Prenatal maternal stress associated with ADHD and autistic traits in early childhood

Journal Article

http://eprints.bbk.ac.uk/4755

Version: Published (Refereed)

Citation:

Prenatal maternal stress associated with ADHD and autistic traits in early childhood –
Frontiers in Psychology 1(223)

© 2011

Publisher version
Prenatal maternal stress associated with ADHD and autistic traits in early childhood

Angelica Ronald1*, Craig E. Pennell2 and Andrew J. O. Whitehouse3

1 Department of Psychological Sciences, Centre for Brain and Cognitive Development, Birkbeck, University of London, London, UK
2 School of Women’s and Infants’ Health, University of Western Australia, Perth, WA, Australia
3 Telethon Institute for Child Health Research, Centre for Child Health Research, University of Western Australia, Perth, WA, Australia

INTRODUCTION

Research suggests that offspring of mothers who experience high levels of stress during pregnancy are more likely to have problems in neurobehavioral development. There is preliminary evidence that prenatal maternal stress (PNMS) is a risk factor for both autism and attention deficit hyperactivity disorder (ADHD), however most studies do not control for confounding factors and no study has investigated PNMS as a risk factor for behaviors characteristic of these disorders in early childhood. A population cohort of 2900 pregnant women were recruited before their 18th week of pregnancy and investigated prospectively. Maternal experience of stressful life events was assessed during pregnancy. When offspring were age 2 years, mothers completed the child behavior checklist. Multiple regression showed that maternal stressful events during pregnancy significantly predicted ADHD behaviors in offspring, after controlling for autistic traits and other confounding variables, in both males (p = 0.03) and females (p = 0.01). Similarly, stressful events during pregnancy significantly predicted autistic traits in the offspring after controlling for ADHD behaviors and confounding variables, in males only (p = 0.04). In conclusion, this study suggests that PNMS, in the form of typical stressful life events such as divorce or a residential move, show a small but significant association with both autistic traits and ADHD behaviors independently, in offspring at age 2 years, after controlling for multiple antenatal, obstetric, postnatal, and sociodemographic covariates. This finding supports future research using epigenetic, cross-fostering, and gene–environment interaction designs to identify the causal processes underlying this association.

Keywords: prenatal, stress, ADHD, autism, autistic traits, Raine Study

Abbreviations: ADHD, attention deficit hyperactivity disorder; CBCL, child behavior checklist; PDP, pervasive developmental problems; PNMS, prenatal maternal stress.
Although their core diagnostic symptoms do not explicitly overlap, high levels of comorbidity between ASD and ADHD have been reported. For example, a population-derived sample that used structured assessments found that 28% of their sample with ASD also had ADHD (Simonoff et al., 2008). Autistic traits and ADHD behaviors are positively correlated in the general population (Constantino et al., 2003; Reiersen et al., 2008; Ronald et al., 2008, 2010), and twin studies suggest that ADHD behaviors and autistic traits share some genetic and environmental influences (Constantino et al., 2003; Reiersen et al., 2008; Ronald et al., 2008, 2010). The identification of risk factors for ASD and ADHD is an important goal for child mental health research and for developmental psychology.

The first aim of this study was to extend the literature reviewed above to explore the association between PNMS and autistic traits and ADHD behaviors in 2-year-olds, using a prospective longitudinal sample, a broad measure of common stressors, and including multiple confounders. Because both ADHD and autism show a male predominance, analyses were split by gender. The second aim was to explore whether PNMS is associated with both autistic traits and ADHD behaviors independently, or whether PNMS is part of a common etiological pathway that could help explain the traits and ADHD behaviors independently, or whether PNMS may be due to inherited factors (Rice et al., 2010).

**MATERIALS AND METHODS**

The Western Australia Pregnancy Cohort (Raine) Study is a longitudinal study of women and their children recruited between 16 and 18 weeks of pregnancy from the public antenatal clinic at King Edward Memorial Hospital (KEMH) or surrounding private clinics in Perth. Approximately 100 women per month were enrolled from August 1989 to April 1992, with a final sample of 2900 pregnancies. The inclusion criteria were English language skills sufficient to understand the study demands, an expectation to deliver at KEMH, and an intention to remain in Western Australia to enable future follow-up of their child (Newnham et al., 1993). From the 2900 pregnancies recruited, 2868 live born children have been comprehensively phenotyped over the past 20 years. Children with intellectual disability with a known cause were excluded from the current study ($n = 29$). Participant recruitment and all follow-ups of the study families were approved by the Human Ethics Committee at KEMH and/or Princess Margaret Hospital for Children in Perth.

**OUTCOME VARIABLES**

Child behavior was assessed at the 2-year follow-up using the child behavior checklist (CBCL) for Ages 1½–5, an empirically validated parent-report measure (Achenbach et al., 1987). Caregivers were provided with 99 statements regarding their child’s behavior and asked to respond on a three-point Likert scale as to whether a particular statement was very true (score of 2), somewhat true (score of 1) or not true (score of 0). The ADHD and pervasive developmental problems (PDP) scales are based upon DSM-IV (American Psychiatric Association, 1994) symptom categories for ADHD and Autistic Disorder, respectively. The ADHD scale consists of six statements assessing a child’s inattentive and hyperactive behavior (e.g., “Cannot concentrate, cannot pay attention for long,” “Cannot sit still, restless, or hyperactive”), and the PDP scale includes 13 statements regarding the child’s social–communicative (e.g., “Avoids looking others in the eye”) and repetitive behaviors/routines (e.g., “Disturbed by any change in routine”). Responses to items within each scale were summed to provide a total score, with higher scores denoting more ADHD symptoms (range: 0–12) or ASD-like traits (range: 0–26). Scores from cases with missing data on up to half of the items on a particular scale were prorated to yield a score out of the maximum for that scale. Data were coded as missing when more than half of the items on a particular scale were not answered.

The PDP preschool scale has an acceptable test–retest reliability of 0.86 and high sensitivity for detecting children with ADOS-G classification of autism (80%) but modest specificity (42%; Sikora et al., 2008). The ADHD CBCL preschool scale has been shown to have test–retest reliability of 0.74 and an odds ratio of 4, that is, children who score in the clinical range have four times greater odds of being from a referred sample than those that do not score in the clinical range (Achenbach and Rescorla, 2000). The internal consistency in the Raine cohort was modest for the PDP Scale (Cronbach’s $\alpha = 0.60$) and adequate for the ADHD scale (Cronbach’s $\alpha = 0.77$).

The PDP scale can be further divided into two subscales, relating to social and non-social autistic-like traits (Ronald et al., 2010). From the CBCL PDP scale, six items related to social behaviors (e.g., paucity of social interaction, not answering to name) and five items to non-social behaviors (e.g., preference for sameness, repetitive body motions), with a further two PDP items excluded because they do not clearly relate to either category (“speech problems” and “strange behaviors”). Within each subscale, individual item scores were tallied to provide an overall index ranging from 0 to 12 (social subscale) or 0 to 10 (non-social subscale), with higher scores indicating greater severity of traits. The prorating procedure described above was applied to these subscales as well. The internal consistency for the social (Cronbach’s $\alpha = 0.41$) and non-social subscales (Cronbach’s $\alpha = 0.50$) in the sample were modest. Both scales were positively skewed and were normalized using cumulative frequency rank-transformation.

**PREDICTOR VARIABLES**

The predictor variable was the number of stress events experienced by mothers during pregnancy. Mothers were asked at 18 and 34 weeks gestation whether or not they had experienced any of 10 major life stress events selected from a broader life stress inventory...
involuntary), money problems, residential move, or other stressful problems with children, job loss (involuntary), partner’s job loss, close friend or relative, separation or divorce, marital problems, (Tennant and Andrews, 1976): pregnancy problems, death of a
in the 34-week gestation questionnaire, whether any of the events
had been experienced since becoming pregnant and, in the 34-week gestation questionnaire, whether any of the events
had been experienced within the last 4 months, ensuring that the
same event was not counted twice. Stress events recorded at 18
and 34 weeks were tallied to provide on overall index of maternal
stress. This approach was taken because the type of stressful events
that were asked about do not have obvious temporal boundaries
(Talge et al., 2007) and therefore an overall stress events score was
considered most appropriate.

The influence of a range of covariates known to have an in-
eflence on ADHD and autistic symptoms was also considered. These
variables included: (1) sociodemographic factors recorded at
18 weeks pregnancy (maternal age at conception, maternal edu-
cation, family income, and the presence of the biological father
in the family home); (2) antenatal variables recorded at 34 weeks
pregnancy (maternal smoking during pregnancy: no smoking;
1–10 cigarettes per day; or 11+ cigarettes per day; maternal alco-
hol consumption during pregnancy: no alcohol consumed; con-
sumed alcohol once per week or less; consumed alcohol several
times per week or daily); and (3) obstetric variables recorded at
birth (parity; gestational age; child’s sex; proportion of optimal
birth weight, a measure of the appropriateness of fetal growth
(Blair et al., 2005); and Apgar scores at 5 min). Postpartum mood
disturbance was measured using an index of 16 postnatal feel-
ings on the Blues Questionnaire, completed by mothers after birth
and while still in hospital. These 16 items were a summation of the
22 item Blues Scale (Kennerley and Gath, 1989), a robust and
valid measure of “baby blues” symptoms immediately postpartum
(Henshaw, 2003).

SAMPLE ATTRITION

Complete PNMS data were available for mothers relating to 2575
children. CBCL data at age 2 years were obtained on 1746 of these
participants, a longitudinal follow-up rate of 67.8%. Complete
PDP and ADHD datasets were available for 94.2% (n = 1644) and
97.9% (n = 1710) of the sample, respectively. The mean age of
the children at CBCL data collection was 2.14 years (SD = 0.15;
range = 1.92–3.29), with 96.2% (M = 39.12, SD = 2.46; remained:
M = 39.38, SD = 2.33; p < 0.05), had mothers who were younger at conception (withdraw: M = 26.17,
SD = 6.14; remained: M = 28.06 years, SD = 5.69; p < 0.01), and
experienced more stress events during pregnancy (withdraw: M = 2.27, SD = 2.08; remained: M = 1.83, SD = 1.81; p < 0.01).
Therefore a modest degree of bias is present in the sample due
to attrition, but overall the sample remains representative of the
general population (Kendall, 2003).

STATISTICAL ANALYSES

Multivariate linear regression analyses using the block enter method
were employed. Missing data were deleted pairwise. Analyses were
conducted separately for males (n = 913) and females (n = 833).
A sample size of 800 is robust to detect an effect size of 0.05 with
99% power and 95% confidence and 15 predictors.

RESULTS

Table 1 presents the frequency characteristics of the cohort with
maternal stress event information during pregnancy and CBCL
data at age 2 years. Figures 1A,B show the distribution of the PDP
and ADHD scores for these participants, respectively. Continuous
variables were normally distributed (Kolmogorov–Smirnov test
of normality, p > 0.05), except for the number of stress events
during pregnancy and during the first year of life, which were
rank transformed using cumulative frequency z-scores. Z-scores
of this variable were used for all analyses. Independent t-tests
and chi-square analyses found a gender difference between one
predictor variable only, with fathers of girls more likely to be
absent from the family home during pregnancy (p = 0.01; all other
comparisons, p > 0.10). Gender differences in PDP and ADHD
scores were then examined. PDP scores were positively skewed
and were rank transformed using cumulative frequency z-scores.
Once again, z-scores for this variable were used for all analyses.
Independent t-tests revealed that males (M = 5.97, SD = 2.72,
range = 0–12) had significantly higher scores on the ADHD scale
than females (M = 5.6, SD = 2.7, range = 0–12, p = 0.01). There
was a trend in the same direction for PDP scores (untransformed
scores for males: M = 3.17, SD = 2.52, range = 0–15; females:
M = 2.97, SD = 2.35, range = 0–16), however the difference did
not reach statistical significance (comparison for transformed
scores, p = 0.14).

Bivariate analyses identified a significant positive correlation
between the number of stress events during pregnancy and the
PDP and ADHD scales in male offspring (r = 0.17 and 0.15, respec-
tively, both p < 0.01). For females, stress events during pregnancy
positively correlated with the ADHD subscale (r = 0.14, p < 0.01),
but not with the PDP scale (r = 0.07, n.s.).

Univariate linear regression analyses examined the relation
between the individual confounding variables and PDP and
ADHD scores. All the variables presented in Tables 2 and 3
showed a significant association with either the PDP or ADHD
scale. No associations were found with either PDP or ADHD
scores at age 2 years for the following variables: maternal country
of birth, moderate maternal smoking (1–10 cigarettes per day)
and alcohol intake (once per week or less) during pregnancy,
gestational age at birth, proportion of optimal birthweight, or
Apgar scores at 5 min. These variables were excluded from fur-
ther analyses.

Table 2 presents the results of the multivariate linear regression
analyses examining the effect of the predictor variable and covari-
ates on PDP scores. There was a significant, positive association
between the number of maternal stress events experienced during
pregnancy and PDP scores in male offspring (p < 0.01), but not
female offspring (p = 0.79), after controlling for all the confound-
ing variables. The inclusion of PNMS in the second block of the
regression analysis for males significantly improved the model,
In additional analyses, the association between the number of stress events during pregnancy and scores on PDP “social” and “non-social” subscales at age 2 years was assessed separately. The number of stress events was positively correlated with the social and non-social subscales in males (social: \( r = 0.11 \); non-social: \( r = 0.13 \); both \( p < 0.001 \)) but not females (social: \( r = 0.03 \); non-social: \( r = 0.06 \); both \( p > 0.05 \)). Multivariate linear regression for males found a significant effect of stress events on scores for the non-social scale (\( p = 0.01 \)) but not the social scale (\( p = 0.16 \)).

Multivariate linear regression models investigating the effect of PNMS on ADHD scores at age 2 years (Table 3) identified a significant positive association in males (\( p = 0.03 \)) and females (\( p < 0.01 \)). PNMS accounted for 1% of the variance in ADHD scores at age 2 years in both genders, after controlling for multiple confounds, including PDP scores. Child scores on the PDP subscale positively predicted child ADHD scores in males and females. Among males, maternal smoking of 11+ cigarettes per day during pregnancy accounting for an additional 1% of the variation in PDP scores at age 2 years. Of the potential confounders included in the models, child ADHD scores were positively associated with child PDP scores in both genders, while maternal baby blues symptoms were associated with higher PDP scores in females only. Among males, child’s age positively predicted PDP scores, while maternal consumption of alcohol several times a week or more during pregnancy was negatively associated with PDP scores.
pregnancy and maternal baby blues symptoms related to higher scores on the ADHD scale, while the child’s age at CBCL assessment and a parity of greater than one was associated with lower ADHD scores.

Attention deficit hyperactivity disorder and PDP scales correlated significantly and positively ($r = 0.38$ for males, $r = 0.34$ for females; both $p < 0.001$). Partialling out PNMS did not significantly diminish these correlations (partial correlation after controlling for PNMS: $r = 0.36$ for males, $r = 0.32$ for females, both $p < 0.001$).

Finally, because one item in the PNMS measure (“pregnancy problems”) could be confounded with perinatal complications, which have been associated with autism and ADHD, analyses were rerun after removing this one item from the PNMS measure. The results were not significantly different: the effect of PNMS without the pregnancy problems item on PDP scores was significant for boys ($p = 0.005$) but not girls ($p = 0.446$), and the effect of PNMS without the pregnancy problems item on ADHD scores was significant for both boys and girls ($p = 0.014$ and $0.028$, respectively).

Table 2 | Multivariate linear regression model for autistic trait scores at age 2 years.

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>STEP 1: COVARIATES</strong></td>
<td><strong>β</strong></td>
<td><strong>SE B</strong></td>
</tr>
<tr>
<td>Maternal age at conception</td>
<td>−0.05</td>
<td>0.01</td>
</tr>
<tr>
<td>Mother did not complete secondary school</td>
<td>−0.04</td>
<td>0.06</td>
</tr>
<tr>
<td>Father not present in family home</td>
<td>0.02</td>
<td>0.09</td>
</tr>
<tr>
<td>Family income &lt;$AUD24,000</td>
<td>0.00</td>
<td>0.06</td>
</tr>
<tr>
<td><strong>MATERNAL INTAKE DURING PREGNANCY</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking ≥7 cigarettes per week</td>
<td>−0.07**</td>
<td>0.13</td>
</tr>
<tr>
<td>Smoking 11+ cigarettes per day</td>
<td>0.00</td>
<td>0.09</td>
</tr>
<tr>
<td><strong>PARITY</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.00</td>
<td>0.07</td>
</tr>
<tr>
<td>&gt;1</td>
<td>−0.02</td>
<td>0.08</td>
</tr>
<tr>
<td>Baby blues symptoms</td>
<td>0.06</td>
<td>0.01</td>
</tr>
<tr>
<td>Child’s age at 2 year assessment</td>
<td>0.07*</td>
<td>0.18</td>
</tr>
<tr>
<td>ADHD score</td>
<td>0.35**</td>
<td>0.01</td>
</tr>
<tr>
<td>$R^2$ for step 1</td>
<td>0.17**</td>
<td>0.15**</td>
</tr>
<tr>
<td><strong>STEP 2: PREDICTORS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N stress events during pregnancy</td>
<td>0.10**</td>
<td>0.04</td>
</tr>
<tr>
<td>$ΔR^2$ for step 2</td>
<td>0.01**</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Change in $F_{model}$</td>
<td>9.22**</td>
<td>0.07</td>
</tr>
</tbody>
</table>

Moderate maternal smoking and alcohol intake during pregnancy, gestational age at birth, proportion of optimal birthweight, Apgar scores (5 min) and maternal country of birth were excluded from the analyses because they did not show a significant univariate association with PDP or ADHD scales for either sex. PDP, pervasive developmental problems (autistic traits) subscale. ADHD, attention deficit hyperactivity subscale. *$p < 0.05$; **$p < 0.01$.

Table 3 | Multivariate linear regression model for ADHD behavior scores at age 2 years.

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>STEP 1: COVARIATES</strong></td>
<td><strong>β</strong></td>
<td><strong>SE B</strong></td>
</tr>
<tr>
<td>Maternal age at conception</td>
<td>0.01</td>
<td>0.02</td>
</tr>
<tr>
<td>Mother did not complete secondary school</td>
<td>0.02</td>
<td>0.19</td>
</tr>
<tr>
<td>Father not present in family home</td>
<td>0.01</td>
<td>0.29</td>
</tr>
<tr>
<td>Family income &lt;$AUD24,000</td>
<td>−0.01</td>
<td>0.20</td>
</tr>
<tr>
<td><strong>MATERNAL INTAKE DURING PREGNANCY</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol ≥7 cigarettes per week</td>
<td>0.02</td>
<td>0.40</td>
</tr>
<tr>
<td>Smoking 11+ cigarettes per day</td>
<td>0.07*</td>
<td>0.28</td>
</tr>
<tr>
<td>11+ cigarettes per day</td>
<td>0.06</td>
<td>0.21</td>
</tr>
<tr>
<td>Parity = 1</td>
<td>−0.09**</td>
<td>0.25</td>
</tr>
<tr>
<td>Parity &gt; 1</td>
<td>0.09*</td>
<td>0.03</td>
</tr>
<tr>
<td>Baby blues symptoms</td>
<td>−0.08*</td>
<td>0.56</td>
</tr>
<tr>
<td>Child’s age at 2 year assessment</td>
<td>0.35**</td>
<td>0.10</td>
</tr>
<tr>
<td>PDP score</td>
<td>0.17**</td>
<td>0.15**</td>
</tr>
<tr>
<td><strong>STEP 2: PREDICTORS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N stress events during pregnancy</td>
<td>0.07*</td>
<td>0.11</td>
</tr>
<tr>
<td>$ΔR^2$ for step 2</td>
<td>0.01*</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Change in $F_{model}$</td>
<td>4.73*</td>
<td>7.50**</td>
</tr>
</tbody>
</table>

$ΔR^2$, pervasive developmental problems (autistic traits) subscale. ADHD, attention deficit hyperactivity subscale. *$p < 0.05$; **$p < 0.01$.

DISCUSSION

The aim of this prospective investigation was to explore for the first time the association between PNMS and autistic traits and ADHD behaviors in 2-year-olds. PNMS was significantly associated with ADHD behaviors in both genders after controlling for autistic traits. PNMS was significantly associated with autistic traits after controlling for the effect of ADHD behaviors in boys only. Autistic traits and ADHD behaviors were moderately correlated in our sample, and partialling out the effect of PNMS did not significantly lower the correlation. These findings suggest that PNMS is independently associated with both autistic traits and ADHD behaviors. In terms of effect size, PNMS explained 1% of the variance of both autistic traits and ADHD behaviors, after controlling for multiple covariates. Although small, this effect was significant for both scales (with the exception of females for autistic traits).

Although previous studies have shown an association between specific prenatal stressors (family discord, hurricanes) and retrospectively recalled stressors (stressful life events) with autism, this is the first study to use a prospective assessment of a broad array of common stressors as an indicator of PNMS, and to report an association with a broader quantitative measure of autistic traits in a preschool sample. In terms of the PNMS and ADHD literature, this study concurs with existing literature in showing a significant...
association between PNMS and ADHD behaviors, and it extends the literature by showing that this association still holds after controlling for a large number of covariates, including autistic traits, and that the association is significant in preschool children.

In terms of the covariates, it is notable that significant associations were observed between ADHD behaviors in 2-year-old boys and prenatal maternal smoking and postnatal maternal baby blues symptoms; findings that concur with some previous literature (e.g., Hay et al., 2003; D’Onofrio et al., 2008). A significant association was also observed between autistic traits in 2-year-old girls and postnatal maternal baby blues symptoms. The gender differences in these findings are intriguing but require replication in other samples.

The prospectively collected data, the large sample, and the statistical adjustment for a large number of covariates are clear strengths of this study. Several limitations of the current design should also be noted. Autistic traits and ADHD behaviors were based on maternal ratings. Correlated rater error would act to inflate the correlation between maternally rated PNMS and maternally rated autistic and ADHD behaviors in the offspring. However, parental assessment of problem behavior is a practical option for large preschool samples, and parents are familiar with behavior across time and a range of contexts. In terms of the measures, it was advantageous to employ scales from the CBCL, which have been widely used and assessed for reliability and validity (Achenbach and Rescorla, 2000). Nevertheless, the reliability, as assessed by Cronbach’s α, for the PDP scale was modest in the present sample. Error of measurement from these scales would act to decrease the phenotypic correlation between PNMS and offspring behavior, which would reduce the observable effect size of the association. As such, if anything this error of measurement acts to make the results more conservative.

The study did not include information on the mothers’ subjective experience of the stressors. There is some evidence that objective measures of stress are better than subjective measures at predicting later child outcome (Laplante et al., 2008). Finally, the sample was subject to a modest degree of attrition bias, with socially disadvantaged mothers less likely to participate. While the loss of these participants may have affected the results of this study, computer simulations using data from the Avon Longitudinal Study of Parents and Children, have found that selective dropout may have affected the results of this study. Several limitations of the current design should also be noted. Autistic traits and ADHD behaviors were based on maternal ratings. Correlated rater error would act to inflate the correlation between maternally rated PNMS and maternally rated autistic and ADHD behaviors in the offspring. However, parental assessment of problem behavior is a practical option for large preschool samples, and parents are familiar with behavior across time and a range of contexts. In terms of the measures, it was advantageous to employ scales from the CBCL, which have been widely used and assessed for reliability and validity (Achenbach and Rescorla, 2000). Nevertheless, the reliability, as assessed by Cronbach’s α, for the PDP scale was modest in the present sample. Error of measurement from these scales would act to decrease the phenotypic correlation between PNMS and offspring behavior, which would reduce the observable effect size of the association. As such, if anything this error of measurement acts to make the results more conservative.

The degree to which the mother’s genes influence PNMS will depend on the nature of the stressor. For example, hurricanes and wars are likely to be stressors that occur independently of the mother’s behavior and of her genotype, whereas the presence of family discord is likely to be partly correlated with the mother’s genotype (this is analogous to life events being distinguished as to whether they are independent or not necessarily independent of disease onset, e.g., Brown and Birley, 1968). In the present study, we included stressors such as “death of a close friend” that, in most cases, are unlikely to be related to the mother’s genotype, whereas “personal relationship problems” and “money problems” may be correlated with heritable components such as maternal temperament (gene–environment correlation). However, our measure of PNMS did not include enough items that might be deemed sufficiently independent of the mother’s genotype to test the association separately for these types of stressful events. The mother’s genotype will also affect the nature of the stress response, regardless of the type of stressor. Further research is needed; our tentative prediction is that the 1% variance that PNMS explained in ADHD behaviors/autistic traits in preschool children in our study is due to both genetic and environmental factors.

Finally, gene–environment interaction studies could reveal further information about causality. In this context there could be both maternal genotype × environment interactions and child genotype × environment interactions. That is, the effects of PNMS on autistic or ADHD traits may differ depending on the mother’s or the child’s underlying genotypes (e.g., Wakschlag et al., 2010). In this vein, a recent study reported a significant gene–environment interaction between the catechol O-methyltransferase (COMT) Val158Met polymorphism and maternal smoking during pregnancy that resulted in increased autistic-like stereotyped behavior in a sample of children with ADHD (Nijmeijer et al., 2010).

The effect size of the association (1%) was notably smaller than that reported in two previous studies on the association between prenatal state trait anxiety/stress and ADHD behaviors in middle childhood which reported effect sizes of 22–23% (Van den Bergh and Marcoen, 2004; Rodriguez and Bohlin, 2005). The different effect sizes may be due to the different prenatal stress variables used: prenatal state trait anxiety versus common stressful life events (employed here), as well as the much larger number of confounding variables that were controlled for in the present study, including autistic traits, which are significantly associated with both PNMS and ADHD. For example, the effect size of the association found in our study was three times greater before all the confounding factors were controlled for. Therefore a study that does not control for these confounders will give inflated estimates of the degree of association. It seems likely that removing the effects of covariates will have
removed variation explained by both genetic and environmental influences. An additional reason for the relatively small effect size compared to studies of older children is the reliability of measurement of ADHD behaviors and autistic traits in 2- to 3-year-olds. The literature on early screening for ASDs has shown that behaviors show a degree of fluctuation across the preschool period and reliable measurement can be challenging (Yirmiya and Charman, 2010). Both ASD and ADHD diagnoses are usually not confirmed until children are slightly older. As such, it might be that the effect size of the association between PNMS and offspring behaviors, in this case those characteristic of autism and ADHD, gets larger as offspring develop and behaviors become more stable.

In conclusion, this study suggests that PNMS, in the form of typical stressful life events, such as divorce or a residential move, show a small but significant association with both autistic traits and ADHD behaviors independently, in offspring at age 2 years, after controlling for multiple antenatal, obstetric, postnatal, and sociodemographic covariates. The findings suggest that intervention that seeks to minimize the number of stressors that a woman experiences during pregnancy could have an effect to reduce the risk of the offspring developing autistic traits or ADHD-like behaviors. These results lay the foundations for future research using epigenetic, cross-fostering, and gene–environment interaction designs to identify the causal processes underlying these associations.

ACKNOWLEDGMENTS

The authors would like to acknowledge the National Health and Medical Research Council (NHMRC) for their long term contribution to funding the study over the last 20 years. Core Management of the Raine Study has been funded by the University of Western Australia (UWA), the UWA Faculty of Medicine, Dentistry and Health Sciences, the Raine Medical Research Foundation, the Telethon Institute for Child Health Research, and the Women's and Infants' Research Foundation. The 2-year follow-up was funded by the NHMRC and the Raine Medical Research Foundation. The authors are extremely grateful to the study participants and their families as well as the Raine Study team for cohort co-ordination and data collection.

REFERENCES


Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 28 September 2010; paper pending publication: 16 October 2010; accepted: 25 November 2010; published online: 19 January 2011.


This article was submitted to Frontiers in Developmental Psychology, a specialty of Frontiers in Psychology.

Copyright © 2011 Ronald, Pennell and Whitehouse. This is an open-access article subject to an exclusive license agreement between the authors and Frontiers Media SA, which permits unrestricted use, distribution, and reproduction in any medium, provided the original authors and source are credited.