Perinatal Nutrition in Maternal Mental Health and Child Development: Birth of a Pregnancy Cohort

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Abstract

Background: Mental disorders are one of the leading contributors to the global burden of disease. The Alberta Pregnancy Outcomes and Nutrition (APrON) study was initiated in 2008 to better understand perinatal environmental impacts on maternal mental health and child development. **Aims**: This pregnancy cohort was established to investigate the relationship between the maternal environment (e.g. nutritional status), maternal mental health status, birth outcomes, and child development. The *purpose* of this paper is to describe the creation of this longitudinal cohort, the data collection tools and procedures, and the background characteristics of the participants. **Subjects**: Participants were pregnant women age 16 or older, their infants and the biological fathers. **Outcome measures**: For the women, data were collected during each trimester of pregnancy and at 3, 6, 12, 24, and 36 months after the birth of their infant. Maternal measures included diet, stress, current mental and physical health, health history, and lifestyle. In addition, maternal biological samples (DNA, blood, urine, and spot breast milk samples) were banked. Paternal data included current mental and physical health, health history, lifestyle, and banked DNA samples. For infants, DNA and blood were collected as well as information on health, development and feeding behavior. **Results**: At the end of recruitment in 2012, the APrON cohort included 2140 women, 2172 infants, and 1417 biological fathers. Descriptive statistics of the cohort, and comparison of women who stayed in the study and those who dropped out are discussed. **Conclusion:** Findings from the longitudinal cohort may have important implications for health policy and clinical practice.

Key words: maternal mood, children development, perinatal nutrition

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Introduction

The Alberta Pregnancy Outcomes and Nutrition (APrON) study was created to address the health concerns and consequences associated with perinatal depression, and the increasing incidence of neurodevelopmental problems in children. Perinatal depression has been well studied in women, and can occur at any trimester of pregnancy, as well as in the postpartum period, and it can last from several weeks to a year after delivery (1). Perinatal depression in fathers has been less studied but is a growing concern (2). Moreover, depression in either or both parents is known to increase the risk of developmental problems in their children (3, 4). The urgent need to more clearly understand the ways in which key elements of the perinatal environment, including parental mental health and nutrition, shape children's developmental risks is highlighted by a 2012 survey conducted in the United States, which found the top five disabilities among children were behavioral or neurodevelopmental in origin (5).

Maternal factors and child development

Maternal mental health: Among adults, depression was the leading cause of disability in 2000, and the fourth leading contributor to the global burden of disease (6). Women are at higher risk for mood disorders than men, and risks are heightened during the perinatal period. Maternal depression has been demonstrated to affect children's cognitive and behavioral development (7). Depressed pregnant women are less likely to seek proper medical care during pregnancy and more likely to engage in risk taking activities such as alcohol and/or drug abuse (8). Poor obstetric outcomes in these women include pre-eclampsia, birthing difficulties, increased risk for postpartum depression (up to 6.5 fold) (9), increased risk of preterm delivery and reduced breastfeeding (8). Children of women with postpartum depression are more likely to have lower scores on developmental scales, reduced motor tone and activity, and increased behavioural

problems (10), including sleep disturbances and increased irritability (9). Thus, maternal depression has broad implications for children's mental and physical health, which in turn can have long lasting social and economic impacts on individuals and societies (11, 12).

Maternal nutrition and mood: Nutrition is a critical factor for both physical and mental health. Deficiencies in folate, vitamin B12, calcium, iron, selenium, zinc, and polyunsaturated fatty acids (PUFAs) are associated with depression (12, 13). Maternal nutrient intake is important to the mother's mental health, as well as to the developing fetus. Pregnant women may be particularly vulnerable to the effects of poor diet, as many of their nutrient needs increase to meet the demands of pregnancy, placental and fetal development and preparation for the postpartum period. It is possible that the combination of inadequate intake and increased nutrient demand increases pregnant women's susceptibility to poor mental health. Although there is less known, excessive intake of nutrients (particularly micronutrients) during gestation may also have maternal and infant health implications (13).

Maternal nutrition and child development: The effect of nutrition on neural development and function is critical throughout the life cycle, from childhood to adolescence and adulthood (14, 15). A review demonstrated the link between inadequate intake of some nutrients to an increased incidence of cognitive and behavioural disorders in children, including depression, learning disability, and attention deficit/hyperactivity disorder (14). Nutrients well documented for their role in brain development and health include iron and iodine, B complex, long chain PUFA, and choline (16). Essential fatty acids (specifically docosahexaenoic [DHA] and arachidonic acid) are critical for brain health because of their role in increasing membrane flexibility and protein-lipid interactions of nerve cells, thus enhancing neuronal activity and cognition (14). However,

specific information on the interaction of prenatal nutrition, perinatal mental health and children's neurodevelopment is limited.

Additional factors affecting mental health: A number of other risk factors for maternal (and paternal) depression have been identified. These include a history of depression, lack of a partner, marital difficulties, poverty, lack of social support (17, 18), as well as increased life stress and substance abuse (9). These risk factors are important covariates that need to be taken into account when examining predictors of perinatal depression in mothers and fathers.

Paternal factors and child development

Perinatal depression in fathers has largely been ignored, at least in regards to child development. A recent review reported that paternal postpartum depression is as common as maternal postpartum depression, ranging from 4% to 25% in the first two month after delivery (19) compared to a point prevalence range from 6.5% to 12.9% (perinatal) and combined period prevalence of 19.2% (postpartum) in women (1). Men with perinatal depression tended to be of lower income levels, were dealing with a partner with depressive symptoms, had a child with special needs, were in poor physical health, and tended to be unemployed (20). Additional risk factors associated with paternal depression included perceived stress and lack of social support (21).

Depression during and after pregnancy in fathers can have long lasting negative impacts on their families. In particular, depression in fathers is associated with increased emotional and behavioral problems among their children and increased conflicts in the marital relationship (2). Results from the Avon Longitudinal Study showed that postpartum depression in fathers was associated with psychiatric disorder in their children, assessed 7 years later; especially strong were

associations with oppositional defiant and conduct disorders (22). A Canadian national survey found mothers' and fathers' depression affected parental nurturance, rejection and monitoring behaviours, resulting in maladjustment (internalizing and externalizing problems) in children (23). The factors affecting paternal mental health may be similar to those of mothers, but the effects of paternal depression on children's development are rarely examined and need to be taken into account when investigating predictors of children's development.

Child neurodevelopmental disorders

There has been a dramatic increase in the prevalence of neurodevelopmental disorders worldwide, including attention deficit hyperactivity disorder (ADHD), learning disabilities such as reading disability (dyslexia), and autism spectrum disorder (ASD) (24-27). A national survey of autism in Canada reported an increase from 9.7% to 14.6% in children age 2 to 14 years, from the period 2002/03 to 2008/10 (28). Furthermore, a report from the Centers for Disease Control (US) of children age 4 to 17, indicated parent reported ADHD diagnosis went from 7.8% to 9.5% from 2003 to 2007, which is a 21.8% increase over 4 years (29). Even if one assumes that half of the observed increases in neurodevelopmental disorders are due to changes in diagnostic practices and greater awareness of these disorders, there still remains an alarming increase that needs to be explained. The long-term implications of these disorders are significant as they affect not only the physical and mental health of children and their families, they also strain the capacities of social, educational, and healthcare systems that must serve all of society. Furthermore, neurodevelopmental disorders are now more prevalent than physical impairments, but there is limited progress in policy and programs to address these problems (5). A number of factors have been associated with neurodevelopmental disabilities including genetics, neurobiological, and environmental factors such as neurotoxicants and nutrition, however, no

definitive cause has been identified. Research is beginning to explore the important role maternal and child nutriton play in children's neurodevelopment (30).

Creation of the APrON Cohort

The APrON study was established to examine the associations between prenatal nutrition, maternal mental health, and child development, with attention to other factors affecting child health, including paternal mental health, social and behavioral factors, and genetic-environmental influences. APrON brought together experts in maternal health, child development, mental health, nutrition, genetics, family medicine, neonatal medicine, and epidemiology to guide the cohort.

The vision of the APrON study is to determine the association between the mental health of mothers and fathers, maternal and paternal factors (e.g. nutrition, social and family, behavioral, and genetics), and children's development. In addition to collecting data on a broad range of physical and psychosocial variables, APrON also set up a DNA bank for future nutritional genomics. Samples from a large cohort of children and their parents were obtained. The development of this DNA biobank is one of the long term legacies of this project. It is anticipated that the DNA bank will provide a unique resource to explore the relationships between genotypes and a variety of maternal and child health outcomes.

The *objectives* of APrON were to:

1. Examine the associations between maternal prenatal nutritional intake and status and mothers' and children's mental health and the children's neurodevelopment;

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2. Investigate the risk factors associated with maternal and paternal perinatal depression, and the impact of maternal and paternal depression on pregnancy and birth outcomes, as well as children's development;
3. Establish a DNA biobank that could be used to examine the influence of nutritional genomics on children's neurodevelopment and behaviour.

The *aims of this paper* are to describe the methods used to establish the APrON cohort, provide an overview of the domains and instruments used for data collection, and present the demographic characteristics of the cohort participants (mothers, fathers, and babies). We also present information about cohort retention rates, as well as the characteristics of women who provided follow up data at three months postpartum compared to women who did not provide data.

The APrON study was approved by the University of Calgary Conjoint Health Research Ethics Board and the University of Alberta Health Research Ethics Biomedical Panel.

Material and Methods

The APrON study cohort

Eligible participants included pregnant women age 16 years and over, gestational age <27 weeks, who lived in the metropolitan areas of Calgary (population 1.1 million) or Edmonton (population 0.8 million), Alberta, Canada (31). Government statistics in 2008 reported 50,164 live births annually in Alberta, with 18,633 in Calgary and 14,866 in Edmonton (32). Recruitment occurred from 2009-2012. Women were excluded if they planned to move out of the region within six months of enrollment in the study. Community based recruitment strategies were used to identify possible participants; these methods and their results have been published elsewhere (33, 34).

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Data collection and follow-up

Written standard operating procedures were developed for data collection that included information on the mailing of questionnaires at each time point, in-person visits, and biological sample collections. Prior to participation in the study, mothers and fathers provided informed consent for themselves and their baby. Participant materials, including questionnaires and cheek swab kits were prepared prior to each clinic visit.

Women had their first in-person visit in either their first or second trimester prior to 27 weeks gestation. Women were seen again in the research lab in each remaining trimester and at 3 months postpartum with their babies. Questionnaires were given to mothers approximately 6, 12, 24, and 36 months after delivery. The time points and variable domains are shown in Figure 1. Information about delivery and birth outcomes was abstracted from hospital or midwife records.

Questionnaires on pre-pregnancy physical activity, pre-pregnancy dietary intake (using a food frequency questionnaire), and changes in diet since becoming pregnant were completed. At this and each subsequent study visit, a non-fasting blood sample was drawn by a phlebotomist and processed by a lab technician. Anthropometric measures were taken by a trained research assistant as previously described (31), and women completed a 24 hour dietary recall. Dietary recall data was collected with the help of a trained research assistant using the multiple pass method (35). Women also provided a random (i.e. time of day not controlled) urine sample at each visit.

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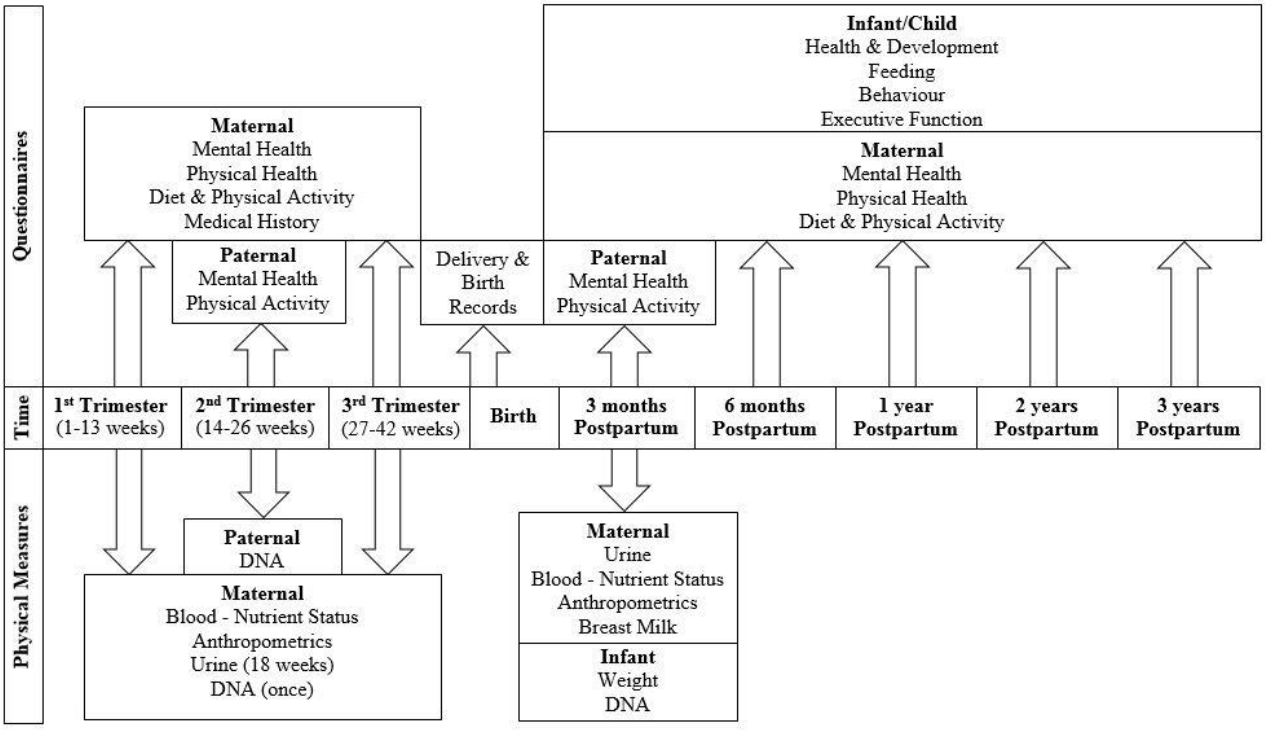
Figure 1 – Graphic summary of APrON data collection



At approximately 3 months postpartum, mothers and their babies returned to the research lab for the final in-person study visit. Maternal anthropometric data was collected, babies were weighed, and a small blood sample was obtained from the baby; if there was insufficient blood for DNA extraction, a cheek swab was obtained. Mothers provided non-fasting blood and urine samples. In addition, mothers who were breastfeeding provided a breast milk sample. Questionnaires about maternal physical and mental health, birth complications, infant temperament, crying, sleep, and behavior were also completed. Mailed or emailed questionnaires were used to follow the women and the infants/children at 6, 12, 24, and 36 months.

Fathers completed questionnaires once during their partner's pregnancy and at approximately 3 months postpartum. A data collection package consisting of a consent form, a set of questionnaires and a cheek swab kit (with collection instructions) was mailed to fathers or given to them at a clinic visit. Completed forms, questionnaires and cheek swab samples were returned

to the APrON office via mail or brought to the clinic at the next visit. The list of data domains for all participants is presented in Tables 1-2.

Table 1 Measures Completed at Each Time Point for Mothers, Fathers, and Child

Assessments								
	Mothers				Fathers		Infant/Child	
	Pregnancy	3M PP	6MPP	12M, 24M, 36M PP	PN	PP	3 M*, 6M, 12M PP	24M, 36M PP
Demographics	X	X	X	X	X			
Medical Information	X				X			
Smoking, drugs & alcohol	X	X			X	X		
Depression/Anxiety	X	X	X	X	X	X		
Stressful Life Events	X	X		X	X	X		
Social Support	X	X		X	X	X		
Pregnancy Information	X							
Physical Activity	X	X		X	X	X		
Dietary/Supplement Recall	X	X						
Breastfeeding Education	X							
Nutrition Counselling		X						
Dietary Intake (infant)							X	X
Physical Health (infant)							X	X
Temperament							X	X
Child Behavior								X
Executive Functions								X
Autism Screen								X
Anthropometry	X	X					X*	
Blood (non-fasting)[1]	X	X					X*[2]	
Urine[3]	X	X						
DNA from blood	X				X		X*	
Spot breast milk[4]		X						

M = Months, PN = Prenatal, PP = Postpartum

** Samples from infants collected at 3 months postpartum only*

[1] A spot sample (serum and plasma) was collected for fatty acid analysis, time of day was not controlled; blood samples collected 2 – 3 times during pregnancy.

[2] If a blood sample was not collected then a saliva sample was collected for DNA extraction.

[3] Urine sample collected at each appointment, but time of day was not controlled.

[4] A spot sample was collected for fatty acid analysis, time of day was not controlled.

Table 2 Data Collected at Delivery from Birth Records

Mother
Demographics
Medical History
Obstetric History
Use of Fertility Treatments
Prenatal Vitamin Intake Supplementation
Smoking
Alcohol and Street Drugs
Medications
Height
Weight
BMI
Fundal Height
Breastfeeding Intentions
Ultrasound Details
Blood Work and Screens
Antenatal Risk Assessments
Intrapartum Risk Assessments
Infant
Newborn Health
Birth Weight
Gestational Age at Birth
Head Circumference
Apgar Scores
Neonatal Intensive Care Details (when
Labour and Delivery
Duration of Labor
Pain Management
Induction
Medications
Anesthesia
Complications

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Results

Of the approximately 4800 pregnant women who provided contact details in order to receive study information, approximately 2600 did not enroll. Of these, 6% did not participate because they became ineligible (e.g., miscarriage, too advanced in pregnancy), and about half did not respond to repeated attempts to contact them. The remaining non-participants cited being too busy or lack of interest as reasons for not enrolling. Background information was not collected from any of the 2600 non-respondents, precluding comparison between women who enrolled in the study and those who did not.

At the end of recruitment, 2140 women, 2172 infants, and 1417 biological fathers had enrolled (see Table 3). Overall, most women were Caucasian, married or in common-law relationships, had completed university, and had a household income of ≥ $100 000. At birth, the average gestational age of the babies was 38 weeks and slightly more boys (53%) than girls were born, consistent with the worldwide gender birth ratio (36).

Table 3 Characteristics of APrON Cohort Participants: Mothers, Fathers and Infants

Demographic Characteristics						
	Mothers		Fathers		Infants	
	n = 2140		n = 1244		n= 2076	
	M	SD	M	SD	M	SD
Age at first visit (years)	31.2	4.5	33.8	4.9	N/A	
Gestational age at birth (days)	N/A		N/A		272.9	14.9
Birth weight (g)					3326	562.6
	n	%	n	%	n	%
Marital Status						
Married	1772	84.7	1161	86.7		
Common-law	236	11.3	152	11.4		
Divorced	8	0.4	7	0.5	N/A	
Separated	7	0.3	2	0.1		
Single	69	3.3	17	1.3		

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Demographic Characteristics						
Education						
Completed post-grad	470	22.7	244	18.2		
Completed University	943	45.5	525	39.2		
Completed trade/tech	401	19.4	383	28.6	N/A	
Completed high school	200	9.6	152	11.4		
Less than high school	58	2.8	33	2.5		
Household Income						
$100,000 or more	1143	55.2				
$70,000-$99,999	463	22.4				
$40,000-$69,999	276	13.3	N/A		N/A	
$20,000-$39,999	122	5.9				
Less than $20,000	65	3.1				
Primiparous						
Yes	1119	53.5	N/A		N/A	
No	971	46.5				
Born in Canada						
Yes	1612	77.1	1056	78.9	N/A	
No	479	22.9	282	21.1		
Ethnicity						
Caucasian	1674	80.2	1113	84.6	N/A	
Non-Caucasian	412	19.7	202	15.4	N/A	
Infant Sex						
Boy	N/A		N/A		1152	53.5
Girl					1002	46.5

N/A = not applicable, M = Mean, SD = Standard Deviation

Note: n's vary because of missing values for some variables

To determine how the APrON cohort composition compared to provincial statistics, a previous paper (33) examined the APrON characteristics against provincial data from the Maternal Experience Survey (MES), which used a stratified method of recruitment based on census data. Compared to the MES, women enrolled in the APrON study tended to be older, to be primiparous, to have higher levels of education (university graduates), and to come from a higher income group (>$40 000) (all $p < 0.05$) compared to provincial data.

Follow-up response rates

Of the 2191 mothers who signed consent forms, 2 withdrew consent, and 49 became ineligible (participants whose pregnancies resulted in no child [i.e., miscarriage, still birth] or lost custody of the child soon after birth), resulting in an adjusted initial enrollment of 2140. Follow-up response rates declined from 87.8% in the 3rd trimester to 66.8% at the 12 month follow-up. Follow-up data beyond 12 months postpartum was not available at the time of this writing. We continue to contact all participants who initially enrolled in the study (with the exception of those who have declined further participation, currently n = 97, and those for whom we no longer have valid contact information, n = 19) to request follow-up data. Some families provided study data even after missing several previous data points. As expected, the percentage of infants for whom we obtained data at 3, 6, and 12 months was similar to mothers (Figure 2).

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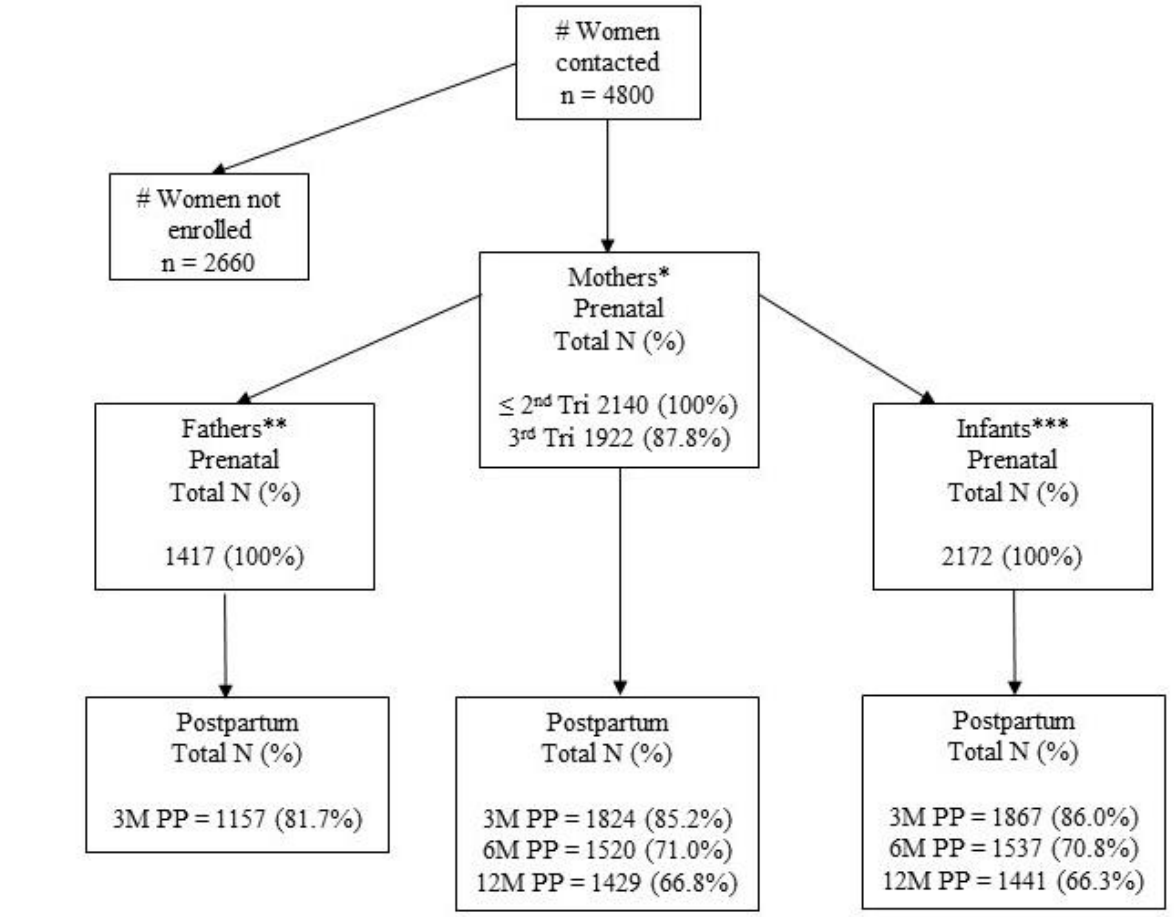
Figure 2 Participation Rates at Time Points Up To 1 year Postpartum



Tri = Trimester, M = Months, PP = Postpartum

* Participants were recruited prior to 27 weeks gestation; therefore the combined 1st and 2nd trimester sample represents the complete initial enrollment.

** Fathers were contacted once during the prenatal period and once at 3 months postpartum.

*** The sample size for babies is higher than mothers due to multiple births (twin/triplet births)

To determine whether women who missed providing follow-up data differed demographically from those who did not miss, we compared those two groups at 3 months postpartum (a time at which data were fully cleaned and available for analysis). Women who did not provide data at 3 months follow-up were, on average, one year younger and more likely to be unmarried; their

infants were born 3 days earlier (all statistically significant; see Table 4). There was also a trend for higher birth weight among infants with missing data at 3 months follow-up.

Table 4 Characteristics of APrON Women Participants Who Completed Questionnaires at 3 months Postpartum Compared to Women Who Did Not

Variable	Did not complete			Completed			P-value*
	Total n	M	SD	Total n	M	SD	
Age (years)	337	30.1	5.6	1803	31.3	4.3	<0.001
Pre-pregnancy BMI (kg/m^2)	286	24.9	6.2	1623	24.1	4.7	0.06
Gestational age at birth (days)	290	270	21	1754	274	14	0.003
Birth weight (grams)	290	3387	527	1754	3322	565	0.05
	Total n	% of total n		Total n	% of total n		
Primiparous	366	61.5		1823	57.4		0.164
No previous pregnancies	308	46.8		1803	47.0		0.99
Married/Common-law	304	91.1		1799	96.8		<0.001
Sex of infants (boys)	293	52.2		1764	52.9		0.86
Preterm Birth (< 37 weeks)	366	8.6		1823	6.2		0.16

Did not complete = women who withdrew consent, became ineligible, and were lost to follow-up (i.e. participant whose contact information is no longer active)

*P values derived from the chi^2 test for categorical variables, and t-test for continuous variables

n = sample size; M = mean; SD = standard deviation

Strengths and Limitations

APrON's strengths come from its prospective data collection throughout pregnancy, the postpartum period and into early childhood, the inclusion of biological fathers, and prospective follow-up of children to at least age three. The breadth of data is large and includes questionnaires, anthropometric measurements, and biological samples. The APrON cohort is actively supporting a number of ancillary studies associated with nutrition and maternal/child health, environmental toxicant exposures, neurodevelopment, neuroimaging, maternal stress biomarkers and parenting quality.

APrON is truly an interdisciplinary collaboration that provides a platform for studying multiple potential exposures and outcomes for different members of the family unit: mothers, fathers and their children. This study is unique with respect to the comprehensive collection of nutrition and mental health data that enables characterization of the pre-pregnancy and intrauterine environment. Although many studies obtain simple dietary recall information, APrON collected three types of nutrition data: a) the Food Frequency Questionnaire was administered at the pregnant woman's first prenatal visit to collect information about dietary habits for the previous 12 months, b) 24 hour recall of foods consumed was collected at each trimester and 3 months postpartum, and c) biological samples were collected at each clinic visit to enable assessment of important nutrients (e.g., iron, B vitamins, PUFAs, choline) using well accepted biomarkers. In addition, the collection of biological samples during pregnancy permits examination of various environmental exposures (e.g., neurotoxicants).

One potential limitation of the overall cohort is that we did not achieve a representative sample relative to provincial population statistics (33). The APrON sample under-represents women in the lowest education and income categories as compared to the Maternity Experiences Survey

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(33), which used a stratified random sample to describe pregnant Canadian women. As detailed in the paper by Manca et al (34), the majority (85%) of enrollment came from Calgary, and the remainder from Edmonton. Thus, our sample is also urban and may not represent families living in rural regions. However, of significant relevance to APrON's objectives and hypotheses, the prevalence rates of depression and anxiety symptoms among the pregnant women were similar to national statistics (37). For the nutrients studied thus far, our analyses show diversity in the intake within the cohort. This variability will enable us to perform future studies aimed at determining the relationships between nutrition, mental health, and child neurodevelopment.

Data Access

To maximize the use and potential of the APrON data set to address important research and policy questions, all APrON data will ultimately be available to the wider research community through the newly formed Child Data Centre of Alberta (CDCA). To find out more about the CDCA and the process of requesting access to data, consult http://www.research4children.com, and click on the link to the CDCA.

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Conflict of Interest Statement

All authors acknowledge there is no conflict of interest.

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