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Cohort Profile: The Maternal-Infant Research on Environmental Chemicals Research Platform

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Abstract

Background: The Maternal-Infant Research on Environmental Chemicals (MIREC) Study was established to obtain Canadian biomonitoring data for pregnant women and their infants, and to examine potential adverse health effects of prenatal exposure to priority environmental chemicals on pregnancy and infant health.
Methods: Women were recruited during the first trimester from 10 sites across Canada and were followed through delivery. Questionnaires were administered during pregnancy and post-delivery to collect information on demographics, occupation, life style, medical history, environmental exposures and diet. Information on the pregnancy and the infant was abstracted from medical charts. Maternal blood, urine, hair and breast milk, as well as cord blood and infant meconium, were collected and analysed for an extensive list of environmental biomarkers and nutrients. Additional biospecimens were stored in the study's Biobank. The MIREC Research Platform encompasses the main cohort study, the Biobank and follow-up studies.
Results: Of the 8716 women approached at early prenatal clinics, 5108 were eligible and 2001 agreed to participate (39%). MIREC participants tended to smoke less (5.9% vs. 10.5%), be older (mean 32.2 vs. 29.4 years) and have a higher education (62.3% vs. 35.1% with a university degree) than women giving birth in Canada.
Conclusions: The MIREC Study, while smaller in number of participants than several of the international cohort studies, has one of the most comprehensive datasets on prenatal exposure to multiple environmental chemicals. The biomonitoring data and biological specimen bank will make this research platform a significant resource for examining potential adverse health effects of prenatal exposure to environmental chemicals.

Keywords: *biomonitoring, biological markers, environmental chemicals, pregnancy cohort study.*

Background

It is well recognised that *in utero* and early life exposures to elevated levels of some environmental chemicals can impact fetal and child health, and potentially chronic conditions of adulthood.[1,2] The global burden of disease attributable to selected chemicals amounts to at least 86 million disability-adjusted life years, with 54% of this burden borne by children under the age of 15 years.[3] The contribution of lead, methylmercury and organophosphate pesticides to IQ decrements in children under 6 years of age is substantial and exceeds those of many nonchemical risk factors.[4] It is generally recognised that prospective pregnancy or birth cohort studies incorporating exposure biomarkers during sensitive windows are required to examine potential health effects of developmental exposure to chemicals.[1]

In 2006, the government of Canada launched the Chemicals Management Plan (CMP), which set priorities for the assessment and management of hundreds of chemicals (http://www.chemicalsubstanceschimiques.gc.ca/plan/index-eng.php). A key element of the CMP is human biomonitoring, with the Maternal-Infant Research on Environmental Chemicals (MIREC) Study being one of the national initiatives.

Consultations were held with the US National Children's Study leaders on the possibility of developing a Canadian pregnancy cohort study in collaboration with the American initiative. However, it soon became apparent that a large Canadian cohort study modelled on the National Children's Study was unlikely. Thus, funding was secured to establish a new cohort building on the clinical infrastructures already established for a multi-site clinical trial.[5] The MIREC Study

(http://www.mirec-canada.ca; http://www.hc-sc.gc.ca/ewh-semt/contaminants/mirec/index-eng.php) is an interdisciplinary collaboration between Health Canada scientists and clinical and academic researchers, and was funded by Health Canada, the Ontario Ministry of the Environment, and a grant from the Canadian Institutes of Health Research.

This paper describes the objectives, study population and the data collected in the MIREC Study, and introduces the MIREC Research Platform, which also includes the MIREC Biobank and follow-up of some of the infants and children. While this research will serve as a resource for the original investigators, it is an example where the exposome is being used to discover new leads in reproductive and perinatal epidemiology.

Aims and objectives

A major aim of the MIREC Research Platform is to study the potential role of environmental chemicals on the health of pregnant women and their children. The primary objectives of the MIREC Study are the following: (i) to determine whether current non-occupational exposure to heavy metals, such as lead (as measured in maternal and infant biospecimens), is related to elevated maternal blood pressure or fetal growth restriction and (ii) to obtain national-level contemporary biomarkers of *in utero* and lactational exposure to priority environmental chemicals (e.g. heavy metals, phthalates, brominated flame retardants, bisphenol A [BPA]). Additional objectives include the following: (i) to obtain Canadian biomonitoring and survey data on smoking behaviour and exposure to tobacco smoke (active and passive) in pregnancy; (ii) to measure selected known or perceived beneficial substances in human milk, such as nutrients and minerals (e.g. vitamins D and E, complete fatty acids profile, folate, calcium and magnesium), relevant immunoprotective end points (e.g. secretory IgA, prolactin, lysozyme) and antioxidative enzymes in mature human milk; (iii) to undertake a comprehensive risk to benefits analysis for human milk (e.g. Schütte and colleagues[6]); (iv) to elucidate the oxidative stress pathways by analysing metabolite and proteomic biomarkers, and examining their association with heavy metal concentrations in maternal plasma, as well as associations with vasoregulatory components such as the plasma endothelins and free nitrite levels; (v) to explore candidate genetic polymorphisms that may explain differences in susceptibility to metals toxicity; and (vi) to examine vitamin D status during pregnancy.

Subsequent funding was obtained for several follow-up studies that form part of the MIREC Research Platform. A Biobank has been established to store biospecimens and data for future research on the health of pregnant women and their children. A process has been set up for investigators to request permission to access the MIREC Biobank (see http://www.mirec-canada.ca); however, privacy rules will not permit individual-level data to leave Canada.

Infrastructure and study design

Study population

The study sites were selected in part if they had established clinical obstetrical research infrastructure in place and also to represent different geographical regions of the country (Figure 1). Clinical site investigators from the 10 cities across Canada were asked to recruit a total of 2000 pregnant women from the general population who were attending prenatal clinics (ultrasound, midwife and/or doctor's clinics) during the first trimester of pregnancy (6 to <14 weeks). Recruitment took place between 2008 and 2011. The selected cities range from some of the largest in Canada, Toronto and Vancouver, where only 53% of the population identify English as their only

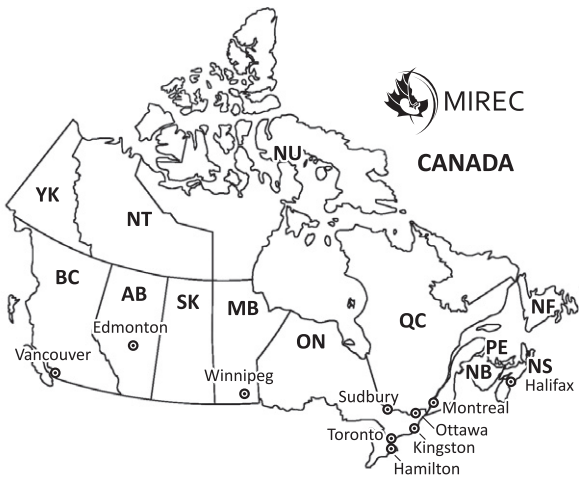

Figure 1. Map of Canadian Maternal-Infant Research on Environmental Chemicals (MIREC) sites.

mother tongue, to a smaller northern city such as Sudbury where 66% are English, and to Montreal where 52% identify their first language as French.

Eligibility criteria included ability to consent and to communicate in English or French, age 18 years or older, <14 weeks gestation, willing to provide a sample of cord blood and planning on delivering at a local hospital. Women with the following medical history were excluded from the study:

1 women who had known fetal abnormalities (e.g. hydatidiform mole), or known fetal chromosomal or major malformations in the current pregnancy; and
2 women who had a history of medical complications, including the following:
   - renal disease with altered renal function;
   - epilepsy;
   - any collagen disease, such as lupus erythematosus and scleroderma;
   - active and chronic liver disease (hepatitis);
   - heart disease;
   - serious pulmonary disease;
   - cancer;
   - haematological disorder (patient with anaemia or thombophilias will be included);
   - threatened spontaneous abortion (women with previous bleeding in the first trimester were included if the site documented a viable fetus at the time of recruitment); and
   - illicit drug use.

Data and biospecimen collection

Contacts were made with participants during each trimester, at delivery and in the early postnatal period (up to 10 weeks) to collect data and biospecimens (i.e. blood, urine, cord blood, meconium, breast milk and hair) for planned laboratory analyses (Figure 2). Under a separate consent form, additional biospecimens were collected to be stored in the MIREC Data and Biological Specimens Bank (MIREC Biobank). Questionnaires were administered by trained research staff to participants during the first and third trimesters to collect demographic, life style (e.g. smoking and alcohol), medical history, use of natural health products and medications, and potential sources of exposure data. Where possible, questions used in previous surveys and studies were used for comparability of results. A validated food frequency questionnaire was administered in the second trimester, along with blood and spot urine collection, blood pressure, clinical laboratory tests, and anthropometric measurements. Medical chart information was extracted at the first trimester ultrasound, second trimester and post-delivery time points. Blood pressure, height, weight and a proteinuria test were taken at each trimester.

Figure 2 provides details on participant contacts and biospecimen collection and analyses for environmental chemicals, nutrients, genetic factors, markers of oxidative stress and immunoprotective factors. Maternal urine was collected in Nalgene® containers (Thermo-Fisher Scientific Inc., Rochester NY, USA), and a Mère Hélène® bioliner (Mère Hélène, Quebec, Canada) was used on the diapers to collect meconium. All collection containers were pretested for phthalates and BPA, and field blanks were incorporated for each major chemical analyte. Post delivery, research staff visited the home of participants to collect samples of maternal milk and hair, and to complete a questionnaire on dietary factors. Women were asked to hand-express hind- and fore-milk over multiple days between 2 and 10 weeks post delivery; if they were having difficulty hand-expressing, a Medela® (Medela International, Zug, Switzerland) manual breast pump was provided, along with instructions for either manually expressing or using the breast pump to collect the milk. The milk was collected in 16-oz wide mouth amber I-CHEM® glass jars with fluoropolymer resin-liner polypropylene closure (Thermo Fisher Scientific, Rockwood, TN, USA) and 16-oz wide mouth TraceClean® clear plastic polyethylene jars (VWR International, Radnor, PA, USA). The breast pump was tested for possible contamination with phthalates and BPA.

Chemical analyses of maternal blood and urine, cord blood, and meconium were carried out by the Toxicology Laboratory, located in the *Institut national de santé publique du Québec* (https://www.inspq.qc.ca/ctq/Default.asp?Page=1&Lg=en), which is accredited by the Standards Council of Canada under ISO 17025 and CAN-P-43. The accuracy and precision of the analyses are evaluated on a regular basis through the laboratory's participation in external quality assessment programmes. DNA was extracted from maternal blood, and genotyping was performed by the *Plateforme de séquençage et de génotypage des génomes* at the *Centre de recherche du CHUL/CHUQ* (http://www.sequences.crchul.ulaval.ca/eng/index.html).

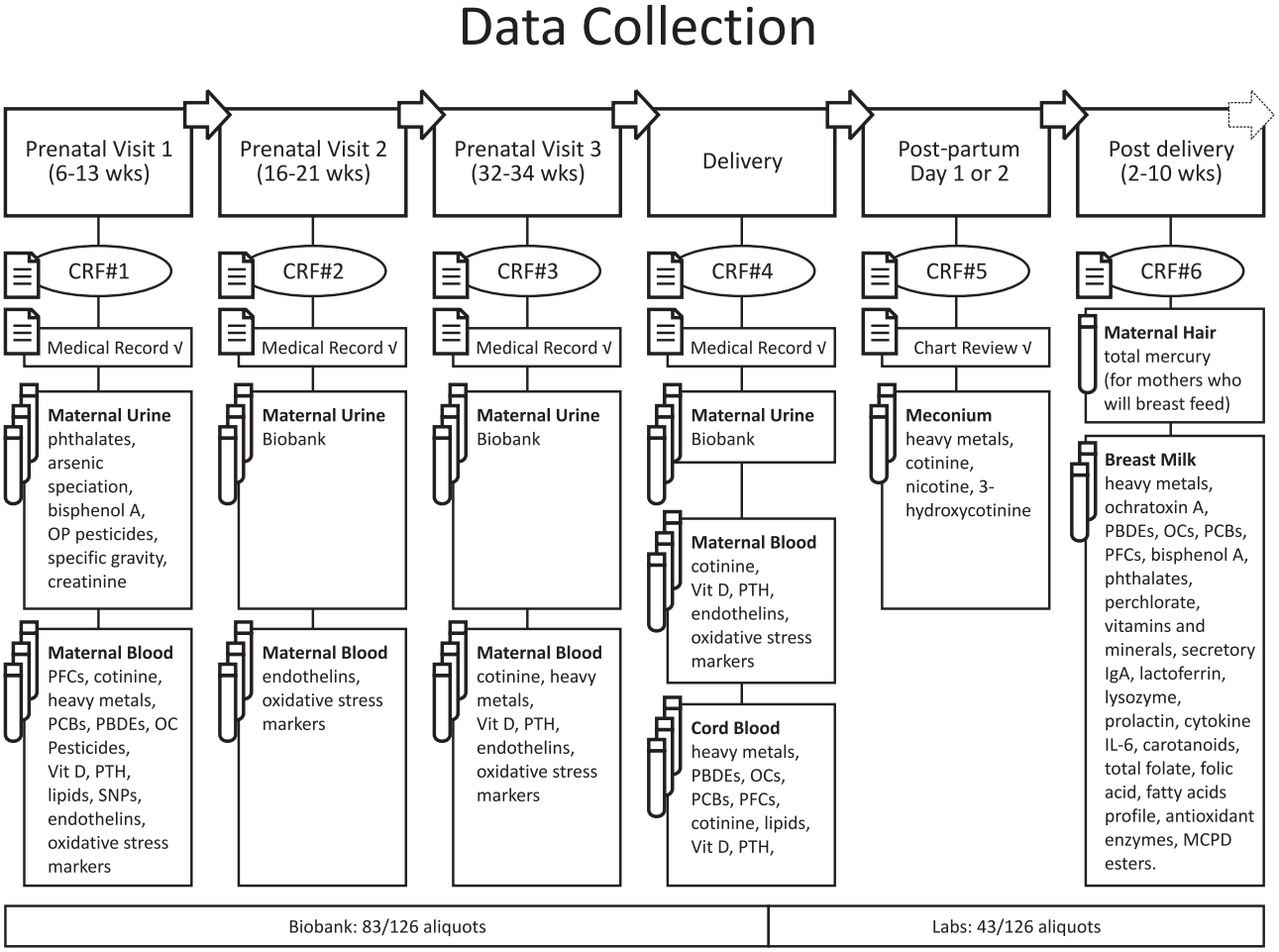

Figure 2. Data and biospecimen collection and analytes to be measured in the Maternal-Infant Research on Environmental Chemicals Study. CRF, case report form (questionnaire); OP, organophosphate pesticides; wks, weeks gestation; PCBs, polychlorinated biphenyls; PBDEs, polybrominated diphenyl ethers; PFCs, perfluorinated compounds; OC, organochlorines; Vit D, vitamin D; PTH, parathyroid hormone; SNPs, single-nucleotide polymorphisms; MCPD, 3-monochloropropane-1,2-diol.

Nutritional analyses of the maternal and cord blood samples, as well as the chemical and nutritional analyses of the breast milk, are being carried out by the laboratories of the Food Directorate at Health Canada. Markers of oxidative stress, inflammation and vasoregulation are being measured by scientists from the Environmental and Radiation Health Science Directorate of Health Canada.

All questionnaires and biospecimens were labelled with a unique ID and barcode, respectively. Data from questionnaires were entered into a database using single data entry with queries and verification of responses dealt with as needed (e.g. values outside range, internal inconsistencies). A separate database which tracked the collection and laboratory analysis of the biospecimens was also created. All blood, urine and breast milk were aliquoted into smaller cryovials and stored at −20 or −80°C as required.

Follow-up studies

In subsequent and ongoing follow-up studies, assessments of child health and development are being made on a subset of the cohort at various ages (see Figure 3). In the MIREC-ID Study (MIREC: infant development to 6 months), in-clinic assessments were performed on approximately 400 infants at birth and 6 months of age to measure growth, sensory function, behaviour and potential indicators of reproductive effects (e.g. anogenital distance). MIREC-CD3 (MIREC: child development at age 3), currently underway, is an online parental survey for children at 36

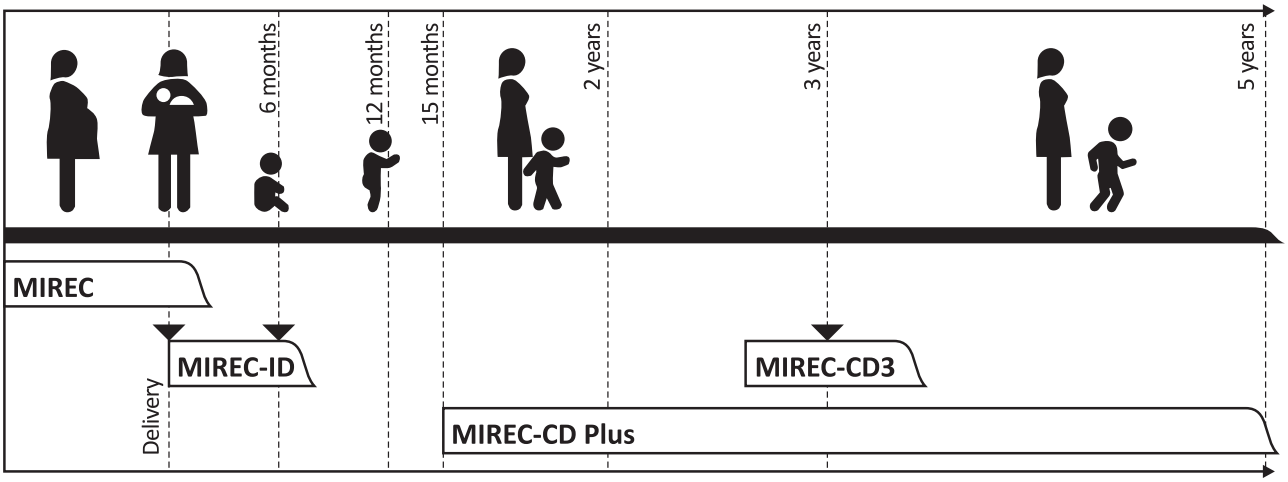

Figure 3. Maternal-Infant Research on Environmental Chemicals follow-up studies timelines.

months of age that is designed to examine potential effects of prenatal exposure to phthalates, BPA and organophosphate pesticides on child neurobehaviour [e.g. subscales of the Behavior Rating Inventory of Executive Function (BRIEF-P)]. The MIREC-CD Plus Study, currently in the planning stage, entails a home visit for children 15 months to 5 years of age to collect a sample of the child's blood and urine, to measure physical growth and only in children older than 2.5 years, to measure important determinants of child neurodevelopment (behaviour, general cognitive abilities, specific executive functions, and language and communications skills). In the MIREC-CD Plus Study, biological specimens will be collected to measure heavy metal exposure for those children under 3 years of age, with additional biospecimens placed in the Biobank. Delays in obtaining funding (which meant some children were too old for some of the assessments), insufficient funding and difficulties in obtaining ethics approvals at some of the recruitment sites have adversely affected our ability to include all of the cohort children in the follow-up studies. In the MIREC-CD Plus Study, to improve efficiency and reduce costs, recruitment is being restricted to six sites with the most MIREC children.

Participation in the MIREC Study

A total of 8716 women were approached at early (<14 weeks) prenatal clinics, 5108 were eligible and 2001 agreed to participate (39%) (Figure 4). Ethical considerations did not permit the collection of information on those who refused to participate, and no sampling frame was available to estimate the percentage of eligible women who were not approached. Among those who were ineligible to participate in the MIREC, 52% were not planning on delivering in the participating hospitals, 20% were outside the required gestational age at recruitment, and 14% were not willing to provide a sample of cord blood for the study. The ability to recruit eligible women varied considerably between cities, with a mean of 50% and ranging from a low of 13% in one city to over 90% in another, with no clear explanation for the differences.

Table 1 shows the participation rates by parity and year of recruitment. The mean and median gestational age at recruitment were 11.99 [standard deviation (SD) 1.51] and 12.43 weeks, respectively, with a minimum of 6.14 weeks and the 90th percentile of 13.57 weeks. After beginning participation in the MIREC Study, 18 women withdrew and asked that all their data and biospecimens be destroyed (0.9%), leaving 1983 participants. Additional loss to follow-up was due to withdrawals from the study ($N = 48$), fetal demise ($N = 41$), therapeutic abortion ($N = 13$) and mobility of the participants outside the study site ($N = 14$). The questionnaires were well responded to with the highest refusal or 'don't know' responses for family income (2.5% and 2.2%, respectively) and pre-pregnancy body mass index (BMI) (7.6% missing) (data not shown). Only 48 women (2.4%) did not consent to having their biospecimens and data stored in the Biobank.

The mean age of participants was 32 years, and 44% had not had a previous viable pregnancy (Table 2).

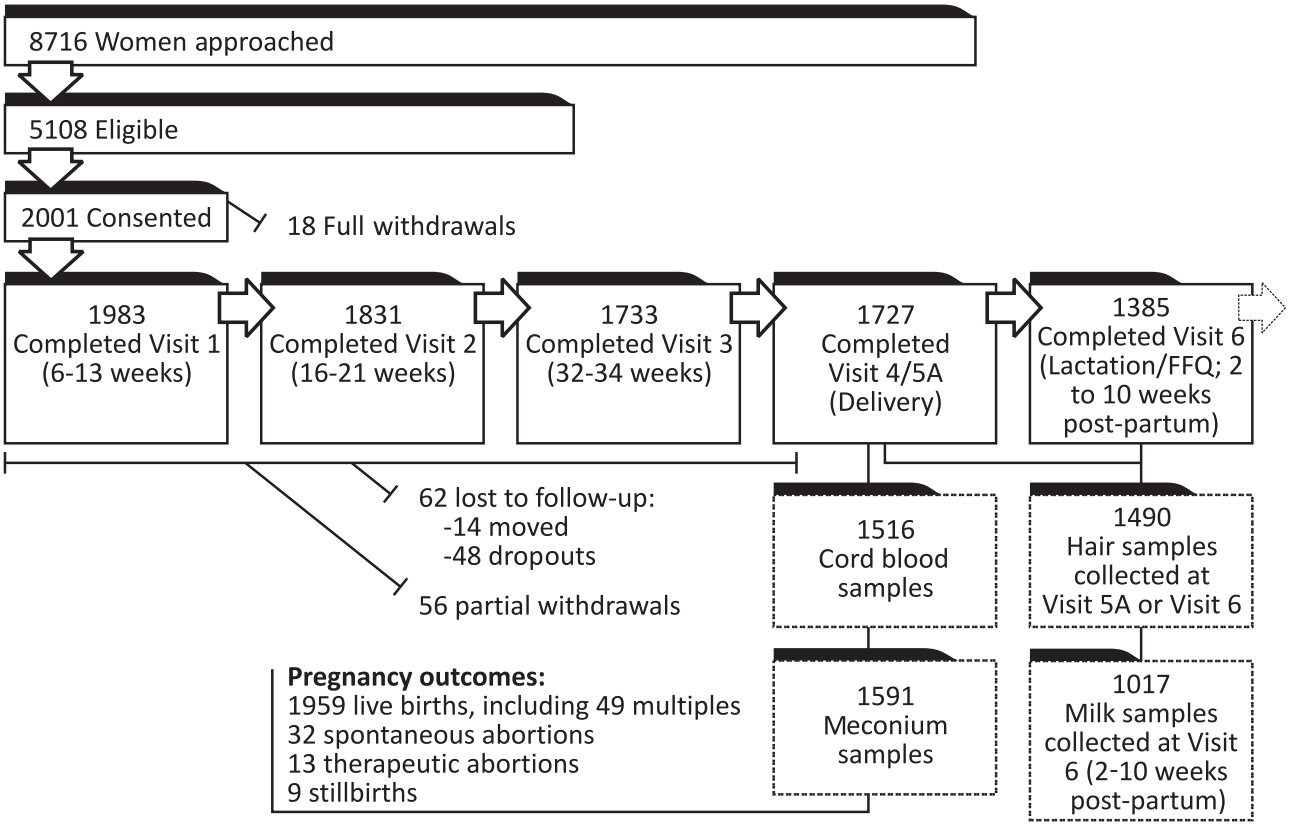

Figure 4. Recruitment and participation in the Maternal-Infant Research on Environmental Chemicals (MIREC) Study. FFQ: food frequency questionnaire.

Over 36% of the women were overweight or obese, based on their pre-pregnancy BMI.

Power calculations

The final sample for MIREC included information on 1983 mothers and 1959 livebirths. The dichotomous outcomes of low birthweight occurred in 5.7% of births, and preterm delivery occurred in 8.7% of births. With such incidence, the power is 86.3% to detect a ratio of geometric mean lead levels of 1.15 µg/dL in low vs. normal birthweight newborns. The power is 96.2% to detect a ratio of geometric mean lead levels of 1.15 µg/dL in preterm vs. term

Table 1. Maternal-Infant Research on Environmental Chemicals recruitment by calendar year and parity

	Parity									
	0		1		2		3 or more		Total	
Year of recruitment	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*
2008	3.0	59	3.3	66	0.9	18	0.4	9	7.7	152
2009	17.4	345	15.6	309	4.4	87	1.3	26	38.7	767
2010	21.8	432	19.5	386	5.6	110	1.9	37	48.7	965
2011	1.9	38	2.0	39	0.8	16	0.2	4	4.9	97
Total	44.1	874	40.4	800	11.7	231	3.8	76	100	1981[a]

Definition of parity: number of previous viable pregnancies, not including index pregnancy.
[a]*N* = 2 missing information on parity.

Table 2. Comparison of Maternal-Infant Research on Environmental Chemicals (MIREC) participants with data on Canadian births (2009) and female participants in the biomonitoring component of the Canadian Health Measures Survey (CHMS) Cycle 1, (2007–09)[14,15]

	MIREC participants (2008–11)	Canadian births, 2009	CHMS (2007–09) women 20–39 years of age[a] [95% confidence interval]
Parity (%): Number of previous viable pregnancies			
0	44.1%	44.0%	49.7% [41.5, 57.9]
1	40.4%	35.0%	16.7% [12.8, 20.6]
2	11.7%	13.6%	25.0% [17.2, 32.7]
3+	3.8%	7.4%	8.6% [5.2, 12.1][b]
Maternal age (%) (years)			
<20[c]	0.7%	4.1%	
20–24	6.4%	15.2%	
25–29	23.2%	30.7%	
30–34	35.8%	31.7%	
35+	34.1%	18.3%	
Mean age (years) (SD)	32.2 (5.10)	29.4	29.9 [29.0, 30.8]
Gestational age (weeks)			
Mean (SD)	39.2 (1.98)		
Median	39.4		
Preterm birth (%): <37 weeks			
Yes	8.7%	7.7%	
Birthweight (g)			
Mean (SD)	3402 (581.89)	3364	
Median	3420	3391	
Low birthweight (<2500 g) (%)			
Yes	5.7%	6.1%	
Mother born in Canada (%)			
Yes	81.3%	72.7%	77.8% [67.6, 88.1]
Infant gender (%)			
Male	52.6%	51.3%	
Female	47.4%	48.7%	
Maternal education (%)		[d]	Highest level of education in household
High school or less	8.8%	26.8%	10.7% [4.6, 16.8][b]
Some college	5.3%		7.9% [3.3, 12.6)][b]
College diploma	23.6%	37.0%	38.9% [30.0, 47.9]
University degree	62.3%	35.1%	42.4% [28.4, 56.5]
Marital status of mother (%)			
Married or common law	95.3%	60.1%	58.7% [51.4, 66.1]
Divorced	0.2%	0.9%	1.4% [0.7, 2.1)][b]
Separated	0.2%	0.4%	2.1% [0.6, 3.5][b]
Single	4.2%	27.2%	37.8% [30.5, 45.0]
Other/Unknown	0.05%	11.5%	[e]
Multiple births (%)			
Yes	2.5%	3.3%	
Fetal death (≥20 weeks) (% of total births)			
Yes	0.5%	0.7%	
Smoking status at first visit (<14 weeks) (%)		During last 3 months of pregnancy[d]:	
Never	61.7%	89.5% did not smoke	59.9% [52.7, 67.0]
Former	26.3%		19.3% [15.4, 23.1]
Quit during pregnancy	6.1%		
Current smoker	5.9%	10.5%	20.8% [16.2, 25.5]
Body mass index (kg/m^2)			
Underweight (<18.50)	2.9%		5.3% [2.1, 8.6][b]
Normal (18.50–24.99)	60.5%		50.4% [39.8, 60.9]
Overweight (25.00–29.99)	22.0%		23.3% [16.2, 30.5]
Obese (>29.99)	14.6%		20.9% [15.6, 26.3]
Household income from all sources[f]			
<$20 000	3.9%		10.7% [5.4, 16.0][b]
$20 000–30 000	3.5%		5.0% [2.7, 7.3][b]
$30 001–40 000	4.9%		9.0% [4.0, 13.9][b]
$40 001–50 000	5.1%		9.3% [5.0, 13.6][b]
$50 001–60 000	5.1%		9.8% [6.6. 13.0]
$60 001–80 000	14.9%		18.2% [14.5, 21.8]
$80 001–100 000	19.6%		9.6% [4.3, 14.9][b]
>$100 000	38.2%		20.6% [16.1, 25.1]
No response	4.7%		7.8% [3.7, 12.0][b]

[a]Estimates weighted for the CHMS complex survey design.

[b]High sampling variability associated with these estimates. Results should be interpreted with caution.

[c]Lowest age category defined as 18 to <20 for MIREC and under 20 years for Canadian births.

[d]Source: Reference 17.

[e]Estimates of unacceptable quality and suppressed by Statistics Canada.

[f]$1 difference in categories between MIREC and Statistics Canada.

deliveries. For the same population size, and birthweight as a continuous variable, the power is 91.3% to detect the risk factor, with an effect size of 0.075 SD.

Comment

Ethical considerations

The research protocol, questionnaires, consent forms, and recruitment posters and pamphlets were reviewed and approved by human studies research ethics committees, including the Research Ethics Board at Health Canada and the research ethics committee at the coordinating centre at Ste-Justine's Hospital in Montreal, as well as >10 academic and hospital ethics committees across Canada – a very time-consuming process. Any changes made to the protocol or survey instruments (amendments) were approved by all ethics committees. Separate consent forms were developed for the data and biospecimen repository (Biobank) and for the infant follow-up studies. Participants could partially (data and biospecimens retained) or completely (all data and biospecimens destroyed) withdraw from the study. Ethical considerations did not permit the collection of any information on the non-participants to examine possible selection bias.

The approach to reporting biomonitoring results to participants was a major point of discussion between the study investigators and the hospital ethics committees at the coordinating centre and recruitment sites.[7] Our initial proposal to the ethics committees was that individual biomonitoring results would be provided to participants (if they so requested) at the conclusion of the data collection and the analysis phase of the initial cohort study, along with information on potential sources of exposure. The exception would be chemicals for which there were health-based tissue guidelines [i.e. blood lead, mercury and cadmium (in the case of cadmium, the workplace health guideline was used)]. Any participant with blood levels exceeding the guidelines would be informed as soon as possible and provided with information on reducing exposure, including possible follow-up blood measurements. However, the hospital ethics committees required that only biomonitoring results exceeding health-based tissue guidelines where preventive or treatment options were available could be shared with participants through their health care provider. This latter process was, therefore, used to share maternal blood concentrations of lead, mercury and cadmium that exceeded established guidelines with the participant's physician. The physicians were also provided with guidance documents to help them identify potential sources of exposure for their patients and to help them interpret the individual results. A physician with expertise in environmental epidemiology of these metals was made available to the participant's physicians to provide further advice, as needed. In the province of Quebec, a number of chemical substances, including lead, mercury, cadmium and manganese, as well as the dialkyl phosphate metabolites, fall under reportable diseases legislation [maladies et intoxications à déclaration obligatoire (MADO)]. Therefore, our Montreal sites were legally obliged to report elevated results to the public health department, according to the MADO guidelines. Recently, we have had a request from an MIREC participant for her individual biomonitoring results for environmental chemicals, and we have been given permission by the ethics committees to provide these results to her with the disclaimer that we cannot provide any interpretation of her results as there is currently no scientific knowledge available to interpret these results at the individual level.

Perspectives

MIREC is a multisite study with a population of obstetric patients from across Canada. One of the unique features of this study is the most extensive assessment of prenatal and lactational exposure to environmental chemicals at multiple time points, but especially in early pregnancy when the fetus is likely most sensitive to toxic chemicals. In addition, the establishment of the Biobank will facilitate future research on additional chemicals and genomic and nutritional susceptibility factors. As such, MIREC is directly responsive to the exposome paradigm,[8] measuring endogenous factors such as oxidative stress, specific external exposures such as chemicals and diet, and general external exposures including economic and educational factors. By doing so, the findings from the MIREC Research Platform will contribute to the identification and quantification of exposomes during sensitive windows of reproduction and development, as recently recommended by Buck Louis and colleagues.[9]

The results of MIREC may not be generalisable to the Canadian population or to each of the recruitment

sites as the study is not population-based. Past experience has highlighted the difficulties in trying to assemble a population-based pregnancy/birth cohort that may be less representative as the cohort is followed over time.[10–12]

The MIREC participation rate of 39% is consistent with participation rates of several large prospective cohort studies.[13] Similar to other pregnancy cohort studies (e.g. Bornehag *et al*.[11]), participants in MIREC tended to be older, more educated, born in Canada, married and less likely to be a current smoker than the Canadian population giving birth in 2009 (Table 2).[14] The MIREC participants were, however, more similar to a population of women 20–39 years of age participating in the biomonitoring component of the population-based Canadian Health Measures Survey (Cycle 1 2007–09).[15,16]

In summary, the multiple contacts with study participants starting in the first trimester, and the collection of data and biospecimen analysis for multiple key chemical risk factors in the MIREC Study, should provide important information on several hypotheses related to prenatal exposure to environmental chemicals and potential adverse health effects for the pregnant woman and her child. The major challenges are funding to maintain the Biobank and to follow the cohort as the child ages, as well as keeping the families actively participating in the various ancillary studies, while limiting biases that might affect the internal validity of the study.

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References

1 Grandjean P, Bellinger D, Bergman A, Cordier S, Davey-Smith G, Eskenazi B, *et al*. The faroes statement: human health effects of developmental exposure to chemicals in our environment. *Basic Clin Pharmacol Toxicol* 2008; 102:73–75.
2 Wigle DT, Arbuckle TE, Turner MC, Berube A, Yang Q, Liu S, *et al*. Epidemiologic evidence of relationships between reproductive and child health outcomes and environmental chemical contaminants. *J Toxicol Environ Health B Crit Rev* 2008; 11:373–517.
3 Prüss-Ustün A, Vickers C, Haefliger P, Bertollini R. Knowns and unknowns on burden of disease due to chemicals: a systematic review. *Environ Health* 2011; 10:9.
4 Bellinger DC. A strategy for comparing the contributions of environmental chemicals and other risk factors to neurodevelopment of children. *Environ Health Perspect* 2012; 120:501–507.
5 Xu H, Perez-Cuevas R, Xiong X, Reyes H, Roy C, Julien P, *et al*. An international trial of antioxidants in the prevention of preeclampsia (INTAPP). *Am J Obstet Gynecol* 2010; 202:239. e1-239.e10.
6 Schütte K, Boeing H, Hart A, Heeschen W, Reimerdes EH, Santare D, *et al*. Application of the BRAFO tiered approach for benefit-risk assessment to case studies on heat processing contaminants. *Food Chem Toxicol* 2012; 50 (Suppl. 4):S724–S735. doi: 10.1016/j.fct.2012.01.044
7 Haines DA, Arbuckle TE, Legrand M, Lye E, Weselak M, Langlois R, *et al*. Reporting biomonitoring results to study participants: a comparison of approaches followed in two studies. *J Epidemiol Community Health* 2011; 65:191–198.
8 Wild CP. The exposome: from concept to utility. *Int J Epidemiol* 2012; 41:24–32.
9 Buck Louis GM, Yeung E, Sundaram R, Laughon SK, Zhang C. The exposome – exciting opportunities for discoveries in reproductive and perinatal epidemiology. *Paediatr Perinat Epidemiol* 2013; 27:229–236.
10 Arbuckle TE. Maternal-infant biomonitoring of environmental chemicals: the epidemiologic challenges. *Birth Defects Res A Clin Mol Teratol* 2010; 88:931–937.
11 Bornehag C-G, Moniruzzaman S, Larsson M, Lindström CB, Hasselgren M, Bodin A, *et al*. The SELMA Study: a birth cohort study in Sweden following more than 2000 mother-child pairs. *Paediatr Perinat Epidemiol* 2012; 26:456–467.
12 Savitz DA, Ness RB. Saving the National Children's Study. *Epidemiology* 2010; 21:598–601.
13 Nohr EA, Frydenberg M, Henriksen TB, Olsen J. Does low participation in cohort studies induce bias? *Epidemiology* 2006; 17:413–418.

14 Statistics Canada. *Live births*. 2012. http://www.statcan.gc.ca/tables-tableaux/sum-som/l01/cst01/health103a-eng.htm; http://www5.statcan.gc.ca/cansim/a03?lang=eng&pattern=102-4516,102-4508,102-4509,102-4501,102-4510,102-4502,102-4511,102-4503,102-4512,102-4504,102-4513,102-4505,102-4514,102-4506,102-4515,102-4507 [last accessed 7 December 2012].
15 Bryan SS, Denis M, Wojtas D. Canadian Health Measures Survey: clinic operations and logistics. *Health Rep* 2007; 18 (Suppl):53–70.
16 Health Canada. *Report on Human Biomonitoring of Environmental Chemicals in Canada: Results of the Canadian Health Measures Survey Cycle 1 (2007–2009)*. Ottawa, ON: Minister of Health, 2010. Catalogue No. H128-1/10-601E. http://www.hc-sc.gc.ca/ewh-semt/pubs/contaminants/chms-ecms/index-eng.php [last accessed 7 December 2012].
17 Public Health Agency of Canada. *What mothers say: the Canadian maternity experiences survey*. 2009. Ottawa. http://www.phac-aspc.gc.ca/rhs-ssg/survey-eng.php [last accessed 7 December 2012].