects for all subscales assessing structural aspects of language, including speech output ($H(3) = 8.27, p = .041$), syntax ($H(3) = 10.78, p = .013$), semantics ($H(3) = 10.92, p = .012$), and coherence ($H(3) = 14.77, p = .002$). There was also a significant effect for the stereotyped language subscale, ($H(3) = 11.93, p = .008$). Follow-up pairwise comparisons with adjusted p-values showed that compared to children whose mothers did not experience any of the probed stressful life events immediately prior to, or during, their pregnancy, children of mothers who experienced 3 or more stressful life events had more difficulties with speech output ($p = .032$), syntax ($p = .021$), semantics ($p = .010$), and coherence ($p = .004$) and more stereotyped language ($p = .005$) compared to those children whose mothers experienced zero stressful life events. There was also a significant difference in syntax and coherence scores between children of mothers who experienced one, versus three or more, stressful life events ($p = .048$ and $p = .006$, respectively) (see Figure 1 in Supporting Information). There were no significant effects for subscales assessing inappropriate initiation of speech, the use of context, or non-verbal communication (all p values $> .05$).

SRS-2 Subscales: Krusal-Wallis H tests comparing subscale scores amongst individuals exposed to zero, one, two, and three or more prenatal stressors revealed overall significant effects for the Restricted, Repetitive Behavior subscale, ($H(3) = 15.85, p = .001$). The Social Communication/Interaction subscale revealed only a trend towards greater severity in this domain amongst individuals exposed to multiple stressors, ($H(3) = 6.69, p = .082$). Follow-up pairwise comparisons with adjusted p-values showed that compared to children whose mothers did not experience any of the probed stressful life events immediately prior to, or during, their pregnancy, children of mothers who experienced 2 or 3 or more stressful life events had more severe Restricted, Repetitive Behavior scores, compared to those children whose mothers experienced zero stressful life events ($p = .004$, and $p = .008$, respectively) (see Figure 2 in Supporting Information).

Discussion

Due to the significant phenotypic heterogeneity amongst individuals with ASD, an understanding of the factors that modulate risk and severity are critical to informing prognosis, stratification and treatment target and selection decisions. In an effort to delineate these factors, we examined the association between prenatal maternal exposure to stressful life events and phenotypic outcomes amongst children and adolescents with ASD. An emerging body of research has demonstrated links between prenatal maternal stress exposure and increased risk of ASD (Beversdorf et al., 2005; Class et al., 2014; Kinney et al., 2008a, 2008b; Roberts et al., 2016) and variability in ASD-associated traits in the general population (Rijlaarsdam et al., 2016; Ronald et al., 2011; Walder et al., 2014). The present findings extend this body of work to demonstrate that maternal report of prenatal exposure to stressful life events is associated with increased severity of ASD-associated symptoms and poorer communication abilities in children with ASD, even after controlling for a range of

sociodemographic and obstetric variables. ASD-associated symptom severity, particularly in the restricted and repetitive behavior domain, was significantly increased in children exposed to two or more common stressful life events during pregnancy compared to those children with no exposure. Communication difficulties were also increased in the context of three or more prenatal stressful life events, with structural aspects of language (i.e., speech output, syntax, semantics, and coherence) and stereotyped language particularly impacted. These findings indicate that prenatal maternal exposure to stressful life events may be one factor that contributes to variability in symptom severity in ASD.

Prenatal maternal stress exposure has been linked to a wide array of adverse outcomes over the lifespan. These outcomes include deficits in language and cognition (Laplante et al., 2004, 2008), increased risk of emotional and behavioral problems (O'Connor et al., 2002, 2003; Ronald et al., 2011) motor atypicalities (Grace et al., 2015; Simcock et al., 2016), alterations in brain structure and function (including the prefrontal cortex, hippocampus, hypothalamus, amygdala, and hypothalamic-pituitary-adrenal axis functioning; Buss et al., 2010; Sandman & Davis, 2012; Weinstock, 2005), gastrointestinal problems (Zijlmans et al., 2015), and immunologic abnormalities (Horvath Marques et al., 2013). While the effects of prenatal maternal stress exposure are not specific to ASD, many of these outcomes map onto behaviors and comorbidities commonly observed in individuals with ASD (Kinney et al., 2008b), suggesting that prenatal maternal stress exposure and its sequelae may exert effects on, or interact with, mechanisms implicated in ASD risk. That is, the downstream consequences of prenatal maternal stress exposure may interact with pre-existing biological vulnerabilities and/or the fetus and mother's genetic background to influence developmental trajectories. Consistent with this idea, Hecht et al. (2016) found that mothers who carried the short-allele of the 5-HTTLPR gene (an allelic variant associated with increased reactivity to stress), reported increased incidence of stressful life events during their pregnancy with a

child with ASD compared to those who carried the long-allele; moreover, this effect was specific to pregnancies of children with ASD.

Due to the nature of the maternal stressors measured in the current study (i.e., typical, objective life stressors such as financial and relationship difficulties), it is possible that the association between prenatal exposure to stressful life events and offspring phenotypic severity represents the combined influence of prenatal stressors and ongoing stressors throughout the postnatal period. However, considering our findings are consistent with prior evidence linking these common stressful life events during the prenatal period (measured prospectively and retrospectively) to ASD risk (Beversdorf et al., 2005; Hecht et al., 2016) and trait severity in non-clinical populations (Rijlaarsdam et al., 2016; Ronald et al., 2011), it seems these potentially chronic stressors are important in shaping developmental outcomes in ASD.

The finding of an association between lower family income and increased phenotypic severity amongst individuals with ASD warrants consideration and further study. As family income in the current study was indexed at the time of assessment, we cannot rule out the influence of reverse causality. However, this finding is consistent with evidence demonstrating links between lower socioeconomic status (SES) and poorer child outcomes in language and socio-emotional development in the general population (Ursache & Noble, 2016). In addition, our results are consistent with population-based studies outside of the United States (US), demonstrating associations between lower family SES and ASD risk (Dodds et al., 2011; Emerson, 2012; Larsson et al., 2005; Rai et al., 2012b); the opposite pattern has been observed amongst US-based studies, where there is increased ASD risk amongst high SES families (Durkin et al., 2010; King & Bearman, 2011). In a Swedish population-based case-control study, Rai et al. (2012b) found that parental income (at the time of the child's birth), though not parental education, was inversely associated with ASD

risk, irrespective of the presence or absence of comorbid intellectual disability. Similarly, in our study, we found that family income, though not maternal education, was associated with phenotypic severity amongst individuals with ASD. Together, these results suggest that, at least in countries with universal health care, family income (possibly reflecting a proxy measure of chronic stress) rather than parental education, influences ASD-associated outcomes in children. These data highlight the importance of considering SES gradients in future studies of children with ASD to better understand this relationship due to the potentially important implications for intervention and policy.

Finally, we also found an association between increased chronological age and greater ASD-related symptom severity in our sample. It is possible, due to the wide age range in the current study (i.e., 4-18 years), that this association is reflective of changes in diagnostic practices over time. Recent, population-level evidence (from the same geographical region as the current study) has shown that there has been a shift over time towards increased rates of diagnosis amongst children with less severe behavioral phenotypes (Whitehouse et al., 2017). Importantly, for the current study, we continued to see associations between maternal prenatal stress exposure and increased phenotypic severity amongst individuals with ASD even when chronological age was taken into account.

Our findings should be interpreted in the context of several limitations. ASD-associated symptom severity, communication abilities and prenatal maternal stress exposure measures were based on maternal ratings, potentially inflating the correlation between the outcome and predictor variables. While we observed similar results to other studies relying on maternal reports of stress exposure and childhood outcomes (Beversdorf et al., 2005; Rijlaarsdam et al., 2016; Ronald et al., 2011), incorporating objective measures of developmental outcomes will be a fruitful avenue for future research in this area. Similarly, maternal prenatal exposure to stressful life events was based on retrospective reports, which

may introduce inaccuracies in recall. However, accuracy in the recall of stressful events, such as those measured in the current study, have been shown to be stable over time (Casey et al., 1967) and consistent across studies (Beversdorf et al., 2005; Hecht et al., 2016; Rijlaarsdam et al., 2016). In addition, similar associations to those observed in the current study have been found in prospective studies examining prenatal maternal stress and childhood outcomes (Ronald et al., 2011). It should also be noted that we did not have any measure of cognitive or intellectual ability, beyond only including individuals who had verbal language. It is possible that prenatal maternal exposure to stressful life events may have impacted more global cognitive development which, subsequently, is reflected in increased ASD-associated symptomatology and poorer communication abilities, rather than exerting specific effects on these latter domains. We were unable to isolate the timing of the stress exposure in the current study, both in terms of the onset and duration of the event(s). Animal and human work has demonstrated that prenatal stress may exert differential impacts on the offspring depending on the timing of the exposure (and hence, the specific organs and systems undergoing development at that time; Beversdorf et al., 2005; Kinney et al., 2008b; Lupien et al., 2009; Talge et al., 2007). Future research should examine whether the timing of prenatal maternal stress exposure also contributes to phenotypic variability amongst children with ASD, beyond just the number of stress exposures. Finally, while we did not find any association between maternal age, paternal age, child gestational age, or maternal cigarette and alcohol consumption during pregnancy with any of our outcome variables, there are other relevant prenatal or obstetric complications that warrant consideration in future research examining prenatal stress influences in the context of ASD, such as obstetrical complications, maternal body mass index, and maternal health conditions (e.g., diabetes).

In conclusion, the current study identified an association between maternal report of prenatal exposure to stressful life events and increased ASD-related symptom severity and

communication difficulties in children and adolescents with ASD, even after controlling for a range of sociodemographic and obstetric factors. While additional research is required using prospective designs with objective measures that can isolate the timing and duration of prenatal stress exposure to more accurately understand the mechanisms influencing ASD phenotypic variability, these findings indicate that ASD in the context of prenatal maternal stress exposure may be associated with a more severe phenotype, particularly when there are multiple prenatal exposures.

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Figure Legends

Figure 1. Box-and-whisker plots (with maximum and minimum value bars) representing significant differences in median scores on the (A) Social Responsiveness Scale (SRS) and (B) CCC-2 Global Communication Composite (GCC) for individuals with ASD whose mothers were exposed to zero, one, two, or three or more stressful life events in the three months prior to, or during, their pregnancy.

Supplementary Figure 1. Box-and-whisker plots (with maximum and minimum value bars) representing significant differences in median scores on the individual subscales of the Children's Communication Checklist (CCC) for individuals with ASD whose mothers were exposed to zero, one, two, or three or more stressful life events in the three months prior to, or during, their pregnancy.

Supplementary Figure 2. Box-and-whisker plots (with maximum and minimum value bars) representing significant differences in median scores on the (A) Social Communication/Interaction subscale and (B) Restricted, Repetitive Behavior subscale of the Social Responsiveness Scale (SRS) for individuals with ASD whose mothers were exposed to zero, one, two, or three or more stressful life events in the three months prior to, or during, their pregnancy.

Table 1. Sample characteristics, sociodemographic and obstetric information, and scores on the parent-rated Social Responsiveness Scale (SRS) and Children's Communication Checklist (CCC-2) regarding children with autism spectrum disorder. Information is presented for the total study sample (Total Group) and by the frequency of maternal prenatal stress exposure.

Continuous Variables	N	Total Group	Number of prenatal stressors			
			0	1	2	3+
Age in years (Mean, SD)	174	9.1 (3.8)	9.3 (3.9)	8.7 (3.6)	8.5 (3.6)	.9 (4.1)
SRS-T Score (Median, IQR)	173	87.0 (21)	81.0 (17)	88.0 (18)	94.0 (20)	90.0 (19)
CCC-2 GCC Score (Median, IQR)	144	29.5 (16)	35.0 (18)	34.0 (22)	26.0 (20)	25.0 (18)
Gestational age, weeks (Mean, SD)	166	38.7 (2.4)	38.3 (3.1)	39.2 (1.7)	38.6 (2.1)	39.0 (2.4)
Maternal age (in years) at child's birth (Mean, SD)	174	31.1 (5.5)	31.5 (5.1)	31.9 (5.3)	31.4 (5.7)	28.9 (6.2)
Paternal age (in years) at child's birth (Mean, SD)	172	33.2 (6.3)	34.0 (6.2)	33.6 (5.4)	33.4 (6.0)	30.9 (7.3)
Categorical Variables	N	Total Group	0	1	2	3+
Child Sex (%)	174					
Male		81.0	86.0	87.5	73.0	73.0
Female		19.0	14.0	12.5	27.0	27.0
Family Income (%)	155					
AUD\$1-50000		9.7	8.7	4.8	5.6	22.6
AUD\$50001-78000		21.9	17.4	23.8	27.8	19.4
AUD\$78001-104000		23.2	28.3	21.4	22.2	19.4
AUD\$104000+		45.2	45.7	50.0	44.4	38.7
Maternal education (%)	172					
Did not complete Secondary School		16.9	17.9	25.5	5.6	15.2
Secondary School/Vocational certificate		47.7	50.0	38.3	50.0	54.5
University degree		35.5	32.1	36.2	44.4	30.3
Maternal cigarette smoking during pregnancy (%)	174					
None		84.5	85.7	83.3	83.8	84.8

1-10 daily	5.2	3.6	4.2	10.8	3.0
11+ daily	10.3	10.7	12.5	5.4	12.1
Maternal alcohol consumption during pregnancy (%)	174				
None	65.5	71.4	66.7	54.1	66.7
Once a week or less	21.8	21.4	14.6	29.7	24.2
Several times a week	12.6	7.1	18.8	16.2	9.1

SD = Standard Deviation; SRS-T = Social Responsiveness Scale, Total Normed Score; IQR = Interquartile

Range; CCC-2 GCC = Children's Communication Checklist Global Communication Composite; AUD = Australian Dollars.

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Table 2. Regression model summaries assessing the association between maternal exposure to stressful life events (zero, one, two, three or more) in the three months prior, or during, pregnancy and scores on the (1) Social Responsiveness Scale (SRS) and (2) Children’s Communication Checklist-2 Global Communication Composite (GCC) amongst children with ASD. Step 1 includes just the control variables (a range of sociodemographic and obstetric variables) and Step 2 includes the addition of the prenatal maternal stress predictor variable.

	Model 1: SRS Total Normed Score					Model 2: GCC Score				
	(n = 147)					(n = 122)				
	B	β	SE B	p	95% CI	B	β	SE B	p	95% CI
Step 1										
Child chronological age	.64	.16	.31	.045	.02, 1.26	-2.15	-.51	.343	<.001	-2.83, -1.47
Child sex	12.52	.33	2.97	<.001	6.65, 18.38	.52	.01	2.96	.860	-5.35, 6.40
Gestational age	.36	-.06	.46	.435	-1.27, .55	-.83	-.14	.44	.059	-1.70, 0.03
Family income	-3.30	-.23	1.11	.004	-5.50, -1.10	2.73	.20	1.05	.011	0.64, 4.81
Maternal age at child’s birth	-.34	-.13	.30	.251	-.94, .25	.32	.12	.29	.264	-.25, .89
Paternal age at child’s birth	-.11	-.04	.26	.681	-.62, .41	-.10	-.05	.24	.670	-.57, .37
Maternal education	-1.15	-.05	1.78	.519	-4.68, 2.38	-.09	-.01	1.75	.959	-3.55, 3.37
Maternal smoking during pregnancy	-2.97	-.13	2.01	.141	-6.94, .99	-3.41	-.14	2.01	.093	-7.40, 0.57
Maternal alcohol consumption during pregnancy	1.42	.07	1.64	.387	-1.82, 4.67	2.32	.11	1.63	.157	-0.91, 5.54

Step 2

Child chronological age	.63	.16	.31	.045	.02, 1.24	-2.07	-.49	.33	<.001	-2.73, -1.41
Child sex	11.84	.31	2.95	<.001	5.99, 17.67	.66	.02	2.87	.818	-5.03, 6.35
Gestational age	-.43	-.07	.46	.353	-1.33, .48	-.68	-.12	.43	.113	-1.53, .16
Family income	-3.01	-.21	1.11	.008	-5.20, -.82	2.26	.16	1.03	.030	.22, 4.30
Maternal age at child's birth	-.33	-.12	.30	.265	-.92, .25	.23	.09	.28	.419	-.33, .78
Paternal age at child's birth	-.06	-.02	.26	.826	-.57, .45	-.16	-.07	.23	.484	-.62, .30
Maternal education	-1.42	-.07	1.77	.423	-4.92, 2.08	.54	.03	1.71	.752	-2.84, 3.92
Maternal smoking during pregnancy	-2.84	-.12	1.98	.155	-6.76, 1.09	-3.04	-.13	1.95	.122	-6.91, .82
Maternal alcohol consumption during pregnancy	1.20	.06	1.63	.461	-2.01, 4.42	2.17	.10	1.58	.170	-.95, 5.29
Number of maternal prenatal stressful events	2.07	.15	1.03	.046	.04, 4.10	-2.91	-.22	.99	.004	-4.89, -.94

Figure 1. Box-and-whisker plots (with maximum and minimum value bars) representing significant differences in median scores on the (A) Social Responsiveness Scale (SRS) and (B) CCC-2 Global Communication Composite (GCC) for individuals with ASD whose mothers were exposed to zero, one, two, or three or more stressful life events in the three months prior to, or during, their pregnancy.

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Author/s:

Varcin, KJ;Alvares, GA;Uljarevic, M;Whitehouse, AJO

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