# Chapter 14
# Using Natural Disasters to Study Prenatal Maternal Stress in Humans

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**Abstract** Animal studies of prenatal maternal stress permit random assignment of pregnant animals to stress and no-stress groups, and allow total control of the type, severity, and timing of the stressor in utero. Human studies have obvious constraints that make the use of experimental methods nearly impossible. Studying pregnant women who experience natural disasters during pregnancy, however, approximates the random assignment to groups enjoyed by animal studies, and can characterize the timing of the stressor in utero with great precision. In this chapter, we briefly describe our three ongoing prospective longitudinal studies of children exposed to prenatal maternal stress from natural disasters. We present results from Project Ice Storm in detail, showing effects of prenatal maternal stress on cognitive and neurodevelopment. We contrast these results with preliminary findings from the Iowa Flood Study and introduce the QF2011 Queensland Flood Project. In the "Discussion" section, we present conclusions to date and discuss the relative effects of the severity of maternal objective disaster exposure and maternal subjective distress levels, the moderating effects of fetal sex and the timing of the stressor in utero, and the longevity of the effects. Finally, we discuss some possible mechanisms that may mediate the effects of prenatal maternal stress on the neurodevelopment of children.

## 14.1 Introduction

Retrospective epidemiological studies suggest that maternal exposure to a severe stressor during pregnancy (e.g., divorce, death of a relative, foreign invasion) increases the fetus' risk for suboptimal growth and for developing a variety of neurodevelopmental disorders later in life, such as autism and schizophrenia. The subsequent challenge is to understand the process that is responsible for these effects: how much of the effect of maternal exposure to an event is due to the objective severity of the event itself, how much is due to her subjective level of distress, how

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much to her hormonal response, and how might these aspects of the stress experience interact to affect the unborn child? And how might the mother's genetic profile moderate her subjective and hormonal response to a potentially stressful event? Similarly, how might the timing of the stressor in utero, the sex of the child, and the child's own genetic profile moderate the effects of the mother's distress on his or her own neurodevelopment?

When testing the "fetal programming hypothesis" prospectively, animal studies randomly assign pregnant animals to stress or nonstress conditions and find that maternal glucocorticoids (GCs) pass the placenta and alter fetal brain development, particularly the hypothalamic–pituitary–adrenal (HPA) axis and immune system, causing changes in a wide variety of outcomes for the offspring. Using experimental animals, the type, severity, and timing of the prenatal stress can be varied and controlled. In humans, however, the criteria for the gold standard of the rigorous experimental method are difficult to meet because we cannot randomly assign pregnant women to different stress conditions to determine the effects on the fetus. Without such rigor in the research design, the internal validity of a study is called into question, and the biopsychosocial mechanisms responsible for the wide variety of consequences of prenatal maternal stress (PNMS) seen in human offspring remain obscure.

Natural experiments offer an opportunity to circumvent the obstacles to random assignment in human research on PNMS. Many forms of disaster distribute their harm in quasi-random fashion, affect sizable communities that include large numbers of pregnant women, and have sudden onsets that allow the researcher to determine the moderating effects of the timing of the event in gestation. In human research, it is also important to distinguish between the pregnant woman's objective exposure to an event and her degree of subjective distress in response to it. Although one may assume that two rats of the same strain will not differ appreciably in their level of distress at having their tails pinched, for example, the human stress response is highly individual. Appraisal theory, which describes the intrapsychic processes that explain why two people experiencing the same event may have completely different emotional reactions to it (Folkman and Lazarus 1988; Lazarus 1991; Smith and Lazarus 1990), suggests that the objective degree of exposure to a stressor and the subsequent subjective distress are relatively independent of each other.

The goal of our research program is to capitalize on natural disasters in order to complement current understanding of how stress to the pregnant woman impacts her unborn child. We aim to determine the relative effects of several objective, subjective, and hormonal components of the stress experience by tracking these aspects of stress as they cascade onto biological processes in mother, placenta, and fetus, and onto development through early childhood and beyond.

In this chapter, we will summarize our three ongoing studies of women exposed to natural disasters during pregnancy and the findings on the child that are relevant to neurodevelopment, and discuss the general trends in the results.

## 14.2 Background

Disasters and other independent life events have been used in retrospective PNMS research and have shown effects on the development of psychopathology in later life. PNMS during specific weeks of gestation significantly increases the risk of developing schizophrenia and major depression: This has been shown in retrospective studies of the death of the mother's husband (Huttenen and Niskanen 1978) or other relatives (Khashan et al. 2008) during the pregnancy, of hurricanes and tornadoes (Kinney et al. 1999a), and foreign invasion (van Os and Selten 1998). Similar conclusions have been made for autism. In a historical analysis of ten severe storms in Louisiana, Kinney et al. (1999b; 2008) report that rates of autism in the state were significantly increased in a dose–response manner according to the severity of the storms. For children exposed during weeks 20–24 or 36–40 of pregnancy, for storms classified by the National Weather Service as moderate or high intensity, the prevalence rates for autism rose above baseline rates of 5.2/10,000 to 9.7, and 26.6/10,000 for moderate- and high-intensity storms, respectively. Although these retrospective studies demonstrate the power of a stressor in pregnancy to disrupt development in the fetus, they are incapable of elucidating the active ingredient in the prenatal stress experience.

Prospective studies of independent stressors, on the other hand, can be designed so as to disentangle the effects of any genetic transmission of maternal traits, the intrauterine environment, and the postnatal rearing environment. Our approach to PNMS research 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). By their nature, disasters tend to have sudden onsets and to be independent of the control of individuals (i.e., "independent stressors"). Using disasters for natural experiments in PNMS presents an approximation of the randomization afforded by true experiments and capitalizes on the relatively large potential subject pool following a disaster to a large community.

We currently have three such studies under way: Project Ice Storm, begun after the January 1998 Quebec Ice Storm in Canada; The Iowa Flood Study, including pregnant women exposed to the floods of June 2008 in the USA; and QF2011, the Queensland Flood Study of pregnant women in and around Brisbane, Australia. Although the samples are relatively small, with initial sample sizes between 200 and 300 women, statistical power is enhanced by having a range of exposure levels from mild to severe; by having a deep level of information on the women, their exposures, and their distress gathered soon after the events; by the fact that the degrees of exposure to the disasters were independent of family psychosocial attributes; and by the acute onsets of the events which allow exact dating of the stressors in the pregnancy. The independent nature of these stressful events allows us to worry less about controlling for potential confounds and allows us to disentangle the effects of objective degrees of exposure to the event from the women's subjective distress and hormonal responses.

As such, the overarching aim of our research program is to increase understanding of the ways in which different aspects of PNMS influence the development of the unborn child. We began this endeavor with the preconceived, underlying hypothesis that the more severe the woman's objective exposure to a disaster, the greater would be her subjective distress, which would result in higher levels of basal cortisol, which should then be the active ingredient in the effects on the fetus.

### *14.2.1 Project Ice Storm*

Project Ice Storm was conceived following one of Canada's worst natural disasters in history: the January 1998 Quebec ice storm. During the first week of the year, a series of freezing rain storms passed through southern Quebec. The weight of the ice toppled high-tension power lines and utility poles, collapsing the power grid to the region. Resulting power outages ranged from a few hours to as long as 6 weeks for 3 million people in the province of Quebec. On Friday, January 9, the downtown core of Montreal was blacked out, leaving the city in darkness and commuters stranded in metro cars. The military were called in to assist local forces in removing broken trees and other debris from roads. Cold fronts followed the mild weather, plunging the region into seasonal temperatures of −10 °C to −20 °C. Without electricity to power central heating, pumps for well water, farm equipment, or factories, the personal and financial costs of the ice storm crisis left a significant impact on the population. Security forces went door to door to rescue isolated individuals in danger from cold and hypothermia, asphyxiation from unconventional heating devices, and fire due to blocked chimneys. There were more than 27 deaths attributed to the ice storm.

We identified physicians who deliver babies in the four main hospitals in the region southeast of Montreal (the Montérégie) which is typified by bedroom communities and rural areas. Physicians who agreed to collaborate indicated the number of patients in their practice who met our inclusion criteria: over 18 years of age, French-speaking, and pregnant on January 9,1998, or became pregnant between January 9 and April 9 (the preconception-exposed group). We delivered the correct number of postal questionnaires to each physician whose office staff addressed and mailed them on June 1,1998. Of the 1,440 questionnaires that were sent, 224 women responded—a 15.5 % response rate. Of the 224 initial responders, 178 women gave us their names and addresses, and permission to recontact them. Some of these women's pregnancies ended in miscarriage or stillbirth, and other families were lost to follow-up over the years. Our largest sample for a single testing was 110 children at age 5½ years. Our most recent assessment, at the age of 13½, included approximately 80 families.

The first questionnaire in June 1998 included a series of objective items about the women's exposure to the ice storm crisis. We constructed items to reflect four main categories of disaster exposure: threat, loss, change, and scope. To create a total score, we attributed a maximum of 8 points to each category and then summed them

to create the Storm32 objective stress score. Table 14.1 presents the Storm32 items and their weightings. Women also completed the Impact of Event Scale-Revised (IES-R; Brunet et al. 2003; Weiss and Marmar 1997) which reflects the severity of their posttraumatic stress symptoms relative to the ice storm: hyperarousal, avoidance, and intrusive thoughts or images. We included saliva sampling kits for the assessment of cortisol levels at seven times points over 24 h. The questionnaire also included scales of current anxiety and depression. At 6 months after each woman's due date, we sent a second questionnaire about the birth and the newborn, and queried about other life events in the preceding year. Mental health and life event scales were repeated at every assessment.

The goal of Project Ice Storm has been to determine the effects of PNMS on the cognitive, behavioral, physical, and motor behavior of the children as they develop. Over the years, and as funding permitted, Project Ice Storm mothers completed postal questionnaires 6 months after their due dates, and when the children were 2, 4, 5, 6, 8, 9, 11, and 13 years of age. The children's school teachers completed rating scales of the children throughout elementary school, and the children have completed self-report questionnaires since the age of 11. We assessed the children's development through direct testing at ages 2, 5, 8, 11, and 13 years, including structural brain magnetic resonance imaginings (MRIs) at age 11, and a social stress test at age 13. DNA, diurnal and reactive cortisol, and blood for assessing glucose tolerance and immune functioning have also been collected from the children at various points. Beginning in 2013, further developmental assessments and brain imaging will continue between the ages of 15 and 18 years, and perhaps beyond as funding permits.

## The Sample

Approximately half of the sample had given birth by June 1, the date the first questionnaire was mailed. The sample had, and maintains, a fairly equal balance of women who were exposed to the ice storm during the first, second, and third trimesters and in the 3-month preconception period. In addition, their infants were in equal numbers of boys and girls. Rates of preterm birth (8 %) and postpartum depression (17 %) were within the normal range. The 224 initial responders to the Ice Storm questionnaire were significantly better educated and had higher family incomes, than the averages for their region; 70.8 % of the participants were from households in the upper-middle class or above, and only 4.5 % were from lower and lower-middle classes. This socioeconomic bias in the sample explains the high cognitive functioning of their children (see sections below).

## Stress Levels

On average, the women in the sample were without electricity for 14 days, with some going without power for as long as 45 days. The families were without phone

**Table 14.1** Storm32: questions used to assess the four dimensions (threat, loss, scope, and change) of our objective stress questionnaire that the mothers completed after the ice storm

| Threat | | Loss | | Scope | | Change | |
|---|---|---|---|---|---|---|---|
| 1 | Were you injured?<br>No = 0<br>Yes = 1 | 1 | Did your residence suffer damage as a result of the ice storm?<br>No = 0<br>Yes = 2 | 1 | How many days were you without electricity?<br>0 = 0–5 days<br>1 = 6–13 days<br>2 = 14–19 days<br>3 = 20–21 days<br>4 = > 22 days | 1 | Did your family stay together for the duration of the ice storm?<br>Yes = 0<br>No = 1 |
| 2 | Was anyone close to you injured?<br>No = 0<br>Yes = 1 | 2 | Did you experience a loss of personal income?<br>No = 0<br>Yes = 2 | 2 | How many days were you without the use of your telephone?<br>0 = 0 days<br>1 = 0.01–1 day<br>2 = 2–4.5 days<br>3 = 5–7 days<br>4 = 8 + days | 2 | Did you spend any time in a temporary shelter?<br>No = 0<br>Yes = 1 |
| 3 | Were you ever in danger due to: | 3 | How much was the total financial loss including income, food, damage to home?<br>0 = < CAD 100<br>1 = CAD 100–CAD 1000<br>2 = CAD 1000–CAD 10,000<br>3 = CAD 10,000–CAD 100,000<br>4 = > CAD 100,000 | | | 3 | How often were you required to change residence during the ice storm?<br>0 = 0<br>1 = 1 time<br>2 = 2+ times |
| 3.1 | …the cold<br>No = 0<br>Yes = 1 | | | | | 4 | Did you take in guests during the ice storm?<br>No = 0<br>Yes = 1 |

**Table 14.1** (continued)

| Threat | | Loss | Scope | Change | |
|---|---|---|---|---|---|
| 3.2 | …exposure to downed electrical power lines<br>No = 0<br>Yes = 1 | | | 5 | Did you experience an increase in physical work during the ice storm?<br>0 = less or same<br>1 = little or lot more |
| 3.3 | …exposure to carbon monoxide<br>No = 0<br>Yes = 1 | | | 6 | Number of nights away from home:<br>0 = none<br>1 = 1–7.5 nights<br>2 = 8 + nights |
| 3.4 | …lack of potable water<br>No = 0<br>Yes = 1 | | | | |
| 3.5 | …lack of food<br>No = 0<br>Yes = 1 | | | | |
| 3.6 | …falling branches and ice<br>No = 0<br>Yes = 1 | | | | |
| 8 points | | 8 points | 8 points | 8 points | |

service for an average of 4 days, and some for as long as 34 days. Only one-third of the families in the study never left their own home, while most families were forced to move to friends', neighbors' and relatives' homes; half the sample moved once or twice, and 15 % moved up to five times during the crisis.

The initial sample scored between 0 and 24 on the Storm32 objective stress questionnaire, with an average score of 10.6 (standard deviation (SD) = 4.7) and a fairly normal distribution of scores (Fig. 14.1). The distribution of subjective stress levels, as assessed by the IES-R, was positively skewed (Fig. 14.2), and mean levels were moderate ($M$ = 11.9; SD = 12.5), with 16.4 % of women scoring above the cutoff of 22 often used for screening for posttraumatic stress disorder (PTSD). In general, cortisol levels for the women showed the usual diurnal patterns and, as expected,

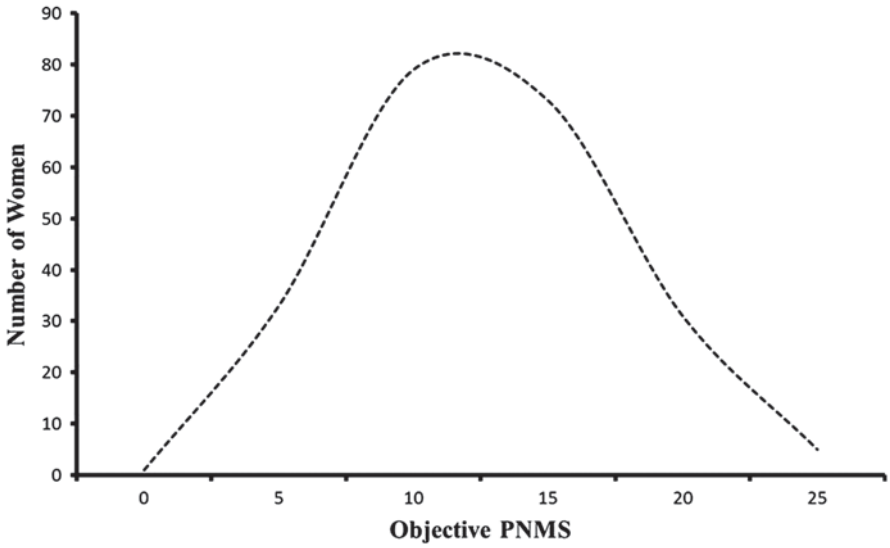


**Fig. 14.1** Distribution of Storm32 objective prenatal maternal stress (*PNMS*) scores for Project Ice Storm cohort

were significantly higher in women who were still pregnant at the time they took the samples. This difference in basal levels according to pregnancy status has made the inclusion of maternal cortisol in statistical analyses untenable for much of our study.

The three forms of stress (objective, subjective, and cortisol) are relatively uncorrelated with each other. Storm32 and IES-R scores tend to be correlated at less than 0.30, and Storm32 and diurnal cortisol levels are uncorrelated ($r<0.20$). In the subsample that was still pregnant at saliva sampling, IES-R and integrated diurnal cortisol correlated −0.26 ($p<0.05$); although statistically significant, these two measures of stress cannot be considered highly associated, and the association that is present is negative: the more severe the women's PTSD symptoms the lower their basal cortisol levels, echoing findings from the PTSD literature (Zoladz and Diamond 2013). Socioeconomic status (SES), as reflected in the Hollingshead Index which takes both maternal and paternal education and occupation into account, has been uncorrelated with both objective and subjective stress ($r<0.20$).

## Cognitive Development

**General Intelligence** Perhaps one of the most obvious clues to any effects of PNMS on neurodevelopment is the effect on general intelligence. As noted earlier, the families in Project Ice Storm are better educated and have higher incomes than the regional averages. Not surprisingly, then, their children, even those from high-stress families, have consistently scored above average on all tests of cognitive development. Statistically, this presents an inherent obstacle to explaining the

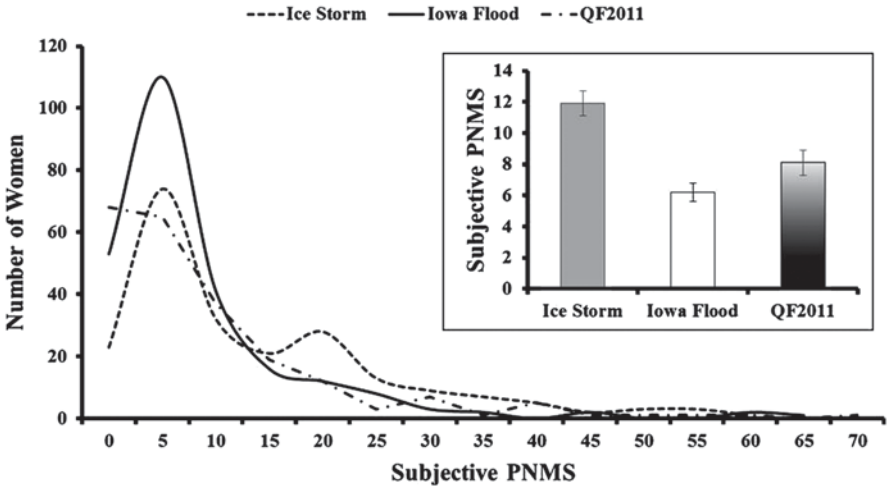


**Fig. 14.2** Distribution and means (with standard errors) of subjective prenatal maternal stress (*PNMS*) levels (IES-R) for women in all three cohorts

limited variance in outcome variables. Psychosocially, this limits the study's generalizability to more disadvantaged families who would have had fewer financial resources for dealing with the ice storm crisis.

We obtained our first small grant for Project Ice Storm in time to test a subset of Project Ice Storm children at age 2 years (Laplante et al. 2004, 2007). To select the sample, we included only children whose mothers were exposed to the ice storm in the first ($n=21$), second ($n=14$), or third ($n=23$) trimesters (that is, we excluded the preconception-exposed group). We also excluded mothers who reported cigarette or alcohol use in pregnancy, and those who reported any other major life events while pregnant. In order to limit the sample size while maximizing the variance between groups, we split the sample into three equal groups according to the Storm32 objective stress scale and invited the low- and high-stress groups for face-to-face testing, but not the moderate-stress group. Children were tested with the Bayley Scales for Infant Development for general intelligence (the Mental Development Index: MDI), the MacArthur Communicative Developmental Inventory (MCDI) for receptive and productive language, and they were videotaped during a 15-min free play session to assess the maturity of their play style.

At this 2-year assessment, as illustrated in Fig. 14.3, we found that children from the high-objective stress group had, on average, approximately one full SD lower Bayley scores than those from the low-stress group, even controlling for birth weight; SES was unrelated to the Bayley MDI, perhaps because of the limited range in SES levels. The large effect of PNMS was obtained with the Storm32 objective stress score; the women's subjective distress level, reflected in the IES-R posttraumatic stress symptom score, had no effect on Bayley scores. At this age, the results demonstrated a significant moderating effect of the timing in utero of the ice storm:

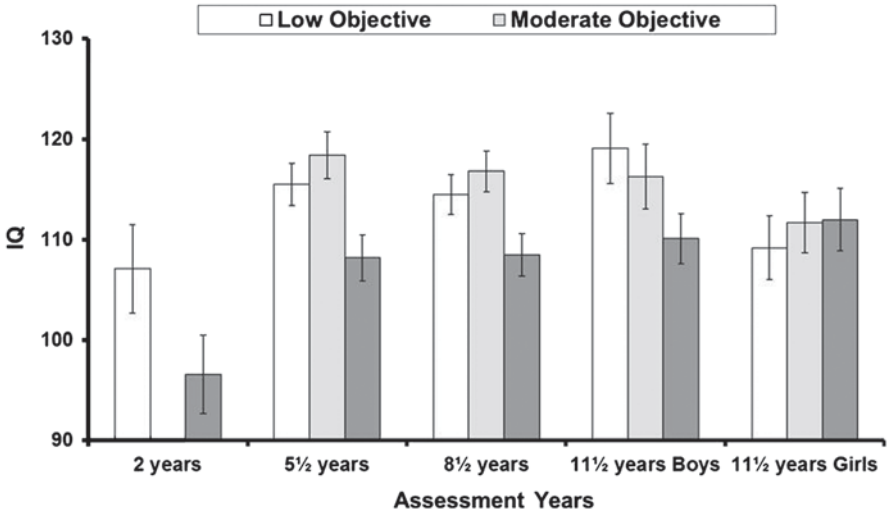


**Fig. 14.3** Means and standard errors for Bayley MDI scores at 2 years and WPPSI/WISC-III IQ scores at 5½, 8½, and 11½ years

The difference between low and high Storm32 groups was significant for children exposed to the ice storm in the first or second trimester, but not in the third.

Given that both animal and human research suggest that prenatal stress or maternal pregnancy anxiety predicts a more difficult temperament in children (Weinstock 2008), we were concerned that scores on the Bayley may reflect effects of PNMS on the children's behavior with the experimenter rather than their cognitive development per se. By observing the children during a free play session while their mothers sat nearby, however, we could circumvent potential confounding by the child's temperament and attempt a replication of the results found by the more structured Bayley test using a more implicit test of cognitive development (Laplante et al. 2007). The experimenter presented all of the children with the same array of toys arranged identically. Raters coded videos of each child's play behaviors, moment by moment, into three categories: stereotypical, such as waving or mouthing a toy; relational, when touching two or more toys together without any specific function; and functional, in which a toy is used according to its intended function, such as rolling the truck along the floor or making pouring motions with the teapot. Results from these ratings replicated the effects of objective stress from the ice storm, as well as the moderation of the effect by the timing in utero: for children exposed to the ice storm in the first or second trimester, the low Storm32 objective stress group engaged in significantly less of the immature stereotypical play, and in significantly more of the more mature functional play, than the high-stress group. On the other hand, although the effect of objective stress was again highly significant, subjective stress (IES-R) levels were also significantly correlated with functional play outcomes.

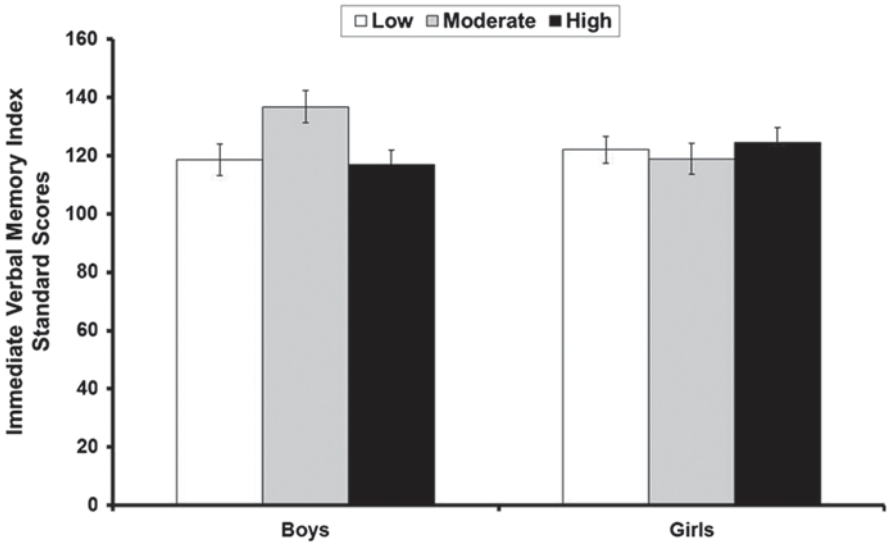


**Fig. 14.4** Immediate Verbal Memory Index standard scores for boys and girls at 5½ years of age (means and standard errors)

The results obtained at age 2 years encouraged the Canadian Institutes of Health Research (CIHR) to support the project, and more extensive cognitive assessments were done at the ages of 5½, 8½, and 11½ years, including Wechsler intelligence scales, memory, and attention measures. Given the new funding, we were able to include all children from the study, including the moderate-stress group. Once again, at ages 5½ (Laplante et al. 2008) and 8½ we found that the high objective stress group had significantly lower full scale IQ than the low-stress group (5½: 108.2 vs. 115.5; 8½: 108.5 vs. 114.5); what we had not anticipated, however, was that the moderate-stress group obtained higher IQ scores than the low-stress group (5½, 118.4; 8½, 116.8). These curvilinear results were confirmed with a significant quadratic term when using the Storm32 score as a continuous measure. We could not have predicted these curvilinear results from the findings at age 2 since we had decided not to include the moderate-stress group in the testing at that age (Fig. 14.3).

**Verbal Memory** In similar fashion, the results using the Immediate Verbal Memory Index of the Children's Memory Scales with the children at 5½ years of age once again show this curvilinearity effect of Storm32 objective stress, although this time in boys only (Fig. 14.4).

**Language Development** The susceptibility of language development to the effects of PNMS has been a recurring theme in Project Ice Storm results. During the assessment at 2 years, we administered the MCDI which presents the mother with a list of words. She indicated, for each word, whether the child understood it (receptive vocabulary) and/or used the word (expressive/productive vocabulary). At this age, the high objective stress group understood 10% fewer words than the low-

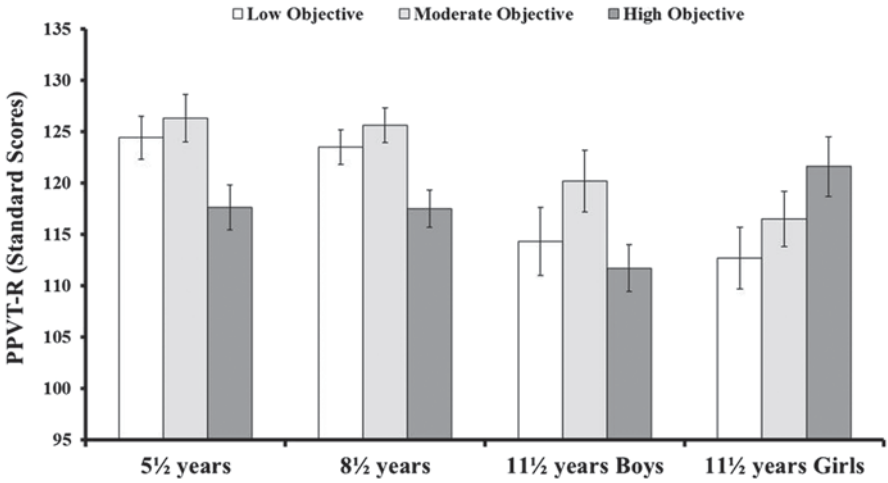


**Fig. 14.5** Receptive vocabulary standard scores as a function of year of assessment (means and standard errors). *PPVT-R* Peabody Picture Vocabulary Test

stress group (82.4 vs. 90.6 words), and used 27 % fewer words than their low stress peers (54.7 vs. 74.9; Laplante et al. 2004). As with the results for the Bayley scales, there was no effect of the mothers' subjective stress scores. However, unlike the results for the Bayley and for the play style, there was no timing effect on language development.

Beginning with the assessment at age 5½ years, we have used the Peabody Picture Vocabulary Test (PPVT-R) to assess receptive language, and have used the verbal tests from the Wechsler scales to assess other components of language development. At age 5½, we found significant effects of Storm32 objective stress, but not subjective stress (IES-R), on PPVT-R scores and replicated the curvilinear effects of PNMS on language that we saw in the full-scale Wechsler IQ scores, with a slight increase in vocabulary with moderate stress but a sharp drop in vocabulary with higher stress levels (Fig. 14.5; Laplante et al. 2008). Within the Wechsler itself, we found similar significant and curvilinear effects of objective stress on the two verbal tests we administered (Information and Similarities), but no effect on the nonverbal Block Design test.

Similar IQ and receptive vocabulary outcomes were observed in boys and girls at 8½ years of age: Children exposed to moderate levels of objective PNMS exhibited the highest scores while those exposed to high levels had the lowest scores. At age 11½, however, the results differed by sex: For boys, the curvilinear pattern was replaced by a significant, negative, linear effect of objective stress on IQ, while for girls there was no longer any effect of prenatal stress (Fig. 14.3). For PPVT-R scores at 11½ years, boys still showed the curvilinear effect, while for girls there was now a significant, linear, positive effect of objective stress on vocabulary. Thus, the effects of PNMS on cognitive outcomes appear to become sexually dimorphic at the onset of puberty (Fig. 14.5).

### Physical Development

Conventional wisdom would suggest that any effects of PNMS on cognitive outcomes would be the result of a direct neurodevelopmental insult during gestation, probably due to the effects of maternal stress hormones passing through placenta. Indeed, a review of the literature (Charil et al. 2010) supports the notion that PNMS has important, negative effects on brain development, at least in laboratory animals. The hippocampus appears to be especially sensitive to PNMS. Unfortunately, these studies are difficult to replicate in humans.

**Dermatoglyphic Asymmetry** Neurodevelopmental insults may be evident in parts of the human body outside of the brain itself. For example, individuals diagnosed with schizophrenia, which is presumed to be neurodevelopmental in origin, exhibit higher rates of some physical traits than do normal controls. Schizophrenia patients have, on average, more minor physical anomalies (Lane et al. 1997) and have greater left–right asymmetry in the number of ridges in their fingerprints (Markow and Wandler 1986). Fingerprints develop out of the same fetal ectoderm as the brain between weeks 14 and 22 which overlaps with the timing of crucial hippocampal development. There was considerable debate within the schizophrenia literature about the causes of this dermatoglyphic asymmetry, whether genetic or neurodevelopmental in origin.

To address this debate, we tested the hypothesis that maternal stress from the ice storm would predict dermatoglyphic asymmetry in the children, but only in those for whom the onset of the ice storm occurred at some point between weeks 14 and 22 of pregnancy (King et al. 2009). Results showed that mere exposure to the ice storm during the key time period resulted in half a standard deviation greater asymmetry than in children exposed at other times of gestation. Within the group exposed during weeks 14–22, greater asymmetry was associated with both more severe objective stress ($r = 0.348$, $p < 0.10$) and subjective stress ($r = 0.500$, $p < 0.05$). Finally, for the 17 children in the 14–22-week exposure target group whose mothers were still pregnant when they took diurnal salivary cortisol samples, higher levels of cortisol were associated with less asymmetry ($r = -0.557$, $p < 0.05$), that is, greater evidence of neurodevelopmental insult was associated with lower levels of maternal cortisol. Although we would have predicted that higher maternal cortisol would have been associated with greater evidence of neurodevelopmental insult, our cortisol assessments were taken 5–6 months after the ice storm crisis and may be poor reflections of actual acute levels of cortisol at the time of the storm. The stress literature is debating the meaning of the low cortisol levels in people diagnosed with PTSD; there is support for the notion that these low cortisol levels pre-existed the trauma exposure (a difficult hypothesis to test) and represent a vulnerability for developing symptoms of PTSD in the face of trauma rather than a concomitant effect of the exposure (Yehuda et al. 2000).

**Brain Structure** The effect of ice storm stress on dermatoglyphic asymmetry suggested the possibility that an effect would also be seen on the development of the

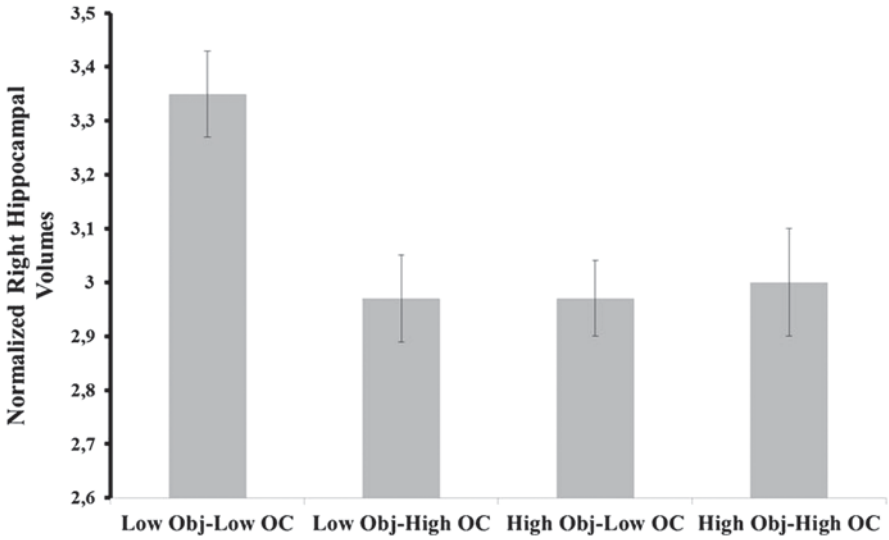


**Fig. 14.6** Normalized right hippocampal volumes as a function of objective PNMS and obstetric complications (OC) (means and standard errors)

hippocampus. Structural brain scans (MRI) were conducted when the children were aged 11½ years; for comparison, we also scanned a matched sample of children who were born in the year before the ice storm. Unpublished results show that in both boys and girls, smaller normalized right and left hippocampal volumes were associated with being exposed to a greater number of maternal obstetric complications. Moreover, boys exposed to higher levels of objective PNMS had smaller normalized right hippocampal volumes. However, an observed objective PNMS × obstetric complication interaction suggests that smaller normalized right hippocampal volumes were observed in boys who were exposed to either high levels of objective stress, irrespective of the level of maternal obstetric complications, or low levels of objective PNMS and high levels of maternal obstetric complications (Fig. 14.6).

Thus, exposure to a major stressor in utero appears to have implications for brain development. But what of our comparison cohort of postnatally exposed children? Near the end of our scanning sessions, we began to wonder whether the neurodevelopment of children in our comparison group, who had been infants during the ice storm, might be influenced by the stress of their mothers and, if so, by what mechanism? Apart from having a stressed mother, or being cold, it occurred to us that maternal stress might be transmitted to infants directly via breast milk. Indeed, studies show that maternal cortisol does reach the infant via breast milk (Patacchioli et al. 1992). For the 15 children who were breastfed during the ice storm crisis, we created a composite score, multiplying the mother's objective stress score times the number of days that her child was breastfed during the disaster. The higher this composite stress exposure score, the smaller the child's left hippocampal volume ($r = -0.581$, $p < 0.10$); examination of the scatter plot ruled out the effects of outliers (Fig. 14.7; King et al. 2012).

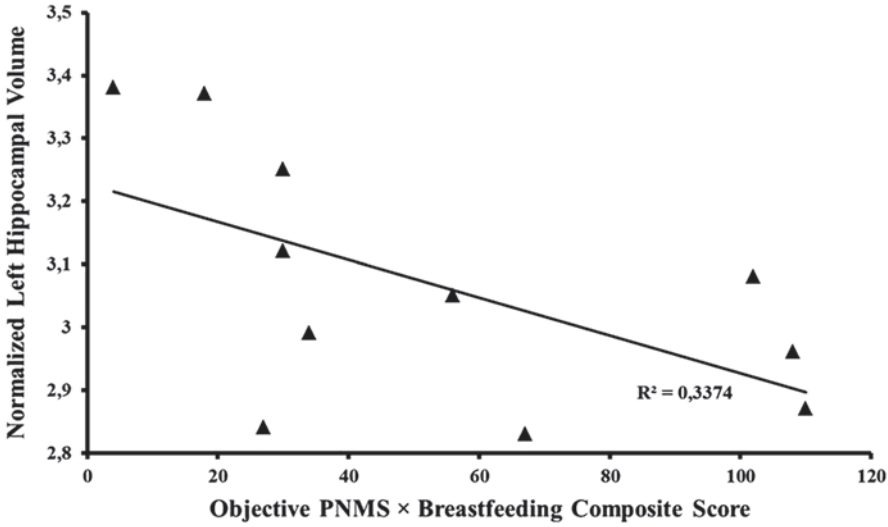


**Fig. 14.7** Scatterplot of the control children's normalized left hippocampal volumes as a function of their mother's objective prenatal maternal stress (*PNMS*) × duration of breastfeeding composite scores

**HPA Axis Functioning** Because the animal literature suggests that PNMS alters HPA functioning in the offspring, we have obtained salivary cortisol samples from our subjects before and after potentially stressful situations on several occasions. At about the age of 5 years, children in Quebec are scheduled to receive vaccinations. We traveled to the medical clinics in order to be present for the vaccinations of 34 children who provided saliva samples while in the waiting room before the injection, and 15 min post injection. Results suggest that neither maternal objective nor subjective stress was related to the children's acute cortisol reaction to the vaccination. In all children, however, lower acute stress response predicted more severe internalizing (e.g., depression and anxiety) and externalizing (e.g., aggression, destructiveness) at age 5½ on the maternal-rated Child Behavior Checklist (CBCL).

We used a similar protocol to determine the children's stress reactivity from the MRI scans at age 11½. Preliminary results from the Project Ice Storm children suggest there is no association between either objective or subjective PNMS and pre- or post-MRI cortisol levels.

For the subjects from the infancy-exposed MRI comparison group who had been breastfed during the ice storm, the results suggest that higher composite stress scores were associated with smaller left hippocampal volumes, which were then associated with smaller acute cortisol responses to the stress of the MRI scan ($r = 0.632$, $p < 0.05$), which were then associated with more severe CBCL internalizing problems at the same age (King et al. 2012). This latter association is consistent with the results from the prenatally exposed Ice Storm cohort for whom more blunted cortisol responses to vaccination were associated with more severe internalizing

problems. The clinical implications of these results are that the failure to mount a stress response is a greater risk factor for psychopathology than an increase in cortisol, something seen in conditions such as schizophrenia (Brenner et al. 2009).

Finally, at age 13½ years, 63 Project Ice Storm teens completed the Trier Social Stress Test (Kirschbaum et al. 1993). Data from that protocol have not been analyzed to date, but will provide useful information on the longevity of the effects of PNMS on the HPA axis into early adolescence. The data collection protocol at age 15½ (2013–2014) will include salivary cortisol awakening responses in association with daily stressors during the school year.

## Project Ice Storm Limitations

Project Ice Storm was the first prospective longitudinal study of a natural disaster that teased apart the objective and subjective aspects of the PNMS experience. As such, it provides unique data about the nature of PNMS and its effects. However, there are several limitations to the project that can neither be overlooked nor remedied.

These limitations are related to the numerous challenges involved in initiating a large study of pregnant women in the immediate aftermath of a natural disaster. First, despite the significant effects that both objective exposure and subjective distress have on a variety of outcomes, we have no data that enlighten us about the biological mechanisms involved in these effects. Part of the problem is that pregnant women in a target population will not all stay pregnant for long; fetuses will not wait for researchers to prepare a protocol that would permit them to collect precious biological samples that may contain clues about the cascade of effects from maternal exposure, through the placenta and umbilical cord to the fetus. In Project Ice Storm, half the sample had already given birth by the time of the first postal survey. Any delay between the disaster and initial data collection may also compromise the prospective nature of the data since the difficulty of the women's birthing experiences may color their recall of the disaster. In addition, the longer the delay between the disaster and the collection of biological data, such as cortisol, the more difficult the interpretation of the hormonal data; we have found it difficult to conduct analyses combining cortisol samples from pregnant women and from women who have already given birth and who may or may not be breastfeeding. Even the subjective stress data must be interpreted within the context of a relatively prolonged stress response: Do high levels of distress 6 months after the ice storm necessarily reflect similarly high levels during the storm itself, and how many of the women with low distress levels at 6 months had had high levels at the height of the disaster? Thus, speed is of the essence in setting up a disaster study.

The second challenge is to initiate a study (including protocol development, ethics approval, subject recruitment, and assessment) in record time in the absence of dedicated funds. When funds are limited, it is difficult to conduct the most effective recruitment methods. Project Ice Storm relied upon inexpensive postal questionnaires for recruitment and obtained a 15% response rate from a potential sample of 1,400 women, rather than using more direct, personal, and costly face-to-face

methods. Carrying a sample of fewer than 180 cases at the beginning of the study, and fewer than 100 cases 15 years later, means the sample size limits the complexity of the statistical analyses that can be conducted; once the sample is separated by child sex and trimester of exposure, additional interactions and nonlinear associations push the sample size beyond its limits.

Another side effect of the cost-saving recruitment method is that the sample is biased towards the highly educated family. This bias limits the generalizability of the results to similarly advantaged families, and also (in theory) reduces statistical power due to the restricted variance in the children's outcomes in the upper ranges of functioning.

Finally, the occasional critic of Project Ice Storm has noted that it is limited by not having evaluated the pregnant women in the study before the ice storm struck. Not being blessed with the gift of prophecy, this limitation seemed quite impossible to overcome.

### *14.2.2 The Iowa Flood Study*

In 2008, we discovered that we could conduct a pre-post disaster study without necessarily being able to predict future disasters. In early June of that year, the Midwest of the USA was hit with back-to-back storms. The record-breaking levels of rainfall lead to the flooding of rivers and breeching of levees. Iowa lay at the heart of the destruction, suffering its worst flooding in more than 50 years. The Cedar and Iowa rivers exceeded record high water levels set back in the early twentieth century. In Iowa alone, 83 of 99 counties were declared federal disaster areas. In Cedar Rapids and Linn County, 1300 city blocks (9.2 square miles) were covered in water, engulfing the city hall, Linn County jail, fire department, and public library. The severe flooding in Johnson County, Iowa City, and the University of Iowa forced the evacuation of 35,000–40,000 people from their homes. The disastrous flooding lasted from early June to early July damaging 5238 homes and 940 businesses. The agricultural industry suffered a US$ 2 billion loss as many corn and soybean crops were destroyed. Approximately two dozen people were killed and 150 injured as a result of the storms and flooding. Overall, the 2008 Midwestern flood ranks among the top ten disasters in US history.

As the flood waters were still rising, we contacted Dr. Michael O'Hara, the well-known postpartum depression researcher at the University of Iowa, to discuss a collaboration. We learned that Dr. O'Hara's doctoral student, Kimberly Nylen (now Hart), was in the midst of conducting a study linking stress in pregnancy to obstetric and birth complications (Nylen et al. 2013a, b). We invited them to collaborate on a replication of Project Ice Storm by piggybacking our disaster protocol onto their birth outcomes project.

## The Sample

The 134 women who had already been recruited into Nylen's doctoral research were invited to join the Iowa Flood Study. Additional participants continued to be recruited for both studies via media advertisements distributed throughout Eastern Iowa, in-person recruiting in the Department of Obstetrics and Gynecology at the University of Iowa Hospitals and Clinics, letters distributed to patients of obstetrics and gynecology practices in Eastern Iowa, and the clinic associated with the Johnson County Department of Public Health.

When our final recruitment phase was completed, we had flood stress data from 268 women who had been pregnant before or during the flooding, of whom 74 had been assessed by Nylen before the flooding for psychopathology, life events and daily hassles, social support, coping style, and other psychosocial variables. Despite efforts to recruit a wider range of participants, the majority of subjects were from either upper-middle class (55 %) or upper class (20 %), with only one woman in the lower-class category, and 25 % in the lower-middle- and middle-class groups—not appreciably more representative than the Project Ice Storm sample. Although the Iowa Flood Study failed to include a preconception-exposed group of any size ($n = 18$), 34 women from Nylen's project, who had given birth before the floods, constituted a postpartum-exposed group that may be followed into the future to determine the effects of maternal stress during infancy and, perhaps, the role of breastfeeding.

## Stress Levels

Much of the initial assessment protocol was similar to that of Project Ice Storm. However, the objective stress questionnaire from the ice storm needed major revisions to be relevant to a flood disaster. The final version included old and new items in the four categories of threat, loss, scope, and change. Weighting each category equally, with a maximum of 25 points each, our Iowa Flood Study scale is named IF100. As expected, a large percentage of women experienced very little hardship from the flood, and a small percentage experienced catastrophic loss and danger (Fig. 14.8).

Although Storm32 and IF100 scores cannot be compared directly between the two events, both studies used the IES-R to measure subjective distress. As in Project Ice Storm, the IES-R distribution is highly skewed, with 6.7 % of women scoring above the cutoff of 22 for potential PTSD. Despite the fact that several women from Iowa lost their homes in the floods, something unheard of in the ice storm sample, the average IES-R scores were significantly lower in the Iowa Flood Study than in Project Ice Storm (Fig. 14.2).

In the hope of circumventing the difficulties noted in Project Ice Storm of assessing persistent PTSD symptoms 6 months post-disaster, in Iowa we introduced two "peritraumatic" measures: the Peritraumatic Distress Inventory and the Peritraumatic Dissociative Experiences Questionnaire. Both measures ask the respondent

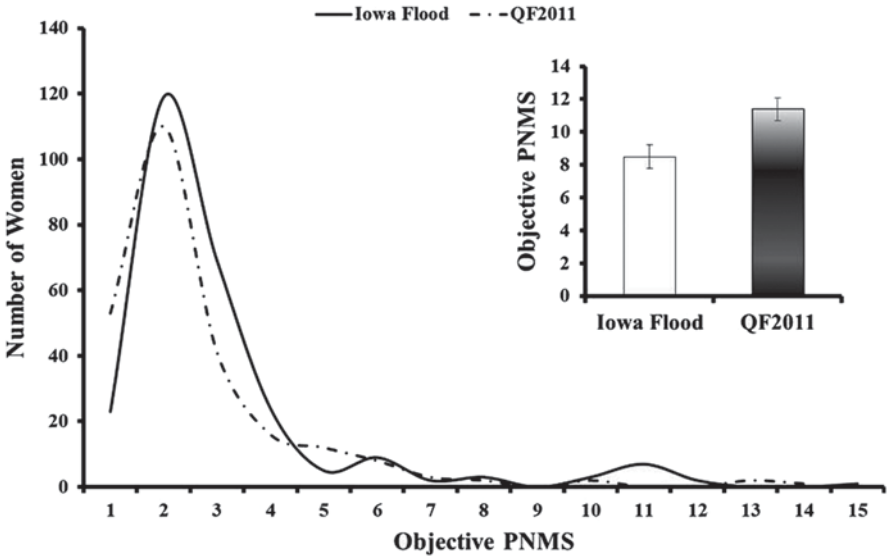


**Fig. 14.8** Distribution and means of objective prenatal maternal stress (*PNMS*) levels for women in the Iowa Flood (IF100) and QF2011 (QIF100) cohorts

to recall and report what they had experienced at the time of the trauma. At recruitment, these peritraumatic measures correlate between 0.60 and 0.70 with the IES-R total score. Future analyses will elucidate the relative contributions these three distress measures make in explaining variance in child outcomes.

## Assessments of Child Development

Funded by the CIHR, face-to-face evaluations of the children's cognitive, behavioral, motor, and physical development have been conducted at ages 2½ ($n = 161$) and 4 years ($n = 130$) with a 5½-year assessment to begin in 2013–2014. To date, only the 2½-year assessment has preliminary results that are sufficiently advanced to present here.

## Cognitive Development

**General Intelligence and Language** As in Project Ice Storm, maternal stress from the disaster explained significant amounts of variance in the children's composite scores from the Bayley. Unlike in the Ice Storm cohort, however, there was no effect of maternal objective stress exposure (IF100). Instead, a significant interaction suggested that high levels of maternal subjective distress (IES-R scores) were associated with lower Bayley scores for those exposed during the first trimester.

Thus, the Iowa results support the idea of a certain vulnerability in early gestation for cognitive development assessed at this age, but suggest that the smoking gun may be maternal subjective distress and not objective hardship in this cohort.

Mothers completed the MCDI during this assessment, checking words on a list indicating their children's receptive and productive vocabulary. Although it appears that the language development of boys and girls were affected in different ways by their mother's flood stress, it appears that for all children exposed to the flood during the first or second trimesters the greater their mother's subjective distress, the lower their productive language at this age.

## HPA Axis Functioning

The Iowa Flood Study included a relatively controlled test of stress reactivity in the toddlers at age 2½. Mothers left the testing room for up to 3 min leaving their toddlers alone (but under surveillance by research staff via camcorder and one-way mirror). Saliva samples were taken before and after the separation. The children's cortisol reactions to the separation were mixed, with some showing an increase in cortisol by 25 % or more (~40 %), others a decrease by at least 25 % (~20 %), and still others showed little change (~40 %). Preliminary analyses of those data, explaining approximately 27 % of the variance in pre-post separation cortisol change, suggest that the association between the mothers' objective stress exposure and the child's cortisol response differed for boys and girls, with girls appearing to be more sensitive to the effects of the stress. Timing also appears to play a role, with greater cortisol responses in children exposed to objective maternal stress in early gestation and lower responses (even decreases in cortisol) in those exposed later in utero.

There was no stress induction included in the 4-year-old assessment, but we plan to follow the effects of maternal stress from the Iowa floods on the children's HPA axis functioning at later ages.

## Iowa Flood Study Limitations

The Iowa Flood Study is the world's first pre-post disaster study of PNMS. Although the data are still being analyzed, it promises to yield unique and crucial results that will further increase our understanding of PNMS. In particular, the ability to control for pre-trauma psychosocial functioning, coping styles, and social support will permit us to better understand pregnant women within their own contexts, and to learn which psychosocial factors may buffer them and their unborn children from adverse outcomes, and which may increase risk.

We had hoped that the Iowa study would provide a larger, more representative sample than the Ice Storm study, and that the range of exposure severity would be greater than that in Project Ice Storm which lacks a "no stress" comparison group. Although the range of hardship is probably greater in Iowa than in Ice Storm, the average IES-R scores were lower. We also failed to recruit a sample with a sig-

nificantly greater range of socioeconomic levels, despite more direct recruitment in sites such as community health clinics. Finally, we had developed a protocol for collecting placentas, umbilical cords, and cord blood in Iowa, but we did not obtain the required funding in time, limiting our ability to study a complete picture of the cascading stress process from mother to placenta to fetus.

### *14.2.3 QF2011 The Queensland Flood Study*

In 2011, after years of severe drought, the Australian state of Queensland experienced some of its worst summer flooding in living memory. Starting late December 2010, the state experienced torrential rainfall, leading to severe flooding throughout much of January 2011. The rains lead to the state's second largest flood in the past 100 years. Severe flooding was recorded throughout most of the Brisbane River catchment, affecting at least 70 towns, including the state capital of Brisbane. Brisbane is the third largest city in Australia and home to more than 1 million people. The flooding in Brisbane alone affected 200,000 people, caused residences on 2100 streets to be evacuated, inundated 18,000 properties, and left 100,000 homes and businesses without electricity. In total, three-quarters of Queensland was declared a disaster zone. Altogether, 35 deaths were directly attributed to the flooding. The flooding severely damaged many roads and bridges leaving many individuals stranded in their homes until they could be rescued by the army. Economic losses were enormous, amounting to around Australian $ 1.5 billion.

Working through our network of contacts, we were referred to Dr. Sue Kildea, director of midwifery research at the Mater Mother's Hospital and at the Mater Medical Research Institute in Brisbane. In Australia, nearly all babies are brought into the world with the aid of midwives, working in hospitals, and 10,000 babies per year are born within the walls of the Mater. Dr. Kildea was coinvestigator on a multisite randomized control trial of two forms of midwifery care, the M@NGO Trial (Tracy et al. 2011), which was in mid-recruitment at the time of the floods. With our invitation to collaborate, she saw an opportunity to determine the extent to which the experimental condition, Group Midwifery Practice, might buffer the effects of stress from the flooding on the pregnant women and their unborn children. She agreed to append a new flood study onto the existing Brisbane arm of the M@NGO Trial. Although flooded out of her home herself, she rallied a team on-site to prepare ethics documents and to put in place procedures for collection of the birth biological samples. Our Montreal team sent a young placentology student to Brisbane to be on-call 24/7 to receive the needed tissues at the time of birth and a research assistant to help the Mater team with the coordination. The number of individuals in Montreal and in Brisbane who were involved in making the QF2011 Queensland Flood Study happen is too great (in quality and in quantity) to describe here. A grant application was submitted to the CIHR on March 1, the first placenta was collected in April, and notification of funding arrived in July of that year.

One advantage of adding QF2011 to the stable of PNMS studies is that it will allow a more direct replication of the Iowa Flood Study—two studies of similar disasters during the same season of the year.

## The Sample

Women who were taking part in the M@NGO trial, and who were still pregnant during the flooding, were recontacted to invite them into QF2011. Additional women meeting the inclusion criteria were recruited in person and by flyer through the Mater Hospital. At this writing, 2½ years post-flood, we are beginning to finalize the description of the QF2011 sample. Objective and subjective stress levels are available for 228 women. Following the birth of the children, we were able to obtain dates of birth and sex of the children from 201 women. Thirty-five women were in their third trimester of pregnancy, 81 in their second trimester, and 75 in the first trimester of pregnancy at the peak of the flooding. An additional 10 women became pregnant within 3 months of the peak of the flooding. The women gave birth to 96 daughters and 105 sons.

## Stress Levels

With the Iowa Flood Study protocol already developed and tested, relatively little adaptation was required to prepare the objective stress questionnaire for the Australian context. Nonetheless, we created more detailed questions about insurance coverage, business losses of the spouse, and other specifics. Once the laborious task of creating the scoring scheme was completed, the Queensland Flood Objective Stress Scale (QFOSS) had a possible maximum of 200 points: 50 points each for the threat, loss, change, and scope scales; we also created an additional scale on nutrition but which does not figure into the QFOSS score.

As in Iowa, the QFOSS scale has a positively skewed distribution, unlike Storm32 which was normally distributed. In both flood studies, a large percentage of women experienced very little hardship as a result of the flood, while a non-negligible percentage lost nearly all of their worldly goods.

Because the QFOSS was essentially an extension of the IF100, we could pull an IF100 score out of the Queensland questionnaire (which we called QIF100). In so doing, we saw that the average objective PNMS score was significantly higher in the Brisbane cohort ($M = 11.4$; SD = 10.8) relative to the Iowa cohort ($M = 8.6$; SD = 11.4; Fig. 14.8).

The IES-R was administered at recruitment, again with the expected skewed distribution. When the IES-R scores were compared across all three studies, women who experienced the ice storm had higher IES-R scores compared to the women who experienced either flood. When comparing the flood victims, women in the Brisbane cohort had higher IES-R scores relative to women in the Iowa cohort (Fig. 14.2).

When comparing the peritraumatic experiences of the flood victims, women in the Brisbane cohort had higher peritraumatic distress levels (recruitment: $M=11.9$, SD=8.9; follow-up survey: $M=9.5$, SD=6.3) compared to women in the Iowa cohort (recruitment: $M=10.4$, SD=7.6; follow-up survey: $M=7.5$, SD=7.2). The women's peritraumatic dissociative experiences did not differ at either assessment point.

As in Project Ice Storm and Iowa, QF2011 subjects provided diurnal cortisol samples, allowing us to study both the cortisol awakening response and the complete diurnal pattern of cortisol secretion. These data have yet to be analyzed.

**Infant Assessments**

The first face-to-face assessment of the QF2011 children was conducted at 16 months of age (2012–2013). The Bayley scales, the VMI Visual Motor Integration, the cognitive free play session, and the MCDI (completed by the mother) were included in the protocol. In addition, the brief separation from the mother, identical to the task used in Iowa, was conducted to assess the child's HPA axis response to stress. This protocol was identical to the one we used in the Iowa Flood Study at 2½ years and will be repeated in the QF2011 2½-year assessments (2013–2014).

To date, there are no results to report. The demands of working out the bureaucratic regulations of multiple institutions, ethical requirements protecting the data, while at the same time keeping up with data collection, keep the production of results from prospective studies of this nature moving at a snail's pace.

## 14.3 Conclusions and Discussion

After 15 years of studying PNMS, we would like to have definitive conclusions to present here. A certain number of patterns have emerged in Project Ice Storm over time, only to be contradicted by our subjects as they approach adolescence and to be challenged by preliminary results from Iowa. It seems that conclusions are moving targets, changing over time, across geographic boundaries and across disasters of different varieties.

### *14.3.1 Objective Exposure, Subjective Distress, and Cortisol*

We began our research program with a preconceived model of how PNMS would work: A pregnant woman would experience an objective stressor, the severity of which would predict her subjective response to it, which would then drive her hormonal response, and the resulting increase in cortisol levels would overwhelm the 11-β-HSD2 in the placenta, sending noxious cortisol to the fetus and interrupting

otherwise optimal neurodevelopment of whichever system was in ascendance at that moment in gestation.

In Project Ice Storm, however, the correlations among objective and subjective stress measures and cortisol have been low (<0.30) suggesting that the three elements of the PNMS experience are relatively independent, at least in the Quebec winter of 1998. For Iowa, these same correlations are in the range of 0.40–0.60. There may well be something about the nature of the different disasters that explain these discrepancies: The 1998 Quebec ice storm created disruptions in daily life for the entire population of the region, even for those who never lost power, which is reflected in the normal distribution of objective stress (Fig. 14.1). Thus, although there was relatively little loss of house and home from the ice storm compared to the Iowa floods, there could also be no "no stress" group in Project Ice Storm as there could be in the Iowa Flood Study and in QF2011 in which some families were never inconvenienced and others lost everything they owned (Fig. 14.8). We also wonder about the possibility of additional physical stress caused by exposure to cold—an oversight in the Storm32 questionnaire—that may have its own effects that are independent of those from psychosocial stress.

Our elaboration of a measure of objective stress exposure in Project Ice Storm was initially intended as a simple control measure, the backdrop against which maternal subjective distress would emerge as the smoking gun in causing suboptimal neurodevelopmental outcomes in the unborn child. Yet, our results from this first study suggest that objective exposure is a powerful agent in influencing the child's cognitive development (IQ, verbal memory, language) and physical development (hippocampal volumes, obesity, insulin secretion) in the absence of a concomitant effect of maternal subjective distress. Similarly, preliminary results suggest that, in both Ice Storm and Iowa, children's HPA axis responses to their own exposure to stress is driven more by maternal objective exposure than by subjective distress. Thus, the strength of the effects of objective stress exposure have surprised us and, to date, we have no data upon which to base a hypothesis about how mere objective exposure to a stressor by the pregnant woman can influence fetal outcomes while bypassing maternal subjective distress.

Much of the effect of maternal objective exposure on child cognitive outcomes in Project Ice Storm appears to be, surprisingly, curvilinear. Thus, 5- and 8-year-old children whose mothers had objective stress scores in the mid-range had higher Wechsler IQs and language and memory scores than those with lower maternal objective stress, although high stress still predicted the worst performance. One might apply the Yerkes–Dodson Law of Optimal Arousal (Yerkes and Dodson 1908) to explain this effect, but the application breaks down when we consider that Yerkes–Dodson would apply to the stress and arousal of the pregnant mother, which would seem to have limited relevance to the performance of her child on an IQ test at age 5 or 8 years. One might rather invoke the notion of hormesis (Calabrese 2008), a concept from toxicology that describes the observation that small doses of some toxins have beneficial effects while effects become catastrophic at larger doses.

Maternal subjective distress from a disaster also has a role to play in the children's neurodevelopment. Although in Project Ice Storm, performance on the Bayley

scales of infant cognitive development at age 2 years was related to objective stress, and not subjective distress, the opposite was true in Iowa with subjective stress explaining the bulk of the variance in general intelligence and language development. Even within Project Ice Storm, there are some inconsistencies in the effects of PNMS on cognitive development. Although at age 2 years it was objective stress predicting Bayley scores, objective and subjective stress explained equal amounts of variance in the maturity of the children's free play. And although objective stress explained the lion's share of variance in cognitive development at ages 5, 8, and 11 years, we are starting to see a shift at age 13 years towards a greater effect of maternal subjective stress, rather than objective. Thus, differences between disasters (winter/summer, ice storm/flood) and between the ages at which assessments occur (childhood, adolescence) seem to influence the relative roles of prenatal exposures to objective and subjective maternal stress.

Thus, one general conclusion from our work is that the degrees of objective exposure and subjective distress of a pregnant woman going through a natural disaster have differential effects on a variety of developmental trajectories of their children. An additional complexity emerges in much of our data, however. Although not mentioned in our review above, for some outcomes (e.g., fetal growth, Dancause et al. 2011; motor skills, Cao et al. 2014), the worst child outcomes are associated with mothers who exhibited a "mismatch" between their objective exposure and their subjective distress; in Project Ice Storm, the shortest birth lengths and the lowest bilateral coordination and visual motor integration performances belonged to children whose mothers either had high subjective stress in the face of mild objective exposure or had low distress in the face of high exposure levels. Preliminary analyses from Iowa suggest that it is these over- and under-reacting mothers who are also at greatest risk of postpartum depression (Brock et al., unpublished data). Further analyses are required to determine whether maternal psychopathology triggered by a mismatch in disaster reaction mediates the effect of the disaster on child outcomes.

Logistic difficulties with maternal cortisol assessment, being too long after the disaster itself to tell us about immediate maternal response to the event, and difficulties equating samples from pregnant and postpartum women, prevent us from drawing conclusions about the role of maternal GCs in these PNMS effects. To date, we have seen that lower (rather than higher) levels of maternal diurnal cortisol, sampled 5–6 months after the crisis, are associated with greater dermatoglyphic asymmetry which is presumed to reflect neurodevelopmental insult in utero. Other research paradigms are required to elucidate the mechanisms by which this unexpected association occurs.

### *14.3.2 Timing in Gestation and Sex Effects*

Another important consideration in PNMS research is the timing in gestation of the stressor and how this might moderate the stress effects. Thanks to the use of sudden onset natural disasters, we have been able to date the stressors with accuracy.

The patterns of results suggest that every moment in pregnancy presents a window of vulnerability for some form of development. Objective exposure (in Project Ice Storm) or subjective distress (in Iowa) predicted lower cognitive development scores at age 2 years, but only when exposure occurred in early gestation. In Project Ice Storm, maternal subjective distress during the second trimester predicted greater dermatoglyphic asymmetry. On the other hand, for motor development, we showed that the later in gestation girls were exposed to the ice storm the lower their bilateral coordination and visual motor integration scores at age 5½. The third trimester also appears to be a sensitive period for the development of attention problems, according to preliminary analyses from the ice storm. These timing effects appear to be fleeting, however. In Project Ice Storm, the timing effects on cognitive development are only seen at age 2 years, and disappear in assessments between ages 5½ and 13½.

The timing of the stressor in gestation is not the only significant moderator of the effects of PNMS on neurodevelopment. The literature presents an inconsistent picture of whether males or females are more sensitive to the effects of PNMS, and our results are similarly irregular. In Project Ice Storm, sex does not moderate effects of maternal stress on cognitive outcomes until age 11½ when the effect becomes negative and linear for boys, and nonexistent in girls; these results are echoed in the hippocampal volume data at the same age. Girls, on the other hand, appear more vulnerable than boys to the effects of late gestation exposure on motor functioning. We have also found girls to be more vulnerable to the effects of maternal subjective stress in predicting childhood asthma (Turcotte-Tremblay et al. 2014). As such, neither sex appears to be more or less at risk of neurodevelopmental consequences of PNMS, but results suggest that we must continue to be vigilant in testing hypotheses about sex as a potential moderator of the effects.

### *14.3.3 The Longevity of Effects*

Children who were born preterm begin life with certain developmental disadvantages compared to their term-born peers. But by elementary school, they tend to catch up to their classmates with few long-term consequences. We suspected to find a similar effect of prenatal maternal disaster exposure. Results suggest, however, that significant effects can still be seen at later ages as preliminary analyses of Project Ice Storm results at age 13½ continue to demonstrate. The magnitude of the effects seems to diminish with age, but remain in the small-to-moderate range at age 13.

Apart from a general weakening of effect over time, the age of the child at the time of the assessment also seems to be an important consideration in the study of PNMS as noted in our review of animal research on PNMS and brain development (Charil et al. 2010). We have seen timing effects at age 2 years that disappear at later ages, and patterns of objective exposure effects on cognition that held stable through childhood suddenly change at age 11½. The onset of puberty may well change many of our conclusions from younger assessment ages.

### *14.3.4 Possible Mediators of PNMS*

The conventional wisdom implicates the maternal HPA axis, and the noxious effects of GCs that invade the placenta, as the mechanism by which PNMS exerts its influence in programming the fetus. Several investigators are testing complementary hypotheses about mediation of PNMS by other agents such as the immune system, epigenetics, and androgens. All three of our disaster studies provide genotyping data with which to study gene-by-environment interactions in the years to come. We anticipate furthering knowledge about these mechanisms through analysis of the biological specimens from QF2011.

In the meantime, our preliminary analyses of blood from a subset of children from Project Ice Storm at age 13 suggest that the degree of maternal objective exposure explains: significant amounts of variance in immune system measures such as cell counts and cytokines; epigenetic signals (Cao-Lei et al., Under review); and (in girls) testosterone levels (Veru et al, Under review). Thus, we anticipate that the field will be expanding in its elaboration of the mechanisms of action of PNMS over the coming years.

### *14.3.5 Limitations of Prenatal Maternal Stress Work in Disasters*

The use of natural disasters as a PNMS paradigm has a number of advantages, as noted in the introduction. There are several disadvantages, however, that render this approach difficult to manage and the results difficult to interpret. Most of these limitations are a function of the disaster itself, as noted above in the section on Project Ice Storm Limitations. Because disasters are unpredictable, there is an inevitable delay between the event and the collection of the first data point: potential on-site collaborators, who may themselves be victims of the disaster, must be found and convinced of the importance of the project; the protocol must be elaborated and adapted to the particular disaster; ethics approval must be obtained; and all of these must be done often at some geographic distance and (as with QF2011) at great time zone differences.

The advantages of having a single, sudden-onset disaster as the PNMS paradigm are tempered by the disadvantage of a potential confound of the timing in gestation of the event by the season of the event. In “normal” years, there may be seasonal patterns in outcomes such as preterm birth, metabolism, or temperament. Without a control group, matched by birth month, one cannot be entirely certain that significant timing effects of a natural disaster are not the result of annual patterns by date of birth rather than a function of fetal windows of vulnerability. Having a suite of three natural disaster studies, one in winter and two in summer, helps us to circumvent this particular challenge.

### *14.3.6 Conclusion*

Despite these limitations and challenges, the advantages associated with studying an independent, sudden-onset stressor that is applied to large populations of pregnant women give added value to these studies and provide data that are not available elsewhere. Project Ice Storm, the Iowa Flood Study, and QF2011 are well positioned to complement the PNMS data generated from other study paradigms. Together, all of these approaches will fill in the gaps in knowledge about the effects of PNMS and its mechanisms and, we hope, guide the development of interventions to circumvent maladaptive fetal programming.

The reader interested in staying abreast of the results from Project Ice Storm, The Iowa Flood Study, and QF2011 may wish to consult our website called "SPIRAL" (Stress in Pregnancy International Research Alliance) at www.mcgill.ca/spiral/.

**Conflicts of Interest** The authors declare no conflicts of interest.

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