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REVIEW

Using Natural Disasters to Study the Effects of Prenatal Maternal Stress on Child Health and Development

Suzanne King,* Kelsey Dancause, Anne-Marie Turcotte-Tremblay, Franz Veru and David P. Laplante

Research on the developmental origins of health and disease highlights the plasticity of the human fetus to a host of potential teratogens. Experimental research on laboratory animals has demonstrated a variety of physical and behavioral effects among offspring exposed to prenatal maternal stress (PNMS). However, these studies cannot elucidate the relative effects of the objective stress exposure and the subjective distress in a way that would parallel the stress experience in humans. PNMS research with humans is also limited because there are ethical challenges to designing studies that involve the random assignment of pregnant women to varying levels of independent stressors. Natural disasters present opportunities for natural experiments of the effects of pregnant women's exposure to stress on child development. In this review, we present an overview of the human and animal research on PNMS, and highlight the results of *Project Ice Storm* which has been following the cognitive, behavioral, motor and physical development of children exposed *in utero* to the January 1998 Quebec Ice Storm. We have found that both objective degree of exposure to the storm and the mothers' subjective distress have strong and persistent effects on child development, and that these effects are often moderated by the timing of the ice storm in pregnancy and by the child's sex. **Birth Defects Research (Part C) 96:273–288, 2012.** © **2013 Wiley Periodicals, Inc.**

Key words: prenatal maternal stress; disaster research; newborn and child outcomes

INTRODUCTION

As early as biblical times, it was recognized that stress to a pregnant woman could have serious consequences for her unborn child (e.g., Exodus 21:22; 1 Samuel 4:19). Since the 1970s, retrospective epidemiological studies have found that prenatal maternal stress (PNMS) increases risk for a variety of negative outcomes to the offspring, including preterm birth (Paarlberg et al., 1995) and severe mental illness (Huttenen and Niskanen, 1978), among others (Beydoun and Saftlas, 2008; Weinstock, 2008; Cottrell and Seckl, 2009; Charil et al., 2010; DiPietro, 2012).

Understanding the mechanisms of the PNMS effect in humans, however, poses a variety of theoretical, ethical, and logistical difficulties. First, there are several, competing uses of the term "stress". Hans Selye (1956) adapted the term from the field of mechanics to the field of psychology. In mechanics, the term stress is used to reflect a measure of physical force on an object; in the social sciences, it has been used in a variety of ways. In psychology, stress may be used to describe the objective, external forces acting upon an individual (i.e., the "stressor"), or the effects of those forces as experienced subjectively (i.e., "distress") or physiologically as reflected, for example, in neuroendocrine measures. Research on prenatal maternal stress may cover any and all of these meanings.

Ethically, stress in pregnancy is difficult to study in humans using experimental methods, which are the gold standard criterion for making causal conclusions. Although animal research allows for random assignment of pregnant animals to a variety of severe stress conditions, this is not ethically acceptable with humans. Research with laboratory animals is informative

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regarding the effects of objective stress exposure and physiological indices of stress, but cannot inform us about the animals' subjective experience of distress. One approach to the ethical research of stress during pregnancy with humans has been to study the stress from naturally occurring events, such as job loss or marital separation, to determine how these correlate with obstetrical and child outcomes. Unfortunately, for the researcher, few women experience severe life events during pregnancy that would qualify as "independent" stressors: these would be events that the woman could not possibly have influenced herself through either behavioral or genetic means, either of which could have its own effects on the child outcomes of study. A woman who is fired from her job or who separates from her partner while pregnant, for example, may have traits that influenced the likelihood of her experiencing the event and which she also passes on to her child genetically or through behavioral modeling.

Logistical challenges arise when attempting to design the ideal study. It would be imperative to identify pregnant women undergoing a severe, independent life event to be able to isolate three dimensions of stress: the degree of objective exposure to the stressor, the level of subjective distress, and the woman's physiological response to the stressor. As well, the onset of the stressor would need to be sudden and discrete to pinpoint the timing of the exposure in pregnancy, such that it can be related to developmental windows in gestation. In addition, the researcher would need access to large numbers of pregnant women experiencing the event to have sufficient sample sizes for advanced analyses. Finally, that access would need to occur very quickly after the event so that stress levels can be measured before women exposed in the last weeks of pregnancy give birth, to preserve the prospective nature of the study.

Our approach for the past 15 years has been to study pregnant women experiencing natural disasters. A disaster is any event that causes "disruption exceeding the adjustment capacity of the affected community" (Lechat, 1979). Natural disasters by their nature tend to have sudden onsets and to be independent of the control of individuals. Using disasters for natural experiments presents an approximation of the randomization afforded by true experiments, and capitalizes on the relatively large potential subject pool following a disaster occurring in a large community. To date, we have three such studies underway, each one with an initial sample between 200 and 300 women. *Project Ice Storm* began in June 1998, studying the effects of the January 1998 Quebec ice storm on pregnant women and their unborn children. *The Iowa Flood Study* recruited pregnant women exposed to severe floods in June 2008, and improves upon *Project Ice Storm* by including a subsample of women with extensive psychosocial measures taken before the disaster struck, rendering it the world's first pre–post disaster study in pregnant women. Finally, the *QF2011 Queensland Flood Study*, undertaken shortly after the January 2011 flooding in Brisbane, Australia, improves upon the previous studies by piggy-backing on a preexisting randomized control trial of two forms of prenatal care, thereby including not only preflood data on a subsample, but also testing a potential intervention. *QF2011* also included the sampling of placentas and other tissues that contain precious clues about the biological cascades underlying the effects of PNMS.

In this review, we will outline what we have learned about the effects of PNMS by taking advantage of these natural experiments. We will focus on the results of *Project Ice Storm*, which as the firstborn and oldest study, has the most complete set of results.

PROJECT ICE STORM

Project Ice Storm was initiated soon after a series of ice storms struck southern Quebec from January 5 to 9, 1998, dropping 10 cm of freezing rain on the region. The weight of the ice damaged 3000 hydroelectric pylons and toppled 30,000 wooden electric poles, knocking out electricity for more than 3 million people in 700 municipalities for as long as 45 days. The ice storm caused 35 deaths, directly or indirectly. The economic costs of the 1998 ice storm to the province are estimated at $1.5 billion (Environment Canada, 2003), and the storm has been counted as the worst and most costly natural disaster in Canadian history (Insurance Bureau of Canada, 2012).

On June 1, 1998, we mailed questionnaires to women in severely affected regions southeast of Montreal, whose doctors identified them as being pregnant during the ice storm, or who became pregnant within 3 months of the storm; this latter "preconception exposed" group was included to test hypotheses about effects of stress before conception. Our Storm32 questionnaire assessed four categories of objective disaster exposure: threat (e.g., being injured or in danger of injury), loss (e.g., financial, home damage), change (e.g., staying in a shelter, housing others), and scope (days without electricity and telephone) (see Laplante et al., 2007 for details). The 224 women in our initial sample spent up to 15 days in temporary shelters, and an average of 15 days (0–42) without electricity in their homes during the crisis, when daily low temperatures dropped to between −10 and −20°C. The extent of objective stress from the ice storm as measured by Storm32 appears to have been randomly distributed, with no association with socioeconomic status.

To estimate the women's subjective distress reaction to the ice storm, we used a validated French version (Brunet et al., 2003) of the Impact of Events Scale-Revised (IES-R) (Weiss and Marmar, 1997), which assesses posttraumatic stress symptoms in three categories: avoidance, intrusive

thoughts and images, and hyperarousal. To assess maternal diurnal cortisol secretion, the postal questionnaire also included a saliva sampling kit consisting of numbered strips of filter paper, instructions, and a stamped return envelope. Women were requested to take six samples of salivary cortisol at defined times between waking and bedtime on the first day and then a seventh upon waking on the second day. After the samples were collected, they were analyzed using a competitive binding radioimmunoassay. Calculations of the area under the curve using the trapezoidal rule, and average hourly rates of salivary cortisol (integrated cortisol: ng/ml/hr) were used in analyses. We also assessed the women's trait anxiety and depression at each assessment, and controlled for maternal symptoms in all analyses.

Project Ice Storm families have participated in up to a dozen waves of assessments to date. Questionnaires have been completed almost annually, and face-to-face assessments of children were done at ages 2, 5½, 8½, 11½, and 13½ years. The families in our study are better educated and have higher incomes than the regional averages. More detailed descriptions of the sample and methods can be found elsewhere (Laplante et al., 2004; King and Laplante, 2005; Laplante et al., 2007; Laplante et al., 2008; King et al., 2009b; Dancause et al., 2011, Dancause et al., 2012).

Our findings demonstrate moderate-to-large effects of PNMS from the ice storm on the development of these children, a fact that is especially impressive given the advantaged upbringing of most of them. In the following sections, we present a brief overview of the existing literature on the effects of PNMS, and then describe *Project Ice Storm* findings showing effects on physical growth (birth outcomes and childhood obesity), neurodevelopmental clues (neuromotor functioning and finger ridge counts), medical illnesses and outcomes (asthma and metabolism), behavioral development (e.g., internalizing, externalizing, and subclinical autistic-like behaviors), and cognitive development (IQ and language).

PHYSICAL GROWTH

Birth outcomes

Stress during pregnancy seems to have adverse effects on fetal growth as evidenced by physical measurements at birth. For example, human studies have shown associations between smaller birth weight or head circumference, as well as shorter gestation length, and pregnancy-related stress or anxiety (Kramer et al., 2009), life events (Lou et al., 1994; Hedegaard et al., 1996; Lu and Chen, 2004; Khashan et al., 2009), and anxious (Mancuso et al., 2004) or depressive (Orr et al., 2002; Andersson et al., 2004; Dayan et al., 2006) symptoms. In general, early-pregnancy to midpregnancy appears to be the most sensitive period (although this depends on the outcome studied), and effects often vary by the sex of the newborn.

In *Project Ice Storm*, regression analyses (controlling for potential confounding variables) indicated effects of PNMS due to the storm on birth weight, length, and head circumference, with effects depending on stress type, timing, and the baby's sex (Dancause et al., 2011). Mere exposure to the ice storm appears to have had an effect on some aspects of growth: mean birth length for gestational age in the full sample was nearly one-third of a standard deviation smaller than Canadian population references; although ours is not a representative sample of the region, the socioeconomic status of our sample should have predicted average, or larger than average, babies at birth.

Some birth outcome results implicate timing and/or the severity of the mother's objective stress exposure or subjective distress. For example, mid-pregnancy and late-pregnancy exposure had little impact on head circumference, but early exposure to high levels of subjective PNMS predicted smaller circumferences. Similarly, higher subjective PNMS levels predicted lower birth weights in general, with exposure in midpregnancy having the greatest impact. Length at birth was shortest among infants of women with a "discrepancy" between their objective and subjective PNMS levels: that is, among women who had low levels of subjective distress in response to high levels of objective stress, with the effect greatest among boys; or who had high levels of subjective distress in response to relatively low levels of objective stress, especially for girls (Fig. 1). Sex differences were also observed for head circumference-to-birth length ratios: subjective PNMS had little effect on girls' ratios, but a marked effect on boys', with higher subjective PNMS levels predicting smaller head circumference relative to birth length among male infants. The effects of PNMS on this ratio suggests the possibility that a "brain sparing" process was at work in male fetuses, such that high maternal distress from the ice storm triggered a shunting of fetal resources to preserve the head at the expense of body length.

All of these effects were modest, but considering the continued public health burden posed by adverse birth outcomes (Hobel et al., 2008), even modest effects might be relevant, especially where risk is already elevated due to known contributing factors, such as poverty, and where psychosocial stress might exacerbate this risk.

Body mass index and obesity

Although data are still limited, PNMS is increasingly accepted as a risk factor for obesity in childhood and adulthood. This might reflect the effects of PNMS on fetal growth patterns, since low birth weight and intrauterine growth restriction are associated with increased risk for later cardiometabolic diseases, such as obesity, hypertension, and insulin resistance (Barker, 2004; Eriksson, 2005). Furthermore, PNMS might result in deregulation of the fetal hypothalamic pituitary adrenal (HPA) axis (Sandman

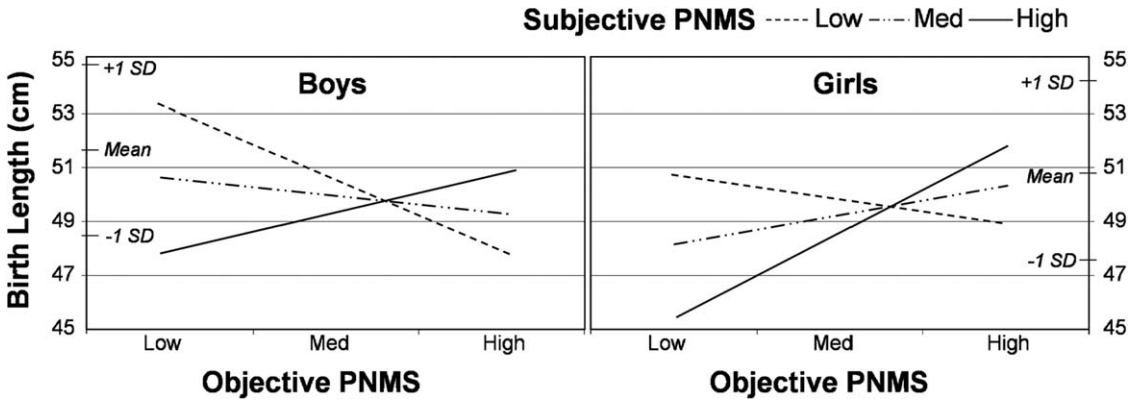

Figure 1. Interaction between objective stress and subjective PNMS for birth length as a function of newborn sex.

et al., 1994), which is involved in metabolic pathways (Nieuwenhuizen and Rutters, 2008) and likely represents a mediating mechanism in the developmental origins of health and disease (Drake et al., 2007; Beydoun and Saftlas, 2008; Cottrell and Seckl, 2009; Entringer et al., 2010; Entringer et al., 2012). Human studies have shown associations between obesity and measures of adiposity in children and young adults with maternal bereavement (e.g., due to the death of a spouse) during or shortly before pregnancy (Li et al., 2010), stressful life events during pregnancy (Entringer et al., 2008b, Entringer et al., 2010), and higher levels of maternal corticotrophin-releasing hormone, which provides a marker of fetal glucocorticoid exposure (Gillman et al., 2006).

We observed similar effects of PNMS due to the ice storm on children's body mass index (BMI) (Dancause et al., 2012). The severity of the mothers' objective stress exposure from the ice storm explained 5% of unique variance in the children's BMI, even after taking maternal height and the child's birth weight into account, with greater stress being associated with larger BMI. In addition, controlling for potential confounding variables, objective PNMS was associated with increased obesity risk among children at age 5½, with odds ratios (OR) ranging from 1.37 to 1.43, depending on the model tested. Similar effects were also seen at ages 8½ and 11½ years (unpublished data). These effects were independent of size at birth, suggesting that PNMS might increase obesity risk through effects on metabolic pathways. For example, PNMS might result in the reorganization of neural pathways involved in appetite regulation and metabolism, and a subsequent "reprogramming" of energy balance (Bouret, 2009; Entringer et al., 2010; Eriksson, 2010). This could increase risk independently of size at birth, as well as potential confounders such as socioeconomic status. More human studies are necessary to clarify the mechanisms underlying the programming effects of PNMS on cardiometabolic outcomes, and their persistence across the lifespan.

COGNITIVE DEVELOPMENT AND LANGUAGE

It is widely accepted that perturbations during fetal development have lasting effects on cognitive and language abilities. In general, maternal stress and/or anxiety during pregnancy result in less than optimal neurodevelopment in both animals and humans (O'Donnell et al., 2009; Charil et al., 2010). How prenatal stress and anxiety impact cognitive and language development remains largely unknown. Because maternal and fetal cortisol levels are highly correlated (Gitau et al., 2001), it is believed that increased levels of maternal stress and/or anxiety result in glucocorticoid levels that exceed the placenta's ability to convert cortisol to cortisone, thereby exposing the fetus to levels of cortisol that may disrupt neuronal development. However, it has been demonstrated that relatively low levels of maternal stress and/or anxiety may have a positive influence on cognitive development (DiPietro et al., 2006; DiPietro et al., 2010). As such, the exact nature of the relationship between pregnancy-related maternal stress and/or anxiety and these outcomes remains unclear.

To date, we have data on the cognitive and language abilities of children in the *Project Ice Storm* cohort at ages 2, 5½, 8½, 11½, and 13½ years. Cognitive functioning was assessed using standardized face-to-face IQ tests at every age (Bayley, WPPSI, and WISC).

All results presented here reflect the children's cognitive (Fig. 2) and language (Fig. 3) abilities after additional maternal (e.g., socioeconomic status, age, major life events, and/or trait anxiety) and/or child (e.g., gestational age, birth weight) control variables have been accounted for in the analyses. Due to budgetary restrictions, our 2 year old sample contains only children whose mothers experienced either low or high levels of objective stress; children whose mothers experienced moderate levels of objective stress were not assessed. Children exposed *in utero* to moderate levels of objective stress were included in the analyses at all subsequent ages.

Our initial assessment of the children at age 2 years indicated that,

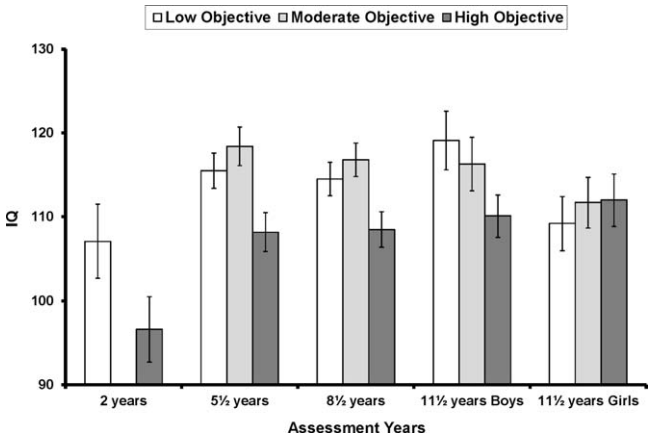

Figure 2. IQ scores at 2, 5½, 8½, and 11½ years of age as a function of objective stress.

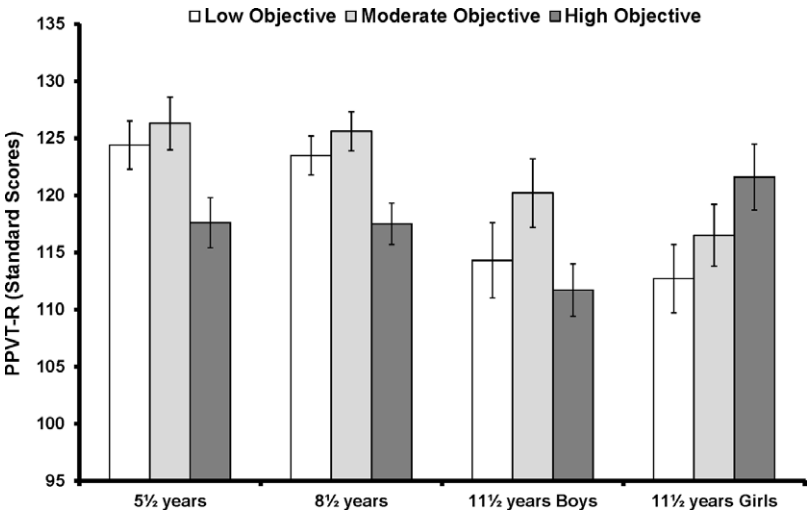

Figure 3. Language scores at 2, 5½, 8½, and 11½ years of age as a function of objective stress.

on average, children who were exposed *in utero* to high levels of objective stress from the ice storm had Mental Development Index scores (Bayley version of an IQ score) that were a full standard deviation lower than that of children exposed to low levels of maternal objective stress (Laplante et al., 2004). Moreover, the effect of objective stress was more pronounced in children exposed to the ice storm during the first or second trimester than during the third trimester. Interestingly, there were no effects of maternal subjective distress.

Similar findings were observed when we assessed the children's play. Because a child's performance on a formal intelligence test may be partly a function of their temperament and behavior problems, that is, how compliant and at ease they may be with the examiner, we also completed assessments of the children's style of play. We assessed the maturity and breadth of the children's play at 2 years of age using a standardized protocol developed by Zelazo and Kearsley (1980). Videotapes were coded to determine the percentage of time the children spent in stereotypical play, in more mature relational play, or in even more mature functional play. Compared to children exposed *in utero* to low levels of objective stress, those whose mothers experienced high levels of objective stress exhibited a higher percentage of immature stereotypical play (14.3 vs. 5.8%), lower levels of mature functional play (41.9 vs. 60.7%), and fewer functional acts with the toys (10.1 vs. 15.2 acts) (Laplante et al., 2007). As with the children's Bayley scores, differences in toy play were greatest in children exposed to the ice storm during the first or second trimesters. Unlike results from the Bayley, however, maternal subjective distress from the ice storm explained significant amounts of variance in the children's performance: objective and subjective PNMS accounted for 13.4 and 12.8% of the variance of the children's functional play levels, respectively.

Language development was assessed using standardized instruments at the same ages as the IQ testing. At age 2 years, after controlling for the toddlers' birth weight, mothers who experienced high levels of objective stress during the first or second trimester reported that their children understood 10 fewer words, and spoke 19 fewer words, relative to toddlers whose mothers experienced low levels of objective stress (Laplante et al., 2004). Objective stress accounted for a significant 12 and 17% of the variance in the number of words understood and spoken by the toddlers.

These results suggest that exposure *in utero* to high levels of maternal stress resulting from a natural disaster negatively impacts cognitive and language development in young children. Moreover, the play of the 24-month old toddlers exposed *in utero* to high levels of objective stress were comparable to those of a group of normally developing 15½ month-old toddlers who had been assessed by Zelazo and Kearsley (1980). Together, these findings suggested that the ice storm cohort's performance on these tasks appeared to be delayed, similar to that of children born prematurely. As with most premature children, we believed that the performance of children exposed *in utero* to high levels of maternal stress would improve with age.

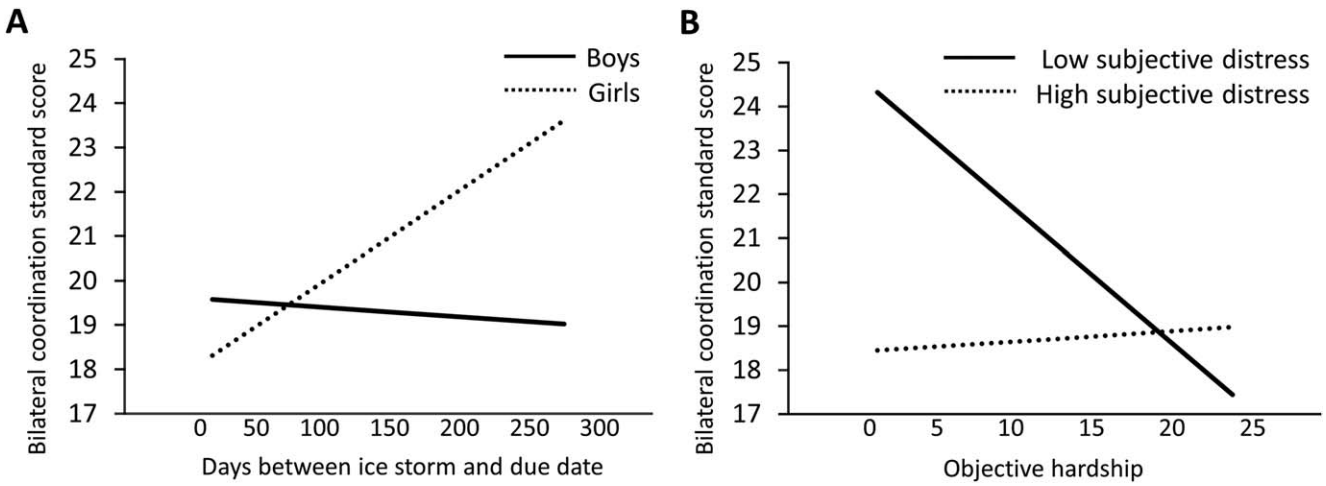

Figure 4. Child sex and timing of exposure interaction (**A**) and objective and subjective PNMS interaction (**B**) observed in the children's bilateral coordination abilities at 5½ years of age.

The effects of prenatal maternal objective stress on cognitive and language development were replicated at age 5½, but with two interesting twists (Laplante et al., 2008). First, we included the moderate objective stress group in the assessments at this age, which revealed a curvilinear association between PNMS, and both IQ and language: scores were higher in the moderate objective stress group than in either the low or, especially, the high stress groups. This finding is similar to that reported by DiPietro et al., 2006; DiPietro et al., 2010), and suggests that exposure to some level of stress by the fetus during prenatal development may be beneficial. However, the optimal amount of exposure has yet to be determined. Secondly, there was no longer a trimester of exposure effect in the results. As before, however, there were no effects of subjective distress on either IQ or language. These patterns were repeated at age 8½ (unpublished data), but then varied by sex at age 11½ (unpublished data).

Our findings are surprising on two accounts. First, contrary to our expectations, maternal subjective distress did not account for any of the variance in the children's psychometrically assessed cognitive or language abilities during childhood; maternal subjective distress levels did, however, account for moderately large amounts of variance in the children's play at age 2 years. We suspect that, because the ice storm affected everybody in the region to some degree, the events and experiences these women faced were sufficiently strong to alter the fetal environments of their children, even in women who perceived the disaster as not being distressing. Second, also contrary to our expectations, the effects of the PNMS exposure on the children have not dissipated with increasing age. While the overall magnitude of the difference in cognitive and language abilities of children exposed to high versus moderate or low levels of PNMS was halved between 2 and 5½ years of age, the difference remained relatively stable between 5½ and 11½ years of age, particularly in boys, suggesting mild, but permanent alterations in performance.

NEURODEVELOPMENT

Neuromotor development

Research suggests that high levels of PNMS or maternal cortisol during pregnancy are associated with poorer motor outcomes at birth (Rieger et al., 2004; Ellman et al., 2008) and within the first two years of life (Buitelaar et al., 2003; Chuang et al., 2011). This might reflect effects of PNMS on development of the cerebellum. Rodents exposed to prenatal stress late in gestation exhibit a reduced volume of granule cell nuclei and reduced synaptic density in the cerebellum, and a decrease in the cerebellar granule-to-Purkinje cell ratio (Ulupinar and Yucel, 2005; Ulupinar et al., 2006). However, data from humans are limited, particularly after infancy.

We analyzed balance, bilateral coordination, and visual motor integration (VMI) skills among *Project Ice Storm* children at age 5½ (Cao et al., in press). Controlling for potential confounding variables, we failed to find effects of PNMS on balance, but did observe significant effects of PNMS on bilateral coordination and VMI. For both bilateral coordination and VMI, boys' coordination and VMI performance did not vary as a function of the timing of exposure, but girls' performance was lower with exposure later in gestation (Figs. 4A and 5A). Furthermore, objective and subjective PNMS had interactive effects, such that when subjective distress was high, performance remained relatively poor regardless of objective stress levels; but when subjective distress was low, there was a negative correlation between objective stress and coordination skills (Figs. 4B and 5B). These data provide support for effects of PNMS on motor

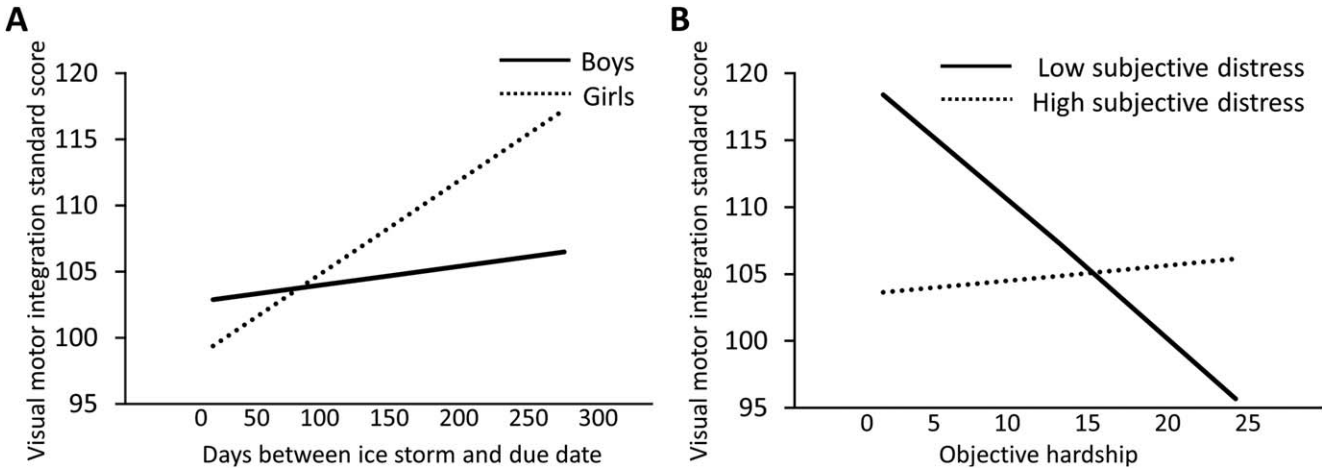

Figure 5. Child sex and timing of exposure interaction (**A**) and objective and subjective PNMS interaction (**B**) observed in the children's visual-motor integration abilities at 5½ years of age.

development that can persist into childhood. Future analyses will test the indirect effects of PNMS on motor function via effects on specific brain structures.

Fingerprint asymmetry

PNMS has been implicated in a number of mental conditions that are presumed to have neurodevelopmental origins, such as schizophrenia (Weinberger, 1995; Talge et al., 2007). Neurodevelopment begins at conception and is generally not complete to adult levels until the early 20s, when myelination of the prefrontal cortex is finished. The early prenatal period lays down the initial foundations of neural tube, then brain and spinal cord, followed by refinement of specific brain structures, nerve cell migration, and synaptic growth in later stages. Conventional wisdom suggests that stress to the pregnant woman increases her glucocorticoid levels, overwhelming the placental barriers and disrupting development of whichever fetal systems happen to be in ascendance at that time. Although it is currently unfeasible to obtain direct images of neurodevelopment in the fetus as it unfolds, insults to neurodevelopment *in utero* may leave permanent traces elsewhere on more visible body parts that are developing at the same time in gestation as the brain. In their review article, Tarrant and Jones (1999) note that all minor and/or major congenital anomalies can be timed to specific stages of fetal development. For example, minor physical anomalies of the feet reflect disruption during gestation weeks 1–8, while abnormalities in the fingerprints may reflect disruption during gestation weeks 14–22 (van Valen, 1962). Fingerprint anomalies are of little interest in and of themselves. However, because fingerprint development occurs during the 2nd trimester of gestation when critical brain structures (such as the hippocampus) are also developing, and because fingerprints and brain develop out of the same fetal ectodermal tissue, and because fingerprints remain unchanged throughout life, dermatoglyphic abnormalities may have important implications for developmental psychopathology.

We used the *Project Ice Storm* cohort to test the hypothesis that PNMS would influence the symmetry of fingerprint ridge counts between homologous (that is, left and right) fingers, but only for those children whose mothers experienced the ice storm at some point during the critical window of fingerprint development: weeks 14–22 (King et al., 2009b). We predicted that, for these children, greater PNMS would be associated with greater left–right asymmetry, as is seen in schizophrenia patients (Mellor, 1992; Weinstein et al., 1999; Reilly et al., 2001).

As anticipated, PNMS correlated with ridge count asymmetry in the children exposed in the target weeks; the effect size for subjective stress in this group could be characterized as "very large" according to conventional criteria. Another aspect of the stress experience is the mothers' hormonal response as measured in salivary cortisol. Although we hypothesized that higher levels of diurnal cortisol in the women would be correlated with greater fingerprint asymmetry, we found a negative correlation instead: the lower the maternal cortisol levels, the greater the fingerprint asymmetry in our target group. The mechanisms responsible for the surprising direction of this association elude us so far, but the fact that the saliva samples were taken several months following the ice storm make it impossible to conclude that our results reflect the direct effects of maternal cortisol at the time of the storm.

The results of these fingerprint analyses highlighted the need to look directly at brain development in the ice storm cohort. We conducted structural brain imaging when the children were aged 11½ years and will report on these findings in the coming years. Our ultimate goal is to test the hypothesis that PNMS influenced the development of particular brain structures and had, thus, indirect effects on a number of

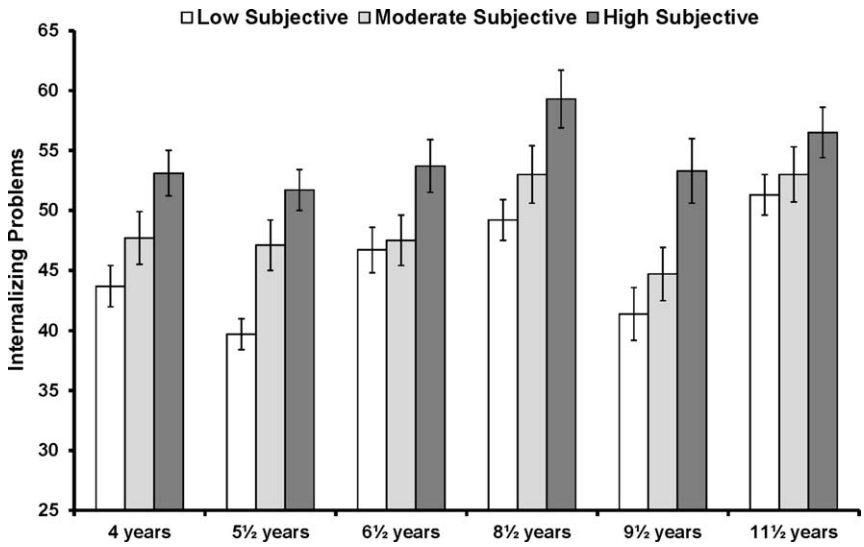

Figure 6. Internalizing problems at 4, 5½, 6½, 8½, 9½, and 11½ years of age as a function of subjective distress.

observable child outcomes such as psychopathology and neuromotor development.

BEHAVIORAL DEVELOPMENT

Internalizing and externalizing problems

A variety of social and environmental factors have been found to be associated with the development of childhood psychopathology. For example, obstetric complications, smoking, and alcohol consumption during pregnancy, low birth weight, socioeconomic status, parental marital status, parental pathology, and maternal age are all known to be associated with behavioral problems in children (Williams et al., 1998; Gray et al., 2004; Tremblay et al., 2004; Kahn et al., 2005; Najman et al., 2005). Recent research has explored the role that maternal stress and/or anxiety during pregnancy has on the subsequent development of behavioral problems during childhood (O'Connor et al., 2003). For example, perceived pregnancy-related stress was found to be positively correlated with observable externalizing problems, such as aggressiveness and destructiveness, in 2-year-old toddlers (Gutteling et al., 2005). Likewise, children whose mothers displayed high levels of anxiety during the final month of their pregnancy were two to three times more likely to display higher levels of behavioral and emotional problems at 4 years of age, relative to children whose mothers experienced low levels of anxiety, even after controlling for postnatal maternal anxiety levels (O'Connor et al., 2003; Huizink et al., 2004; Van den Bergh and Marcoen, 2004; Glover, 2011). As such, prenatal maternal stress and anxiety are now considered potential risk factors for the development of psychopathology in later life (Huizink et al., 2004).

Yet, how might one determine how much of these effects are due to the stressor versus the mothers' "distress" when the two are difficult to disentangle? Nonhuman primate research has found that either mild daily social stress to the mother (Schneider and Coe, 1993) or 2 weeks of adrenocorticotropic hormone treatment to the mother at midgestation (Schneider et al., 1992; Weinstock, 2001) results in greater internalizing behaviors, such as anxiety, in infant monkeys. This work, and similar research in rodents, suggests that the independent, "objective" stressors imposed by the researchers are sufficient to increase risk for behavioral problems in animals, and that this stress has its effects via maternal stress hormones. However, as discussed above, animal research cannot determine the relative effects of the subjective distress from the objective exposure.

In *Project Ice Storm*, we analyzed maternal ratings of their children's internalizing problems (anxiety, depression, social withdrawal) (Fig. 6) and externalizing problems (aggression, destructiveness) (Fig. 7) assessed at ages 4, 5½, 6½, 8½, 9½, and 11½ years (King et al., 2009a). Zero-order correlations between internalizing problems and objective stress (Storm32) were low-to-moderate at each age, whereas correlations with subjective distress (IES-R) were strong and significant at every age (correlations range from 0.348 to 0.512). Controlling for maternal depression and anxiety in June 1998 following the ice storm, and also at the time of the assessment, subjective distress still explained an additional 8 to 12% of unique variance in internalizing problems at each age. Results of multilevel modeling showed that, first, even though average scores in this group have been below average until recently, the severity of internalizing problems in this group of children is increasing over time relative to the norm group (i.e., using standardized scores from the manual). Second, results show that internalizing problems at 4 years were predicted by subjective maternal distress, which explained 34% of the between-subjects variance in internalizing. Finally, objective and subjective PNMS interact such that when the mother's subjective distress was low, the greater her objective stress the greater the child's internalizing problems; but when the mother's subjective distress was high, the child's internalizing problems are more severe, and maternal objective stress has no additional effect.

Unlike internalizing problems, externalizing problems in the sample appear to be lessening in severity with age relative to the published norms, even though the group average has consistently been below the published means. As with internalizing, the severity of the children's externalizing

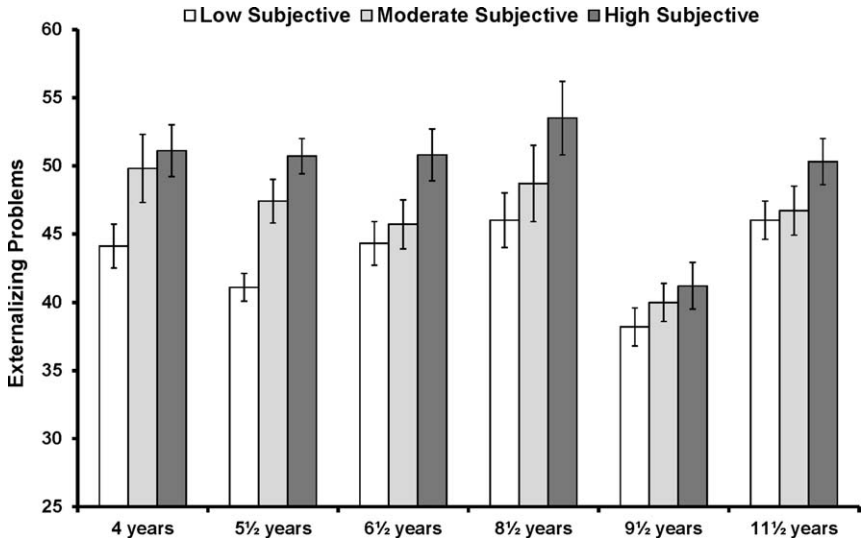

Figure 7. Externalizing problems at 4, 5½, 6½, 8½, 9½, and 11½ years of age as a function of subjective distress.

problems had low, positive correlations with objective maternal stress at all ages, but had stronger correlations with subjective distress (0.275–0.554). After controlling for maternal mood, as above, subjective maternal distress explained an additional 8 to 20% of unique variance in externalizing problems. Multilevel modeling of trajectories over time showed a significant interaction between objective and subjective PNMS that parallels the results for internalizing problems described above.

The effects of PNMS on behavioral development may be mediated by puberty and/or sex hormones. Huizink (2008) showed that adolescent girls from a prenatally stressed cohort had significantly higher testosterone levels at age 14 than a nonstressed comparison group. Testosterone levels in adolescence are associated with more adverse alcohol consumption and other antisocial behaviors (Eriksson et al., 2005). As *Project Ice Storm* continues to monitor psychological symptoms in this cohort throughout adolescence, we will also consider the role played by puberty and androgens.

Autistic spectrum disorders

One way to study the effects of PNMS on risk of severe psychopathology is to use retrospective analyses of prevalence rates and see how these change due to exposure to severe weather events *in utero*. In a historical analysis of the impact of PNMS caused by 10 severe weather events in Louisiana, Kinney et al. (1999, 2008) reported that rates of autism were significantly increased as a function of prenatal exposure to storms rated as severe by the National Weather Service, increasing the usual prevalence rate from 5 per 10,000 births to 13 per 10,000 births. Moreover, the impact of these storms was greatest for children exposed during certain months of the pregnancy, with prevalence rates for autism jumping to 18 per 10,000 births for children exposed to storms in months 5 or 6 of gestation. Finally, storm severity and timing interacted such that for children exposed in months 5 and 6 of pregnancy, for storms classified as low, moderate, and severe intensity, the relative risks for autism were 3, 10, and 27 per 10,000 births, respectively. This is one of a handful of studies suggesting that severity and timing of stress interact to influence risk of psychopathology.

In *Project Ice Storm*, we did not expect any children to develop autism per se, but instead investigated subclinical autistic symptoms along a continuum (King et al., 2009a; Walder et al., Under review). Mothers completed an autism screening questionnaire when the children were 6 years old. Subclinical autistic symptoms correlated significantly with objective stress (r=0.43), and with subjective distress (r=0.45). Combined, these two aspects of PNMS explained about 23% of the variance in subclinical autistic symptoms rated by mothers. There was, however, a significant interaction between objective and subjective PNMS. High subjective distress levels were associated with high scores, regardless of the level of objective hardship. Objective hardship, however, was only related to high scores when subjective distress levels were either low or moderate in intensity. Finally, the objective hardship × timing of exposure interaction explained additional variance in scores: higher objective hardship levels were associated with higher autistic-like traits, only when the exposure occurred early in the pregnancy. Together, these variables explained 42.7% of the variance in the scores.

Although Kinney found greater susceptibility to autism in children exposed to tropical storms in midgestation, we found that exposure in early gestation presented greater vulnerability to the effects of PNMS.

MEDICAL ILLNESSES AND OUTCOMES

Metabolism

As discussed above, PNMS has been associated with later cardiometabolic diseases, including diseases of glucose–insulin metabolism. Results from animal studies suggest that prenatal exposure to high levels of maternal stress or glucocorticoids is associated with hyperglycemia and features of insulin resistance (Lindsay et al., 1996; Nyirenda et al., 1998; Moss et al., 2001; Cleasby et al., 2003; Lesage et al., 2004; Nyirenda et al., 2009). Furthermore, among humans, retrospective case–control studies indicate increased risk

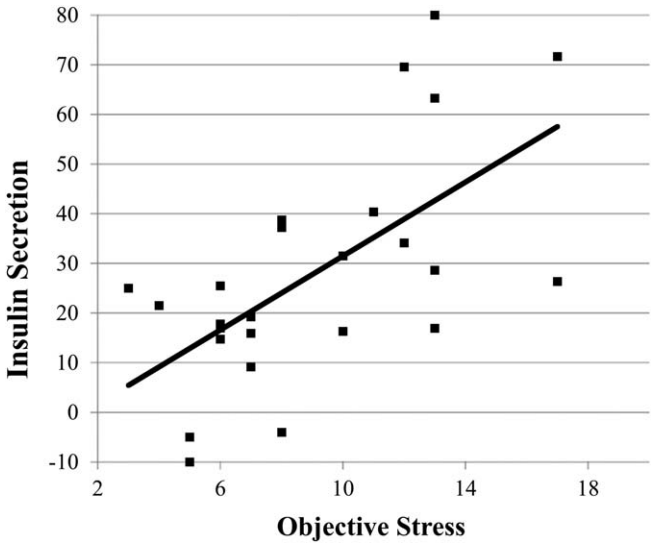

Figure 8. Insulin secretion (insulinogenic index [(I30–I0)/(G30–G0); mU/mmol]) at 13 years of age as a function of objective stress.

of insulin resistance among young adults whose mothers experienced stressors during pregnancy (Entringer et al., 2012). As in the case of obesity, this might reflect direct effects on metabolic pathways, as well as indirect effects through traits such as birth weight or adiposity (Entringer et al., 2012; Rinaudo and Wang, 2012). Based on the effects of PNMS on size at birth (Dancause et al., 2011) and on childhood obesity (Dancause et al., 2012) in *Project Ice Storm*, we hypothesized that PNMS might affect glucose–insulin metabolism in this cohort.

We conducted 30-min glucose tolerance tests among a subset of 15 boys and 10 girls from *Project Ice Storm* in adolescence (mean age 13.4 years) (Dancause et al., under review). Despite the small sample size, regression analyses controlling for the adolescent's birth weight, percent body fat, pubertal stage, and number of family members with diabetes showed that greater levels of objective stress were associated with greater insulin secretion, explaining 15.7% of unique variance (Fig. 8), which is a feature of insulin resistance, increasing risk for Type 2 diabetes.

These results support previous studies suggesting that PNMS negatively affects metabolic health, and highlights that these effects are manifest in adolescence. As observed for obesity, the effects of PNMS on insulin secretion were independent of size at birth, suggesting effects on central mediators of metabolism. However, larger samples are needed to test these potential mediating pathways. As the global burden of metabolic disorders escalates (Danaei et al., 2011), the contribution of PNMS to metabolic health represents an important area of research.

Immune Function

The ontogeny of the immune system starts around the second embryonic week and only reaches a mature state of development in late childhood (West, 2002). However, it is during intrauterine life that exogenous agents produce more notorious and long-lasting consequences (Holladay and Smialowicz, 2000). Psychosocial stress, especially chronic stress, has been found to be immunosuppressive (Ashcraft and Bonneau, 2008). Such findings have motivated the search for the consequences of stress exposure during pregnancy.

Most research on the effects of PNMS on the immune system has been conducted on animals. Consequences on the developing immune system depend on the type of stressor, the sex of the offspring, and the timing of exposure in gestation, as well as the type of cell analyzed. For example, T helper lymphocyte percentages have been found to be reduced in PNMS exposed animals (Llorente et al., 2002; Götz and Stefanski, 2007; Götz et al., 2007). In innate cells, Natural Killer cell cytotoxicity and phagocytic and oxidative burst capacities in macrophages are decreased in PNMS-exposed animals, with marked sex differences (Kay et al., 1998; Fonseca et al., 2005; Coe et al., 2007). In adaptive cells, proliferative responses increase or decrease, depending on the type of stressor, mitogen, and the stage of immune development (Sobrian et al., 1997; Tuchscherer et al., 2002). Humoral responses may be enhanced in some cases, also depending on stressor-related factors (Klein and Rager, 1995), while complex cellular responses (e.g., delayed type hypersensitivity) are mostly decreased (Gorczynski, 1992; Sobrian et al., 1997). This is consistent with the fact that cytokine function in the offspring has been found to be predominantly skewed towards the production of Th2 (anti-inflammatory) mediators following PNMS (Coe et al., 2002; Pincus-Knackstedt et al., 2006; Vanbesien-Mailliot et al., 2007; Couret et al., 2009; Collier et al., 2011).

To date, only two studies in humans have explored the effects of PNMS on mitogen-induced cytokine function. The first showed that adult women whose mothers experienced stressful life events during pregnancy had a skewed pro-Th2 response (Entringer et al., 2008a). The second, using umbilical cord blood from babies whose mothers had faced multiple difficult life circumstances, evidenced a Th2 shift in adaptive cytokines, whereas innate cytokines were skewed towards Th1 (Wright et al., 2010). In *Project Ice Storm*, we are currently investigating the effects of the mothers' objective exposure and their subjective distress on their children's cytokine function in adolescence. In the meantime, we have indirect

evidence of the effects of PNMS on immune function by using maternal reports of children's health, as reported in the next section.

Asthma

Research has found that self-reported maternal anxiety during pregnancy explains variance in the risk for respiratory illnesses and asthma in children (Cookson et al., 2009; Beijers et al., 2010). Since both animal and human studies suggest that PNMS influences the immune system in a sex-specific manner, immune-mediated disorders such as asthma could also be influenced by PNMS. Indeed, according to Pincus-Knackstedt et al. (2006), prenatally stressed female mice were more at risk of airway hyper-responsiveness, inflammation, as well as dysregulated pathways of cellular and humoral immune response. In humans, Pincus et al. (2010) found that low levels of maternal progesterone, which can be triggered by activation of the HPA axis, predict immune disorders in girls only. The placenta may play an important role in the process by which PNMS differentially affects girls and boys. Genes related to immune pathways are expressed differentially in female compared to male placenta (Sood et al., 2006), and sex differences are observed in placental cytokine expression, insulin-like growth factor pathways, and placental response to glucocorticoids (Clifton, 2010).

Building on such findings, we sought to examine whether disaster-related PNMS would increase risk of asthma in children from *Project Ice Storm* (Turcotte-Tremblay et al., unpublished manuscript). Sixty-eight mothers participated in a brief telephone interview on asthma when their children, 32 boys and 36 girls, were 12 years of age. Lifetime asthma symptoms, diagnoses, and corticosteroid utilization were assessed using a modified version of the International Study of Asthma and Allergies in Childhood questionnaire (Asher et al., 1995; Ellwood et al., 2005). Hierarchical logistic regression models indicated a gender-specific effect. In girls only, higher levels of subjective distress from the storm were associated with greater lifetime risk of wheezing (OR=1.13), asthma as reported by the mother (OR=1.15), asthma as diagnosed by a doctor (OR=1.11), and lifetime utilization of corticosteroids (OR=1.29) (Fig. 9). The mothers' objective stress scores and timing of the stressor in pregnancy did not predict asthma in this sample.

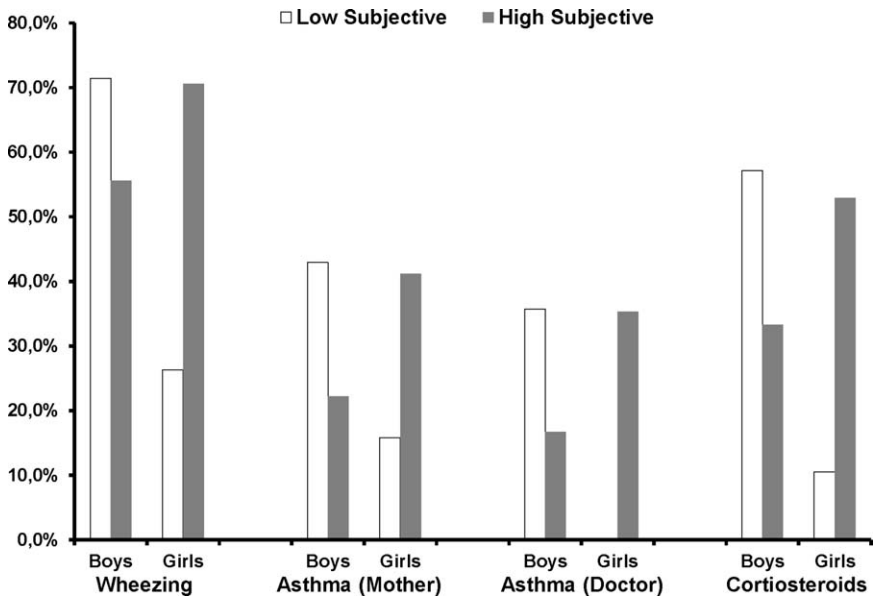

Figure 9. Percentage of lifetime wheezing, asthma (mother-rated and doctor-diagnosed), and corticosteroid usage as a function of subjective distress and sex of the child.

Together with the existing literature, these results highlight the complexity of the association between PNMS and fetal programming of immune disorders. There is a need to produce evidence-based knowledge on the biological mechanisms by which a pregnant mother's distress in the face of a natural disaster affects the immune functioning of her child over time. We hope that our cytokine analyses from *Project Ice Storm*, as well as results from the birth biological samples from *QF2011* in Australia, will provide important clues to this question.

CONCLUSIONS

Overall, the results from *Project Ice Storm* suggest that more severe PNMS from an independent stressor predicts worse performance on assessments of cognitive, behavioral, and motor development, and have a significant impact on a wide variety of physical outcomes related to metabolic or immune function, body size, and putative neurodevelopmental markers. The results for a particular outcome vary, however, and implicate either objective or subjective PNMS or their interaction, and may be moderated by the sex of the child or the timing of the ice storm in pregnancy.

Results from this study are surprising in a number of ways. First, we had not anticipated that the severity of the Quebec ice storm would be sufficient to produce the moderate to very large effect sizes seen in our results. Although the storm and its aftermath produced considerable hardship for large numbers of people and for up to 6 weeks or more, there was little loss of life or real physical threat compared to other recent events around the globe, such as earthquakes, hurricanes, tsunamis, and tornados. The fact that our sample consists of families from upper-middle and upper classes, and that the children are in the above-average range of IQ with below

average behavior problems, makes the magnitude of effects in this restricted sample even more impressive.

Second, we had expected that the effects of prenatal exposure to the ice storm would not persist beyond the first years of life, and that variations in the postnatal environment would dilute and perhaps erase any prenatal stress effects. Yet this has not been the case, and effects are still seen in early adolescence. Our current research grant is allowing us to assess this cohort at ages 13½ and 15 years; results will give insights about the effects of PNMS throughout adolescence.

Third, we have been struck by the predictive power of the objective stress score, which we originally designed to be a simple control variable. Our working model of PNMS suggested that our subjects would be confronted with varying degrees of hardship from the storm, which may or may not correlate with their subjective distress. Subjective distress was expected to be the "smoking gun" that would increase the pregnant women's cortisol levels, which would have negative effects on the developing fetus. Yet, we have found that objective stress exposure has significant effects on physical development (BMI, insulin secretion), behavioral development (internalizing, externalizing, subclinical autistic symptoms), and especially cognitive and language development. To date, however, we have no explanation for the power of objective stress in this sample. If this pattern holds in our flood study in Australia, the birth biological samples may provide clues to the mechanisms by which objective stress wields its effects.

Fourth, we were surprised by the curvilinearity of the effects of objective stress on cognitive development seen at ages 5½ and 8½ years: scores on general intelligence, language, and memory (not shown) are highest in children whose mothers had moderate scores on our objective stress measure. This is especially astounding, given that *Project Ice Storm* does not have a control group of families with no stress. The ice from the storm covered much of southern Quebec and disrupted normal services and transportation for the entire population, including those who never lost power. There is a hypothetical subgroup of no-stress children whose cognitive performance could be higher or lower than that of our low-stress group, but there are no children in the ice storm study who were not exposed to PNMS. Both our Iowa and Australian flood studies may provide clarity to the issue of the range of stress exposure: both samples include a wider range of hardship, from a complete absence of inconvenience, to complete loss of house and home resulting from the flooding. In the meantime, our curvilinear results echo similar PNMS results of DiPietro et al., 2006 and DiPietro et al., 2010.

Study results demonstrate that the mother's subjective distress, as reflected in the severity of posttraumatic stress disorder symptoms assessed several months after the storm, has significant effects on a number of outcomes, including physical development (birth outcomes, fingerprint asymmetry) and asthma risk, but especially strong effects on the behavioral and motor development of the children throughout childhood. The results suggest that, in some ways, the mother's subjective distress "trumps" the effects of her objective exposure to the hardship from the storm. This is seen in the effects on the children's internalizing and externalizing problems, subclinical autistic-like traits, and their bilateral coordination and visual-motor integration: for each of these outcomes, performance was lowest for children whose mothers had high levels of subjective distress, irrespective of their degree of objective stress; but for children whose mothers had low levels of subjective distress, their performance varied only as a function of their mothers' objective stress.

Project Ice Storm makes a unique contribution to the research on PNMS. By using a natural disaster as the "independent life event" to which our sample was exposed in a quasi-random fashion, we have approached the degree of experimental control attained by animal research, permitting us to make causal conclusions about prenatal stress, if somewhat tentatively. We have also been able to tease apart the relative effects of objective exposure and subjective distress of the mother. Our results also increase our understanding of the moderating effects of the timing of the stressor in gestation, since the onset of this stressor was sudden and unpredictable; the majority of life events, such as the death of a loved one or a marital separation, tend not to have such discrete onsets. The moderating effects of timing seen in this study suggest that there is no single period of vulnerability, but that the effects vary whether the exposure occurs in the first trimester (head circumference, cognitive development at age 2, subclinical autistic symptoms at age 6), second trimester (cognitive and language development at age 2 years, fingerprint asymmetry), or third trimester (motor development). The nature of the stressors used in our three PNMS studies will allow us to generalize our results to other independent, sudden onset events occurring in pregnancy; however, our use of natural disasters will not allow us to generalize our findings to situations of chronic stress such as poverty or war.

The greatest challenge for PNMS researchers will be to identify the mechanisms of action within a complete biopsychosocial model. The *Iowa Flood Study* and the *QF2011 Study* in Australia will augment our ability to test such a model by providing pre-flood data on subsamples of women, and by providing (in *QF2011*) samples of placenta, umbilical cord, and cord blood. These biological samples will allow members of our research group to study the cascade of events beginning with the mother's objective exposure, continuing through placenta and umbilical cord to influence the glucocorticoid, catecholamine, and immune systems, and ending in the

phenotype of the child. We will also be able to see the moderating effects of psychosocial variables, such as family socioeconomic status, maternal health, and coping styles. Our research plan also includes extensive analysis of gene-by-environment interaction effects and mediation by epigenetics and brain development.

Ultimately, the goal of our research program is to increase understanding of the effects of PNMS and its biopsychosocial mechanisms, such that interventions may be developed that optimize the overall development of the unborn child.

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