Psychiatry Research 219 (2014) 353–360

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Prenatal maternal stress predicts autism traits in 6½ year-old children: Project Ice Storm

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ARTICLE INFO

Article history:
Received 28 October 2013
Received in revised form
13 March 2014
Accepted 16 April 2014
Available online 10 May 2014

Keywords:
Prenatal maternal stress
Autism spectrum disorder
Natural disaster
Sex differences
Dimensional model
Developmental psychopathology
Pregnancy

ABSTRACT

Research implicates prenatal maternal stress (PNMS) as a risk factor for neurodevelopmental disorders; however few studies report PNMS effects on autism risk in offspring. We examined, prospectively, the degree to which objective and subjective elements of PNMS explained variance in autism-like traits among offspring, and tested moderating effects of sex and PNMS timing in utero. Subjects were 89 (46F/43M) children who were in utero during the 1998 Quebec Ice Storm. Soon after the storm, mothers completed questionnaires on objective exposure and subjective distress, and completed the Autism Spectrum Screening Questionnaire (ASSQ) for their children at age 6½. ASSQ scores were higher among boys than girls. Greater objective and subjective PNMS predicted higher ASSQ independent of potential confounds. An objective-by-subjective interaction suggested that when subjective PNMS was high, objective PNMS had little effect; whereas when subjective PNMS was low, objective PNMS strongly affected ASSQ scores. A timing-by-objective stress interaction suggested objective stress significantly affected ASSQ in first-trimester exposed children, though less so with later exposure. The final regression explained 43% of variance in ASSQ scores; the main effect of sex and the sex-by-PNMS interactions were not significant. Findings may help elucidate neurodevelopmental origins of non-clinical autism-like traits from a dimensional perspective.

1. Introduction

Autism spectrum disorders (ASD) affect approximately 1% of 8-year-old children, disproportionately affecting males more than females (4.5:1). Prevalence rates increased by 57% from 2002 to 2006 in the United States (Center for Disease Control, 2009) and by 150% in Canada from 1998 to 2004 (Autism Society of Canada, 2004). This surge prompted increased efforts to elucidate ASD etiology, with substantial evidence indicating a genetic contribution (Buxbaum, 2009). The absence of perfect concordance rates among monozygotic twins, however, highlights the contributory role of environmental factors (Rosenberg et al., 2009). High heritability (e.g., 90–93%) in the context of less than 100% concordance implies polygenic influences rather than a single gene operating in Mendelian fashion (Bailey et al., 1995). This is consistent with a growing appreciation (Lawler et al., 2004) that many complex clinical presentations reflect the interactions among genetic susceptibility and environmental exposures at particular stages of development (see Walder et al., 2012a).

The literature suggests a role of noxious prenatal factors (viral infections, maternal smoking in early pregnancy, small for gestational age at birth, fetal hypoxia during delivery, and parental psychopathology) and male vulnerability in risk for psychiatric disorders with neurodevelopmental origins including ASD (Gardener et al., 2009; Pardo and Eberhart, 2007; Walder et al., 2012a, 2012b). Accentuated male vulnerability is supported by studies showing that males are more sensitive than females to effects of perinatal risk factors and other disruptions in early neurodevelopment (Walder et al., 2012a; Walker et al., 2002).

Prenatal maternal stress (PNMS), such as exposure to independent life events (e.g., hurricanes and tropical storms (Kinney, 2001; Kinney et al., 2008a), death of a pregnant woman's husband (Huttenen and Niskanen, 1978), and invasions by foreign forces (van Os and Selten, 1998)) have been associated with increased risk for autism, depression and schizophrenia among exposed offspring. In an historical analysis of the impact of PNMS caused by 10 severe weather events in Louisiana, Kinney et al. (1999, 2008a) reported significantly increased autism rates as a function of prenatal exposure to storms rated as severe by the National

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http://dx.doi.org/10.1016/j.psychres.2014.04.034
0165-1781/

Weather Service, increasing the usual prevalence rate from 5/10,000 births to 13/10,000 births. Two recent population studies, however, did not support a link between ASD risk and prenatal stress following, in one study, maternal bereavement (Li et al., 2009) and, in a second study, following a wide range of relatively rare stressful life events during pregnancy (Rai et al., 2012). These discrepant findings may be attributable to methodological factors such as type of stress exposure; for example, natural disaster research involves sudden-onset exposure to a more uniform type of stressor than do studies simultaneously examining a wide range of stressors with potentially gradual onset in many cases.

The manner in which prenatal insults are expressed may be a function of the timing of exposure during gestation (Beversdorf et al., 2005; Goldstein and Walder, 2006; Huttenen and Niskanen, 1978; King and Laplante, 2005). Timing is of particular interest given that disruptions at different periods may differentially impair specific fetal central nervous system (CNS) developmental events such as maturation of the brainstem, limbic system, and neocortex (Celani, 2003). Evidence among humans is mixed regarding gestational periods during which disruption is associated with increased risk of cognitive and behavioral difficulties and psychiatric disorders. Stressors occurring during early pregnancy (e.g., 2nd month of gestation) have been linked to increased incidence of neurodevelopmental disorders such as schizophrenia (Malaspina et al., 2008). Alternatively, some research points to PNMS exposure in middle and late gestation as critical for risk for neurodevelopmental disorders among offspring (Cederlund and Gillberg, 2004; Davis et al., 2007; Huttenen and Niskanen, 1978; Kinney et al., 2008a; O'Connor et al., 2003). Timing effects appear to depend, in part, on the type of exposure and the outcome measure (Charil et al., 2010a). In Kinney et al.'s (2008a, 2008b) study of prenatal exposure to tropical storms in Louisiana, the effect on autism risk was greatest for children exposed during certain months of pregnancy, with autism prevalence rates elevated from the baseline of 5/10,000 to 11/10,000 when exposed during the last 8 weeks, and to 18/10,000 when exposed during months 5 or 6, of pregnancy. Storm severity and timing interacted such that for children exposed in months 5, 6, 9 or 10 (dividing 40 weeks into 4-week months) of pregnancy, for storms classified as low, moderate and severe intensity, the relative risks for autism were 3, 10, and 27/10,000 births, respectively. These studies highlight the importance of considering potential interaction effects of severity of exposure or child sex by timing of exposure.

Clues to the etiology of major mental disorders may be found in the study of subclinical levels of disturbance. As reflected in the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5; American Psychiatric Association, 2013), emerging contemporary conceptualizations of psychiatric disorders consider dimensional perspectives. Psychiatric diagnosis captures a magnitude of dimensional traits that falls beyond a particular clinical threshold. Recent research supports the notion of a continuum of autism traits/symptoms (Constantino, 2009; Robinson et al., 2011). Closer examination of the relationship of risk factors with dimensional traits at various points along this continuum holds potential for elucidating underlying etiology, including neural mechanisms of illness (including ASD) manifestation. Various clinical implications include the possibility that subclinical symptoms may have functional consequences that fall short of impairment.

Consistent with a continuum (or dimensional) model of psychiatric disorders, PNMS predicts cognitive and behavioral features that are associated with clinical or subclinical levels of ASD, such as poorer cognitive and language development in infancy and childhood (Huizink et al., 2002a; Laplante et al., 2004, 2008), more negative temperaments in infancy (Gutteling et al., 2005; Huizink et al., 2002b), and greater behavioral problems during childhood (O'Connor et al., 2002; Van den Bergh and Marcoen, 2004). One recent population-based, prospective study found that prenatal maternal exposure to typical stressful life events (e.g., divorce, residential move) was associated with autism-like traits among male (but not female) offspring at 2 years of age, independent of attention deficit hyperactivity disorder and potential confounds such as obstetric and sociodemographic factors (Ronald et al., 2011).

Despite growing evidence linking PNMS with neurodevelopmental disorders (including subclinical presentations), the retrospective design of many studies limits researchers' ability to understand underlying mechanisms. Specifically, it remains unclear whether it is the mere objective exposure to the stressful event, and/or the pregnant woman's subjective reaction to the event, that accounts for associations between these events and mental health outcomes in the prenatally exposed offspring. Studying independent life events, such as natural disasters or spousal death, minimizes threat to internal validity posed by potential self-selection bias in life event studies, and offers a more uniform type of exposure than studies that include a wide range of stressful life events. Moreover, natural disasters often have a sudden onset which allows for identifying precise timing of PNMS exposure. Finally, only prospective studies enable assessment and disentanglement of maternal objective exposure and subjective distress soon after the event occurs. To date, we are unaware of any prior studies designed to concurrently address the aforementioned methodological challenges that face the complex investigation of prenatal determinants of early childhood mental health problems that are believed to have early neurodevelopmental origins.

As part of Project Ice Storm, the current study aimed to determine the association between PNMS and severity of autism-like traits in a sample of prenatally exposed children at age 6½ years. The prenatal stressor was a series of freezing rain storms (from January 5–9, 1998) that deprived more than three million people of electricity for as long as 45 days during the coldest months of the year, across the southern region of the Canadian province of Quebec. The ice storm crisis caused significant logistical disruptions, health hazards, and 30 deaths. According to the Insurance Bureau of Canada (www.ibc.ca), the financial costs rendered it the worst natural disaster in Canadian history.

In line with a dimensional model of psychopathology, we hypothesized that greater severity of objective and/or subjective PNMS would be associated with more severe autism-like trait ratings of the offspring during early childhood, with the magnitude of this effect being greater among boys than girls. Second, since studies have linked timing of teratogen exposure – particularly early stages of fetal development – with increased risk for ASD, timing effects were explored. Finally, the effects of potential confounds (e.g., maternal and perinatal factors) were considered.

2. Method

2.1. Participants

Following the ice storm, we identified 1140 women who had been pregnant during the ice storm with help from the offices of doctors who deliver babies in the four regional hospitals south-east of Montreal. The offices addressed questionnaire packets to patients meeting inclusion criteria: pregnant on January 9, 1998, or became pregnant in the 3 months after the storm, and living in the affected area; over age 18 years; French-speaking. The initial packets were mailed June 1, 1998 to which there was a 15% response rate ($n=224$). Little is known about the nonresponders beyond each woman's date of birth, due date, and the region where their physicians worked. From this information, it was calculated that responders were an average of one year older than non-responders ($p < 0.01$), were exposed to the ice storm later in pregnancy and, thus, were more likely to have been past their due date on June 1 (38% versus 25%; $p < 0.01$), and were more likely to have been from rural areas (19.4% response rate) than from suburban areas (11.2% response rate; $p < 0.01$). Of the 224 respondents to the initial questionnaire,

178 women agreed to further contact. A handful of subjects miscarried or had still births, one mother died, and a number of women were lost to follow-up in the initial years due to lack of funding. By the time first major funding was obtained to test the children at age 5½ years, the pool of available subjects was reduced to approximately 140.

Eighty-nine women completed the questionnaire packet, sent by mail, when their children were 6½ years of age. These women were in their first ($n=28$), second ($n=33$) or third ($n=28$) trimester of pregnancy during the ice storm; the pre-conception exposed group was not included in the results presented here. Offspring included 43 boys and 46 girls. The women in Project Ice Storm have a higher socioeconomic status and education than the regional averages. According to the Hollingshead classification, based on maternal and paternal education and occupation, 63 families (70.8% of the sample) were in the upper-middle or upper socioeconomic class at the time of the first questionnaire, 23 families (25.8%) were in middle or lower-middle class, and only three families (3.4%) were in the lower socioeconomic class.

2.2. Instruments

2.2.1. Predictor variables

The severity of storm-related events experienced by pregnant women was assessed based on responses to the first set of questionnaires sent June 1, 1998; specifically, the measures of objective hardship (Storm32) and subjective distress (IES-R).

2.2.1.1. Objective hardship. The Storm32 Scale (King and Laplante, 2005) included questions specific to the ice storm such as days without electricity, danger due to falling ice or tree branches, and spending time in temporary shelters. Items tapped four categories of exposure used in other disaster studies; namely, Threat, Loss, Scope, and Change (Bromet and Dew, 1995). Each natural disaster presents unique experiences; thus, questions pertaining to each category are tailor-made. Each dimension was scored on a scale of 0–8, ranging from low exposure to high exposure. A total objective PNMS score was calculated by summing scores across all four dimensions using McFarlane's approach (McFarlane, 1988). In the present study, scores ranged from 0 to 24, out of a possible 32.

2.2.1.2. Subjective distress. The mothers' distress related to the ice storm was assessed using a validated French adaptation (Brunet et al., 2003) of the Impact of Event Scale – Revised (IES–R; Weiss and Marmar, 1997). This scale is one of the most widely used measures in the disaster literature to assess distress following trauma. The 22-item instrument provides scores for symptoms in three scales relevant to post-traumatic stress disorder; namely, Intrusive Thoughts, Hyperarousal, and Avoidance. Scale items were written to reflect the mothers' symptoms relative to the ice storm crisis. For example, "When I think about *the ice storm*, my heart beats faster", or "Images of *the ice storm* suddenly appear in my thoughts". Participants respond on a 5-point (0–4) Likert scale, from 'not at all' to 'extremely', to reflect how they felt over the preceding seven days. Total scores were used in all analyses. IES-R scores are commonly described as: either "low" = 0 to 8 (sometimes < 10), "medium" = 9–19 (sometimes 10 to 19), or "high" >= 19 (Church and Vincent, 1996; Stadlmayr et al., 2006).

2.2.1.3. Trimester of exposure. The trimester of pregnancy during which the women were exposed to the ice storm was determined using the difference in days between the mothers' anticipated due date and January 9, 1998, the date of the ice storm peak when the downtown core of Montreal was completely blacked out. Specifically, 3rd trimester exposure corresponded to due dates between 0 and 93 days following January 9; 2nd trimester exposure corresponded to between 94 and 186 days; and 1st trimester exposure corresponded to between 187 and 279 days between January 9 and the due date.

2.2.2. Outcome measure

Autism Spectrum Screening Questionnaire (ASSQ; Ehlers et al., 1999). The ASSQ is a 27-item checklist assessing traits and symptoms (e.g., social interactions, communication, restricted and repetitive behaviors, motor clumsiness, and motor and vocal tics) characteristic of Asperger syndrome and other high-functioning ASDs in children and adolescents with normal intelligence or mild mental retardation (Ehlers et al., 1999). This measure was demonstrated to have excellent test–retest reliability (Pearson r) over a 2-week period for parent ASSQ total scores ($r=0.96$, $n=86$, $p<0.0001$), excellent inter-rater reliability ($r=0.66$; $n=105$; $p<0.0001$) and reasonable divergent validity ($r=0.70$; $n=102$; $p<0.0001$) (Ehlers et al., 1999). The ASSQ was designed as a screening instrument to determine whether a more comprehensive clinical evaluation is required. The ASSQ can be completed by any person familiar with the child. The 27 items are rated on a 3-point scale (0 indicating "normality", 1 "some abnormality", and 2 "definite abnormality"). The range of possible scores is 0 to 54, with higher scores indicating higher degree of autism symptomatology; a score of 13 is the suggested cut-off for further evaluation (Ehlers et al., 1999).

2.2.3. Covariates

Maternal factors. In order to control for psychosocial factors other than the ice storm-related stress, we assessed the mothers' anxiety (June 1998 and current levels) using the anxiety scale of the 21-item General Health Questionnaire (GHQ; Goldberg, 1972). We asked mothers about major life events using the Life Experiences Survey (LES; Sarason et al., 1978) which was included in the 6-month post-partum questionnaire (covering the period from 6 months before conception to 6 months following delivery) and 6½ years of age (covering the previous 12 months). We assessed maternal postpartum depression at 6 months using the Edinburgh Postpartum Depression Scale (EPDS; Cox et al., 1987). Parental socioeconomic status (SES) was computed using Hollingshead index criteria (Hollingshead, 1973).

2.2.3.1. Perinatal factors. Because perinatal factors are frequently associated with developmental outcomes (Siegel, 1982), gestational age, indices of fetal growth, and number of reported pregnancy and birth complications were included as covariates. Measures of fetal growth included ponderal index (birth weight/birth length^3), and head circumference to body length ratio (HC:BL). These measures were calculated using information transcribed from the "Vaccination Booklet", which all mothers in Quebec receive from the hospital upon discharge with their newborn, and which they transcribed into the 6-month postpartum questionnaire. Obstetric complications were obtained by maternal recall in the 6-month questionnaire using an adaptation of the checklist used by Kinney (Jacobsen and Kinney, 1980) and, when available, by examination of medical charts. Obstetric complication severity was rated with the McNeil–Sjostrom Scale (McNeil and Sjostrom, 1995) and the number of moderate-to-severe complications was used in analyses.

2.3. Procedures

The Research Ethics Board of the Douglas Mental Health University Institute approved the research protocols for this study. The first questionnaire, mailed on June 1, 1989, included informed consent documents, the items for scoring Storm32, the IES-R, the GHQ, and demographic variables needed for computing the Hollingshead Index. Six months after each woman's expected delivery due date, a second questionnaire packet was mailed to those who gave permission for follow-up, which included the LES, the EPDS, the GHQ, and questions about pregnancy complications and birth outcomes. When the children were 6½ years of age, another questionnaire was mailed to the mothers; this included the LES, GHQ, and ASSQ.

2.4. Statistical analyses

Pearson product–moment correlation coefficients were calculated among all variables. Means (M) and standard deviations (S.D.) were also calculated for all variables.

The outcome variable, ASSQ, demonstrated a severe L-shaped positively skewed distribution. Therefore, an inverse transformation was conducted on the ASSQ variable as suggested by Tabachnick and Fidell (1989). Thus, *higher scores reflect less severe autism-like traits*.

We conducted hierarchical multiple linear regression analyses, regressing ASSQ scores on independent variables by adding them in successive blocks (either forcing them to enter, or allowing them to enter stepwise) in order to determine the significance of the additional variance explained by each block. For stepwise blocks, p-values for enter and removal were set at 0.10 and 0.15, respectively, because of the relatively small sample size. Maternal and perinatal factors were allowed to enter into the first block of the model using the stepwise procedure. Child's sex, timing of exposure, objective hardship, and subjective distress were each individually forced to enter the model in the subsequent four blocks. Finally, the interaction terms of objective hardship × subjective distress, objective hardship × timing of exposure, subjective distress × timing of exposure, objective hardship × sex of the child, and subjective distress × sex were allowed to enter into the final block of the model using the stepwise procedure.

3. Results

3.1. Descriptive statistics

Means and standard deviations for all variables are presented in Table 1. Untransformed average ASSQ scores were low; six children (6.8%; two males, four females) scored at or above the recommended screening cut-off score of 13. Average ASSQ scores were higher among boys (mean=4.419, S.D.=3.929) than girls (mean=3.978, S.D.=4.69); this difference was significant after data were log transformed ($t(87)=-2.55$, $p=0.012$).

Table 1
Correlation coefficients among all outcome and predictor variables, and mean and standard deviations of all outcome and predictor variables.

		1	2	3	4	5	6	7	8	9	10	11	12	13	14	*M*	S.D.
Outcome variable																	
1	ASSQ (inverse)															4.2	4.3
Child variables																	
2	Gestational age (weeks)	0.11	–													39.6	1.8
3	Ponderal index	−0.07	0.35***	–												27.6	3.7
4	Head circumference – body length ratio	−0.22*	0.03	0.65***	–											68.9	3.4
Maternal variables																	
5	Anxiety (6 months)	−0.10	−0.04	0.05	0.03	–										0.3	0.3
6	Anxiety (6½ years)	−0.17	−0.07	0.01	0.02	0.95***	–									0.3	0.3
7	Life events (6 months)	−0.22*	0.02	0.02	−0.03	0.06	0.08	–								5.1	3.6
8	Life events (6½ years)	−0.20†	−0.03	0.03	−0.02	0.07	0.08	0.96***	–							4.1	3.0
9	Postpartum depression	−0.27*	0.01	−0.01	0.01	0.17	0.11	0.03	0.03	–						5.7	3.9
10	Obstetric complications	−0.07	−0.35**	−0.28**	−0.09	0.10	0.11	0.02	−0.08	0.01	–					4.4	2.9
11	Age at child's birth	−0.06	−0.05	−0.15	−0.12	0.11	0.13	0.15	0.13	−0.12	0.15	–				30.4	4.7
12	Socioeconomic status	−0.17	0.11	0.14	0.14	0.14	0.14	−0.07	−0.09	0.26*	−0.12	−0.28**	–			27.3	12.6
Ice Storm variables																	
13	Objective hardship	−0.43***	0.10	0.22*	0.35**	0.07	0.05	0.23*	0.18	−0.03	0.05	0.16	0.01	–		10.6	4.4
14	Subjective distress	−0.45***	−0.03	0.13	0.08	0.29**	0.30**	0.13	0.12	0.20†	0.08	0.04	0.19†	0.38***	–	10.0	10.5
15	Timing of exposure (days)	0.10	0.13	−0.12	−0.27*	0.11	0.13	0.14	0.10	0.01	−0.03	−0.09	0.17	−0.18	0.05	143.4	78.8

Note: all tests are two-tailed †p < 0.10.

* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.

Table 2
Summary of linear hierarchical regression analyses; each variable entered in a separate block.

Predictor variables	Values in final model				Values after initial entry of each variable				
	B	SE *B*	*β*	*B* *p*-value	R^2	ΔR^2	F*	ΔF	ΔF *p*-value
Constant	1.199	0.239							
Postpartum depression[a]	−0.022	0.008	−0.256	0.007	0.070	0.070	6.555*	–	0.012
Life events (6 months)[a]	−0.015	0.008	−0.160	0.078	0.116	0.046	5.634**	4.453	0.038
Child's sex (0=male)[b]	0.075	0.060	0.111	0.214	0.278	0.048	5.554**	4.884	0.030
Timing of exposure (days)[b]	−0.001	0.001	−0.324	0.157	0.341	0.011	4.459**	1.146	0.287
Objective hardship[b]	−0.065	0.017	−0.837	< 0.001	0.363	0.131	7.310***	15.612	< 0.001
Subjective distress[b]	−0.027	0.008	−0.842	0.001	0.367	0.061	7.915***	7.899	0.006
Objective hardship × subjective distress[a]	0.002	0.001	0.747	0.019	0.401	0.034	7.738***	4.597	0.035
Objective hardship × timing of exposure[a]	0.000	0.000	0.485	0.061	0.427	0.026	7.443***	3.620	0.061

* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.
[a] Stepwise entry.
[b] Forced to enter equation.

3.2. Correlations

Correlation coefficients for all variables are presented in Table 1. Higher scores on both objective and subjective PNMS were significantly correlated with more severe ASSQ scores. Objective and subjective PNMS were moderately, but significantly, positively correlated with each other. Of the remaining variables, only postpartum depression, life events (at 6 months and 6½ years), and HC:BL ratio were significantly related to ASSQ scores. Since the two maternal anxiety and life events variables were highly correlated, only the 6-month measures were included in the regression analysis.

3.3. Hierarchical linear regression analyses

As seen in Table 2, maternal postpartum depression entered the equation first, and explained 7.0% of the variance in the ASSQ scores ($p=0.012$): more severe maternal depression at 6 months was associated with higher ASSQ scores in the child. In the next block, perinatal maternal life events explained an additional 4.6% of the variance ($p=0.038$): more life events were associated with higher ASSQ scores. Male sex of the child was associated with higher ASSQ scores at entry into the equation, explaining an additional 4.8% of the variance at entry ($p=0.030$). The main effect of timing of exposure to the ice storm was not a significant predictor. Objective hardship explained an additional 13.1% of the variance at entry ($p < 0.001$): higher objective hardship scores were associated with higher ASSQ scores. Subjective distress explained an additional 6.1% of the variance at entry ($p < 0.006$): higher maternal subjective distress was associated with higher ASSQ scores.

The objective hardship × subjective distress interaction term explained an additional 3.4% of the variance in the ASSQ scores ($p=0.035$ at entry). Using the principle of regions of significance (Aiken and West, 1991; Hayes and Matthes, 2009; Preacher et al., 2006), we applied the results of the interaction to the program

provided by Preacher et al. (2006) (http://www.quantpsy.org/interact/mlr2.htm), which locates the point on the *x*-axis at which there is a significant ($p < 0.05$) effect of the second independent variable on the dependent variable. As illustrated in Fig. 1, when setting all other independent variables at their mean, high subjective distress levels were associated with more severe ASSQ scores regardless of the level of objective hardship. However, when subjective distress levels were below a value of 9.1, which is squarely within the "moderate" range, objective hardship was significantly related to ASSQ scores.

Finally, the objective hardship × timing of exposure interaction explained an additional 2.6% ($p = 0.061$) of the variance in ASSQ scores. As illustrated in Fig. 2, testing for the region of significance revealed that objective stress had a significant effect on ASSQ scores for children exposed during the first trimester, that is, before day 86 of pregnancy.

Together, these variables explained 42.7% of the variance in ASSQ scores in the final equation, for which all variables except sex and timing were statistically significant, and for which life events and the objective stress × timing interaction were significant at trend level ($p < 0.10$).

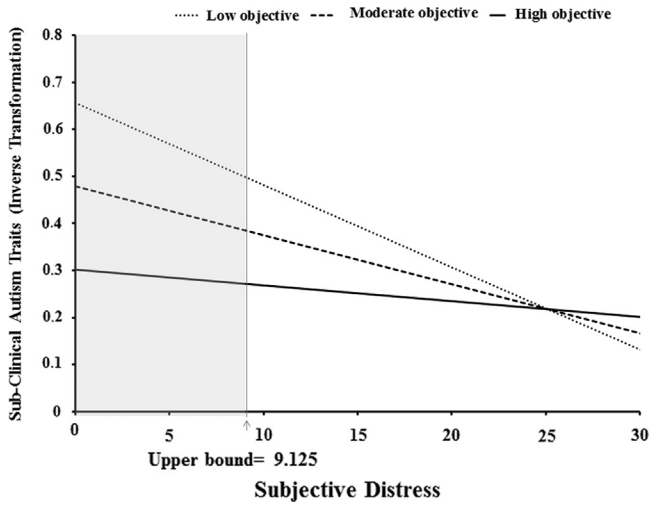

Fig. 1. Relationship of subjective PNMS with autism traits as a function of objective hardship (*Note*: lower scores on *Y*-axis denote more severe autism-like traits). Regression lines were predicted by holding all control variables at their means, and calculating slopes for low-, moderate-, and high-objective stress levels using regression coefficients from the final model. The shaded area indicates the region of significance for the observed interaction. For children whose mother's subjective PNMS scores were 9.125 or less, there was a significant association between objective stress severity and ASSQ scores.

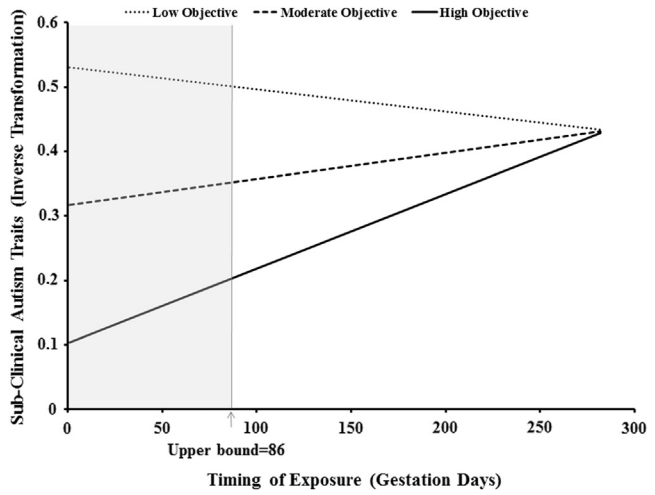

Fig. 2. The moderating role of timing of prenatal stress exposure in the relationship between objective hardship and autism traits (*Note*: lower scores on *Y*-axis denote more severe autism-like traits). Regression lines were predicted by holding all control variables at their means, and calculating slopes for low-, moderate-, and high-objective stress levels using regression coefficients from the final model. The shaded area indicates the region of significance for the observed interaction. For children exposed to the ice storm at 86 gestational days or less, there was a significant association between objective PNMS and ASSQ scores.

4. Discussion

The goal of this study was to use a prospective design to determine the extent to which PNMS resulting from a major natural disaster predicted autism-like traits among non-clinical offspring in early childhood. Secondarily, we aimed to examine the moderating effects of the child's biological sex and timing of exposure, and potential effects of other maternal and child factors, on the association between PNMS and autism-like traits. As hypothesized, and consistent with some prior literature evidencing that autism spectrum traits (Ronald et al., 2011) and autism-prevalence rates (Kinney et al., 2008a) increased with exposure to increasingly severe stress exposure, the current study found both objective hardship and subjective distress were associated with more severe autism-like traits, although most children scored in the subclinical range. Findings are not, however, consistent with two recent population studies (Li et al., 2009; Rai et al., 2012). This discrepancy may be attributable to differences in nature of stress exposure (e.g., sudden-onset of uniform natural disaster versus variable stressors with more diffuse onset).

In the final multivariate model, greater objective hardship and subjective distress strongly predicted autism-like traits in exposed offspring, above and beyond contributions of other predictors and potential confounds. Consistent with some prior literature demonstrating maternal psychopathology and life events are significant risk factors for ASD (Larsson et al., 2005), postpartum depression and perinatal life events (but not other potential confounds) contributed substantially to the model, accounting for 11.6% of variance in children's ASSQ scores.

Child sex accounted for a significant 4.8% of the variance in ASSQ scores in the expected direction: male sex was associated with more severe ASSQ scores. This association did not hold, however, after timing of exposure and the two interaction terms entered into the model. Contrary to prediction, child sex was not a moderator, suggesting males were not more vulnerable to PNMS effects than females. This may have been due to the relatively small sample size and, in turn, limited power to detect statistically significant interactions.

The significant objective hardship × subjective distress interaction suggests that high levels of subjective distress were associated with increased levels of autism-like traits regardless of the magnitude of objective hardship. When subjective distress was low, however, more severe objective hardship was strongly associated with ASSQ scores. Thus, fairly uniformly high autism-like traits among children whose mothers reported high subjective distress in response to the ice storm were similar among children whose mothers experienced high objective hardship, irrespective of subjective distress levels. In this way, both objective and subjective PNMS appear to play important, independent roles in exposed offspring outcome. There also lies the possibility, however, that the 6-month lag between time of ice storm occurrence and stress assessment may have accounted for the apparent uniform effect of high subjective distress on autism-like traits irrespective of objective stress.

Our study and that of Kinney et al. (2008a) concluded that timing of PNMS exposure during pregnancy moderates stress effects. In contrast to Kinney et al. (2008a), who found mid- and late-pregnancy exposure to tropical storms were associated with increased autism risk, our findings (i.e., moderately significant objective hardship × timing of exposure) suggest early-pregnancy exposure to high levels of maternal objective hardship was associated with increased levels of autism-like traits. Notably, a recent population study found prenatal maternal bereavement did not increase risk, and hazards ratios were comparable irrespective of nature and timing (7–12 or 0–6 months before pregnancy and 1st, 2nd or 3rd trimester) of exposure. Again, discrepancies across this literature may be related to methodological differences (e.g., nature/uniformity, severity and duration of stress exposure), as well as complexity of co-occurring factors not readily controlled across studies. As such, findings are interpreted with caution with respect to drawing conclusions about prenatal periods that may render individuals more susceptible to effects of adverse exposures. More research in this domain is warranted.

Our results extend recent literature highlighting the importance of temporal-specificity of effects of prenatal disruptions on integrity of fetal and postnatal development (Mueller and Bale, 2007, 2008), including programming of stress pathways (Bale, 2010). High prenatal anxiety during mid-gestation has been linked to neuroanatomical integrity (e.g., diminished gray matter density) in 6- to 9-year-old children (Buss et al., 2010). Moreover, prenatal disruptions and adverse exposures during early- to mid-pregnancy have been shown to predispose to later development of psychiatric disorders (e.g., Malaspina et al., 2008), although some studies point to mid- to late-prenatal periods (e.g., Kinney et al., 2008b).

Taken together with the existing literature, the current findings in a non-clinical sample support a dimensional model of autism-like traits in which expression is influenced by adverse prenatal events, partly in a time-sensitive manner. Accordingly, symptoms vary across a continuum from the non-clinical to subclinical traits, to clinically significant symptoms, with more prominence among males in general, and greater vulnerability to exposures during early pregnancy. This fits nicely with evidence supporting dimensional conceptualizations of psychiatric symptoms and associated neurobiological factors (Daly et al., 2012; Walder et al., 2012b).

While a comprehensive discussion is beyond the scope of this paper, we speculate as to some potential theoretical mechanisms by which PNMS may impact offspring autism traits from a developmental perspective. First, it is possible that PNMS influences developmental outcome via programming of the fetal hypothalamic-pituitary-adrenal (HPA) axis, a key system involved in the mammalian biological stress response (Charil et al., 2010b; Glover et al., 2010; Weinstock, 2005). This makes sense in light of evidence that HPA dysregulation is linked with a variety of adverse psychiatric conditions such as autism (Corbett et al., 2008) and psychosis during premorbid and prodromal periods (Walder et al., 2010; Walker et al., 2010, 2001), and psychiatric traits in a non-clinical sample (Walder et al., 2012b). HPA dysregulation is clearly not disorder specific; rather, it is evident in a wide range of neuropsychiatric disorders (including several with neurodevelopmental origins). Second, animal studies suggest that maternal stress and anxiety may impact fetal programming via the placenta, given that it controls fetal exposure to the maternal environment (O'Donnell et al., 2009). PNMS may reduce blood flow to the uterus, impact transplacental transport of maternal hormones, and influence release of placental corticotrophin-releasing factor to the intrauterine environment, all of which may adversely impact fetal development (de Weerth et al., 2005; King et al., 2005; Mulder et al., 2002). Finally, epigenetic influences are an important consideration. Epigenetics refers to heritable changes in gene expression independent of variation in DNA sequence, and a mechanism of environmental influence on gene expression (see Bale, 2011). Epigenetic mechanisms involve DNA methylation, histone acetylation and noncoding RNAs (e.g., microRNAs). Mounting evidence suggests early developmental factors such as prenatal stress, maternal diet, behavior and infection may influence programming of neurodevelopmental disorders via epigenetic pathways (Bale, 2011). One example relevant to ASD is Methyl CpG binding protein-2 (MeCP2). MeCP2 helps regulate neurodevelopment via neuronal activity-dependent synaptic maturation, particularly during postnatal brain development (see Gonzales and LaSalle, 2010).

With regard to sex differences, in the context of hippocampal abnormalities in ASDs (Brambilla et al., 2003; Mengotti et al., 2011), both sexual differentiation of hippocampal dendritic spine density and opposing effects of stress (Shors et al., 2001), and opposing sex effects of prenatal maternal restraint stress on hippocampal plasticity (Darnaudery and Maccari, 2008) have been proposed to account for sex differences in behavior. Moreover, PNMS has been shown to decrease aromatase activity in the fetal rat brain, which may contribute to structural neuroanatomic and behavioral changes induced by prenatal stress (see Weinstock, 2011). It is possible that the hippocampus and amygdala, both highly sexually dimorphic and involved in regulating the neurobiological stress response and implicated in autism (Aiello and Whitaker-Azmitia, 2011), are sensitive to early neurohormonal disruptions during prenatal development and are prime candidates in sexually differentiated outcomes in ASDs, in a manner similar to that discussed in relation to neurodevelopmental risk for psychosis (Walder et al., 2006). In addition to early organizational effects of hormones that may set the stage for vulnerability, there is the possibility of later activational hormonal effects on non-clinical psychiatric traits (see Walder et al., 2012b), which may also help explain sexually differentiated findings. Finally, from an epigenetic perspective, MeCP2 is X-linked and may, therefore, contribute to higher rates of autism-like symptomatology among males.

There were several limitations to this study. First, the small sample size (relative to epidemiological catchment area samples) and the bias toward upper SES limit generalizability. Significant findings were all the more striking, however, in light of restricted statistical power and relatively high resources available to these higher SES families. Second, only six (of 89) offspring scored above the ASSQ screening cut-off suggestive of possible ASD; thus, results are interpreted with respect to risk for autism-like traits in the non-clinical range (not ASD). Third, this study relied on retrospective (5 to 6 months post crisis) self-report data. Some studies suggest maternal response bias may account for symptom severity, as mothers of children with autism may be more apt to retrospectively recall stressful events (Beversdorf et al., 2005). This potential confound of retrospective report was circumvented in a variety of ways. Specifically, prospectively studying an independent, sudden life event (natural disaster) minimized threat to internal validity, enabled identification of precise timing of PNMS exposure, and enabled assessment and disentanglement of effects of maternal objective exposure from subjective distress soon after exposure. In natural disaster research, it is inherently challenging to measure acute distress immediately post-event. Project Ice Storm has the fastest post-disaster assessment of any published prenatal maternal stress study. Moreover, with acceleration of disaster research over the past 15 years, new (more feasible) methodological strategies have evolved to better control such limitations. Finally, the measure used to index exposure timing was based on one peak day of storm activity, although the onsets of power outages occurred over approximately 5 days.

Despite these limitations, the consistency of our findings using a non-clinical sample, with existing natural disaster research in the clinical ASD literature (Kinney et al., 2008a), strengthens

conclusions about a relationship between in utero stress exposure and emergent subclinical symptomatology that is not an artifact of maternal response bias. Moreover, our maternal self-reported subjective distress can be considered as reflecting prolonged (versus acute) stress reaction.

Our results in a non-clinical sample may have implications for understanding the origins of ASD, using a continuum/dimensional perspective. Consistent with the animal literature (Mueller and Bale, 2008), our evidence supports the notion that early stages of pregnancy signify a *sensitive period* for fetal programming of the developing nervous system that is particularly susceptible to stress effects with behavioral consequences (Dawson et al., 2000). This advocates for the promotion of prenatal health through, for example, stress reduction interventions. Post-natal interventions may also be warranted since PNMS effects may be tempered through psychosocial support intervention (Rothberg and Lits, 1991), physical or social enrichment in the early postnatal period and adolescence, and pharmacological intervention (Marco et al., 2011), with potentially significant effects on birth and infant outcome. A cautionary note is extended, however, in light of the predictive adaptive response model, which posits that a 'mismatch' between the pre- and post-natal environments (even if impoverished and resource abundant, respectfully) confers a disadvantage in early development (Glynn and Sandman, 2011). This area of research is in its nascent stage, warranting further exploration.

Future investigations using similar methodologies with larger and more diverse samples, as well as new lines of research with even more rigorous research designs, are warranted. For example, a naturalistic study may offer rapid stress reduction interventions to quickly identify a random sample of expectant mothers experiencing severe distress early post-disaster. The experimental group may receive a theoretically, maximally effective intervention tailored for acute disaster exposure (versus an empirically validated, general stress-reduction program). This approach might provide a more powerful method for testing a priori hypotheses and elucidating causal pathways. In turn, this may spearhead efficacy trials of novel preventive interventions that might help protect children (and parents) from potentially harmful effects of PNMS.

In conclusion, our results demonstrate that prenatal exposure to an environmental disaster such as the 1998 Quebec Ice Storm, which deprived millions of people of electricity although it incurred little threat to life, explained significant variance in children's autism-like traits, even in a highly socioeconomically advantaged sample. Results from this unique study may have implications for other types of events that may befall pregnant women, and extrapolation to more vulnerable populations suggest effects on developing offspring could be even greater among the socioeconomically disadvantaged; this remains open to future empirical scientific investigation. It is also possible, however, that some less socioeconomically advantaged groups may carry protective factors that buffer adverse stress effects. Finally, our results suggest some adverse effects are due to the mother's objective hardship and subjective distress level, and somewhat moderated by gestational timing of ice storm exposure. Our results highlight the need for continued investigation of prenatal maternal stress effects on offspring development (particularly mental health risk) and elucidation of underlying mechanisms.

Acknowledgments

We thank the families who have participated in Project Ice Storm since 1998. We thank Shannon Woo, Cheryl Chanson, and Sawsan Mbirkou for data entry. This study was supported by Grants from the McGill University Stairs Memorial Fund, the Canadian Institutes of Health Research (Grant no. MOP-57849), and the Douglas Hospital Research Centre, and a research fellowship from the *Fonds de la recherche en santé du Québec* awarded to Suzanne King.

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