SPIRAL: THE STRESS IN PREGNANCY INTERNATIONAL RESEARCH ALLIANCE
AN ICE STORM, A WILDFIRE, AND THREE FLOODS

Suzanne King (Quebec), Michael W. O'Hara (Iowa), Sue Kildea (Queensland), David Olson (Alberta), Johanna Bick (Texas)

BACKGROUND:
Little is known about the effects of prenatal maternal stress in humans because it would be unethical to randomly assign pregnant women to stress conditions. However, Mother Nature does that for us with natural disasters.

OBJECTIVES:
Our goals are to determine:
(1) To what extent do different components of stress during pregnancy influence the development of the unborn child?
(2) Are these effects moderated by the timing in pregnancy or the child's sex?
(3) What are the mechanisms of these effects?

METHODS:
We run five studies of pregnant women exposed to natural disasters (see below). We recruit women soon after the disaster and assess maternal stress:
- OBJECTIVE HARDSHIP (Threat, Loss, Scope, Change)
- SUBJECTIVE DISTRESS (PTSD symptoms, peritraumatic distress and dissociation)
- COGNITIVE APPRAISAL: "Taking all the consequences of the disaster into account, I would say the disaster was:
  V Negative --- Negative --- Neutral --- Positive --- V Positive

We assess their children's development every couple of years:
- Cognitive: IQ, language, memory, attention;
- Behavior: Depression, anxiety, autistic-like, eating disorder, psychotic-like, substance use;
- Physical: Obesity, immune function, puberty, insulin, brain, DNA methylation;
- Motor: Balance, coordination, visual-motor integration, fine motor, gross motor.

PROJECT ICE STORM

JANUARY 1998: A series of ice storms struck Southern Québec in January 1998 knocking out electricity for more than 3 million people for as long as 6 weeks during the coldest months of the year. The ice storm caused 27 deaths, and created financial and logistical hardships for everyone. The Insurance Bureau of Canada and Environment Canada count the ice storm as the worst and most costly natural disaster in Canadian history.

MULTIDISCIPLINARY: Children have been assessed for immune function, insulin secretion, epigenetics (DNA methylation), heart rate variability. Brain MRIs at ages 11, 16 and 19 years.

CHILD ASSESSMENTS: 2, 5½, 8½, 11½, 13½, 15, 16, 19 years.
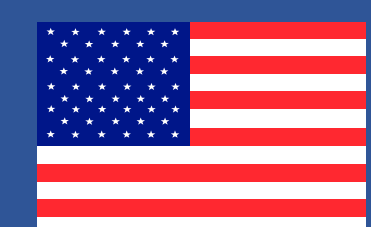
IOWA FLOOD STUDY

JUNE 2008: In 2008 Iowa suffered the worst floods in more than 50 years. By June 15, 2008, 1800 blocks of Cedar Rapids, Iowa were under water. By July 22, the Midwest storms and torrential rains had killed at least 24 people. More than 38,000 people had been driven from their homes, mostly in Iowa where 83 of 99 counties had been declared federal disaster areas. This flooding may rank among the top 10 disasters in U.S. history.

PRE-POST DESIGN: Includes subsample of women from an ongoing study of stress in pregnancy who had been assessed before the flooding; and then re-assed afterwards.

CHILD ASSESSMENTS: 16m, 2½, 4, 5½ and 7 years.

QF2011 QUEENSLAND FLOOD STUDY

JANUARY 2011: Heavy rainfall in the Australian state of Queensland caused severe flooding in January 2011. At least 70 towns, including the state capital of Brisbane, and over 200,000 people were affected. Three-quarters of Queensland was declared a disaster zone. Residents of 2,100 Brisbane streets were told to evacuate, and 20,000 homes were inundated. 35-40 deaths have been directly attributed to the floods. Damage was estimated at around $1.5 billion Australian

EMBEDDED CLINICAL TRIAL: To test whether Group Midwifery Care buffers mother and fetus from the effects of a major stressor; PRE- POST DESIGN: Women had depression assessments before the flooding.

BIRTH BIOLOGICALS: Samples of placenta, umbilical cord, and cord blood are available for ~ 150 women.

**CHILD ASSESSMENTS:** 16m, 2 ½, 4, 6 years

FORT MCMURRAY MOMMY BABY STUDY

MAY 2016: The first week of May the city of Fort McMurray in northern Alberta was suddenly consumed by wildfires. All 88,000 residents were told to evacuate using the only highway in and out of the city. The logistical difficulties of families attempting to reunite for the mid-day evacuations caused traffic chaos. Although no lives were lost directly from the fire, more than 2,500 homes and buildings were destroyed. This disaster is the most costly disaster in Canadian history. Stress levels in this sample are 2-3 times higher than in the previous 3 studies.

ONLINE WRITING INTERVENTION: Recruitment has been done online using social media and a web platform for assessments. Using James Pennebaker's expressive writing exercise, we randomly assigned women to three treatment groups.

INFANT ASSESSMENTS: 12 and 18 months.
MORE DATA TO ANALYZE: Ages & Stages, Language, BITSEA, Growth
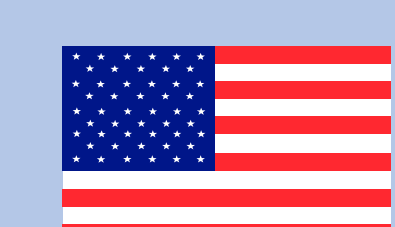
HURRICANE HARVEY STUDY
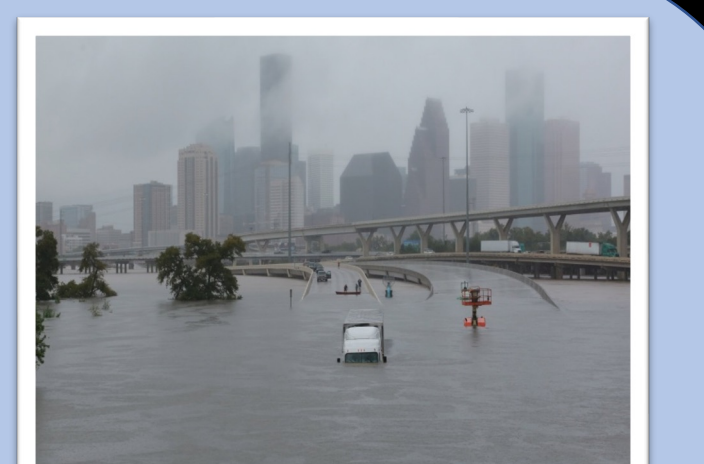
AUGUST 2017: Hurricane Harvey was the costliest hurricane on record, nearly doubling the cost of Hurricane Katrina, and was the second costliest natural disaster on record after the 2011 Japan earthquake and tsunami. The region received more than 40 inches of rain, with peak accumulations of 65 inches. Hundreds of thousands of homes were flooded displacing more than 30,000 people, and prompting 17,000 rescues. There were 63 direct fatalities and 27 indirect. Houston and Harris County see 72,000 births per year.

ONLINE WRITING INTERVENTION: Recruitment will be done by several means, including online using social media. The web platform designed for the Fort McMurray Study has been duplicated for the Harvey Study, and will go live in November 2017.

INFANT ASSESSMENTS: 6 months, 2 years, 4 years.

MORE DATA TO ANALYZE:

SELECTED RESULTS

	Cognitive Development	Behavioral Development	Physical Development	Motor Development
Quebec Ice Storm	**PLAY STYLE:** At age 2, children played with a standard set of toys. Their play style assessed from video. For children exposed in the 1st or 2nd trimester, greater objective maternal stress predicted less mature play style. **IQ:** At age 2, for children exposed in the 1st or 2nd trimester, those in the low objective stress group scored 10 points higher on the Bayley scales than those in the high stress group. **IQ:** This significant effect continued at ages 5 and 8 years. **IQ:** At age 11, there was a significant negative effect for boys, but no longer any effect of prenatal stress on girls. **IQ:** At none of these ages did maternal subjective distress have a role. **LANGUAGE:** Effects of maternal stress on language mirror those for IQ. **IQ AND LANGUAGE:** At ages 5 and 8 years, moderate objective stress predicted slightly better development, while high stress still predicted significantly worse development. **MORE DATA TO ANALYZE from multiple ages:** IQ, Language, Attention, Executive Function, Memory, etc.	**TEMPERAMENT AT 6 MONTHS:** Maternal subjective distress, and maternal illness in the 1st trimester predicted more difficult temperament. **DEPRESSION & ANXIETY:** Both objective and subjective maternal stress predict more severe symptoms throughout childhood and adolescence. **DEPRESSION & ANXIETY:** in the group are increasing in severity over time compared to the normative levels. **AUTISTIC-LIKE TRAITS AT 6:** At age 6, both objective and subjective maternal stress predict more severe autistic-like traits in the children. **EATING DISORDER SYMPTOMS AT 13:** Exposure to high levels of objective stress, and exposure to the ice storm in 3rd trimester, predicted more severe eating disorder-like symptoms. **AUTISTIC-LIKE TRAITS AT 19:** At age 19, objective hardship predicts more severe autistic traits as assessed by self-reported Broad Autism Phenotype Questionnaire. **MORE DATA TO ANALYZE from multiple ages:** Attentional bias (Dot-Probe), K-SADS, Theory of Mind, Substance use, CBCL/Youth Self Report, Eating, Childhood trauma, Empathy, Attributional style, Impulsivity, etc.	**PRETERM BIRTH:** Women exposed to the ice storm in the 1st or 2nd trimester were more likely to give birth preterm; on average, 2 weeks earlier. **OBESITY:** Objective maternal stress predicted larger BMI and greater rates of obesity from age 5 to 15; the correlation increases with age. **EARLIER PUBERTY:** Objective stress predicts higher BMI at age 5 which predicts earlier age at first menstrual period in girls. **INSULIN SECRETION:** Objective stress predicts higher insulin (OGT) at 13. **IMMUNE FUNCTION:** Objective stress predicts higher pro-inflammatory cytokines and a Th2-shift at age 13. **EPIGENETICS:** Objective stress and cognitive appraisal are associated with DNA methylation of 1,000 and 2,000 CpG sites; not subjective distress. **MEDIATION BY EPIGENETICS:** The effects of objective stress and cognitive appraisal on child BMI, cytokines, and other outcomes are mediated by DNA methylation. **DISRUPTED SEXUAL DIMORPHISMS:** Compared to control groups that were not exposed to the ice storm in pregnancy, Project Ice Storm girls have a masculinized 2D:4D finger ratio, and cortical thickness in brain.	**COORDINATION:** At age 5, girls are superior to boys in motor abilities; however, the later in pregnancy the mother exposed to the ice storm, the poorer girls' motor skills. **VISUAL-MOTOR COORDINATION:** Same results as above. **MEDIATED BY BRAIN:** Maternal objective stress predicts larger volume of the cerebellum in the brain at age 11, which mediates the effects of objective stress on poorer bilateral coordination and balance at age 13. **MORE DATA TO ANALYZE from multiple ages:** Ages & Stages, Milestones, Visual Motor Coordination, Balance and coordination, Physical activity (Actigraph), and more.
Iowa Flood	**IQ AT AGE 2:** Exposure to the flood in early pregnancy, and greater maternal subjective distress predicted lower IQ and language development. **LANGUAGE AT AGE 2:** Maternal subjective stress predicted poorer language scores. In boys, however, greater objective stress predicted better language. **MORE DATA TO ANALYZE :** IQ, Language, attention, NEPSY…	**TEMPERAMENT AT 16 MONTHS:** **STRESS RESPONSE AT AGE 2 YEARS:** Toddlers were stressed during a maternal separation protocol. Both objective and subjective maternal stress in pregnancy predicted greater cortisol secretion following the separation, especially in girls. **MORE DATA TO ANALYZE from multiple ages:** Child Behavior Checklist, CBCL, etc.	**BIRTH WEIGHT AND SOCIAL SUPPORT:** High social support buffered the effects of objective exposure on birth weight and, indirectly, on BMI at age 2. **BMI AT AGES 2 AND 4 YEARS:** Exposure to the flood during the 1st trimester predicted greater adiposity at age 2. Early exposure, and greater maternal objective and subjective stress predicted a greater increase in BMI between ages 2 and 4. **MORE DATA TO ANALYZE from multiple ages:** Growth, cortisol, DNA,	We have not yet explored effects of prenatal maternal stress on motor function in the children of the Iowa Flood Study. DATA TO ANALYZE from multiple ages: Bayley Scales, Visual-Motor Integration, Coordination and balance,
Queensland Flood	**COGNITIVE DEVELOPMENT AT 6 MONTHS:** Although at low stress levels there were no sex differences, at high levels of subjective stress boys had significantly higher "problem solving scores" than girls. There were no effects of prenatal stress on Communication scores at this age. **AT 16 MONTHS:** Lowest cognitive development scores were associated with high objective stress in combination with late pregnancy exposure to the flood. **MORE DATA TO ANALYZE from multiple ages:** IQ, Language, attention, Ages & Stages, NEPSY …	**TEMPERAMENT AT 6 MONTHS:** Objective maternal stress predicted more irritable temperament in boys. Exposure in early pregnancy predicted more arrhythmic temperament. Mothers who had high subjective stress in the face of low objective stress rated their infants as more active-reactive. **THEORY OF MIND AT 2 YEARS:** Higher maternal subjective stress predicted worse ToM. In girls, their mothers' negative cognitive appraisal of the flood predicted worse ToM. **ANXIETY AT AGE 4 YEARS:** Greater maternal objective stress predicted greater anxiety in children. **MORE DATA TO ANALYZE :** CBCL, Temperament, Autism traits, BITSEA	**SIZE AT BIRTH:** Greater objective stress from the flood predicted worse maternal diet which then predicted a larger head-circumference-to-length ratio, especially when exposure was in early pregnancy. **THE PLACENTA:** Analyses of gene expression related to glucocorticoids shows that maternal subjective stress from the flood, and timing in pregnancy, predicted these outcomes. **METABOLOMICS:** Patterns in hair and urine correlate with Objective Hardship and Subjective Distress **MORE DATA TO ANALYZE :** DNA, Cortisol, Growth, Testosterone, Prenatal ultrasound, Cord blood, Umbilical cord	**FINE MOTOR DEVELOPMENT AT 16 MONTHS:** Lowest fine motor scores were associated with high maternal PTSD symptoms combined with exposure in the 3rd trimester. **GROSS MOTOR DEVELOPMENT AT 16 MONTHS:** Lowest gross motor scores were associated with maternal negative cognitive appraisal of the flood combined with exposure during the 2nd half of pregnancy. **GROSS MOTOR DEVELOPMENT BETWEEN 2 MONTHS AND 4 YEARS:** During the first year of life, high maternal objective stress and negative appraisal predicted worse gross motor development, but also faster improvement, such that by 4 years all children were functioning at the same level. **MORE DATA TO ANALYZE :** Ages & Stages, Bayley, Balance and coordination, NEPSY, etc.

CONCLUSIONS: Using a natural disaster to study prenatal maternal stress is a powerful approach. Every aspect of maternal stress has significant effects on one outcome or another.
Every moment in pregnancy is a vulnerable time for the development of the fetus.
We are gradually building a model showing the mechanisms by which prenatal stress influences the fetus, and are showing how epigenetic, brain, and placenta seem to be conduits of maternal stress on fetal outcomes.

SPIRAL publications can be found at: www.mcgill.ca/spiral/

Suzanne.King@mcgill.ca