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Cohort Profile: The Alberta Pregnancy Outcomes and Nutrition Cohort Study

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Conflict of Interest

None declared.

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ABSTRACT

Purpose: The purposes of the Alberta Pregnancy Outcomes and Nutrition (APrON) study were: to determine the relationship between maternal nutrient intake and status before, during, and after pregnancy, and (a) maternal mental health, (b) pregnancy and birth outcomes, and (c) infant neurodevelopment; to examine the relationship between maternal thyroid status and neonatal outcomes, and to establish nutrient predictors of infant behavioral patterns; and to establish a DNA biobank to examine the influence of nutritional genomics on children neurodevelopment and behavioral patterns.

Participants: APrON is an ongoing prospective transgenerational cohort study consisting of participants who reside in Calgary and Edmonton, Alberta, Canada. Data comprise of: self-completed mother, father, and child questionnaires; maternal and paternal dietary interviews; clinical assessments; linkage to hospital obstetrical records; and biological samples. DNA samples were banked for future studies of nutrient/gene and genetic links to infant development.

Findings to date: Key findings pertaining to mental health and nutrition outcomes are presented. Specifically, risk factors for depressive symptoms and the positive association between maternal exposure to adverse childhood experiences and prenatal depression and anxiety are discussed. The consumption of specific food groups that is associated with meeting choline adequate intake recommendations is discussed, along with findings pertaining to mothers' gestational weight gain and reported dietary Vitamin D intake.

Future plans: The APrON cohort offers a unique opportunity to follow a group of Canadian children to advance understanding of the fetal origins of diseases. The APrON study aspires to transition to an intergenerational study in order to investigate current child participants in

adulthood. Accordingly, the APrON study will use a detailed array of standardized validated psychological and physiological measures and biospecimens to collect detailed information on maternal nutrition during pregnancy and maternal and paternal perinatal mental health.

ARTICLE SUMMARY

- The APrON study used a detailed array of standardized validated psychological and physiological measures and biospecimens. The prospective data collection and follow-up enabled investigation of a wide range of maternal and paternal health outcomes.
- The APrON team has been successful in continuously engaging participants, as evidenced by high response rates during pregnancy, postpartum and early childhood.
- One limitation is that the sample characteristics are skewed toward a high percentage of white, well-educated and married participants. Consequently, generalizability of findings to those with different socio-demographic backgrounds should be made with caution.
- Another limitation is that selective attrition bias has likely occurred, which may lead to underestimation of the effect of parental mental health and lifestyle choices on the child's development.

INTRODUCTION

The Alberta Pregnancy Outcomes and Nutrition (APrON) study is a longitudinal cohort of pregnant women, their partners[1], and children in Alberta, Canada. The APrON study was designed to investigate the effect of nutrient intake and status during pregnancy on maternal mental health and children's neurodevelopment [1, 2]. The original grant of $5 million provided the foundation for the APrON study, which has expanded its focus and contributed to over 50

[1] Mothers in our study are biological mothers. Fathers self-identified as fathers of their children, whether biological or not.

additional projects on the psychobiology of stress, parent-child relationships and attachment, neurotoxicant exposure, genetics, epigenetics, inflammation, and immune activity, probiotics, the microbiome and children's brain development. To date, the APrON study has received over $14 million in additional funding. This funding enabled follow-up of APrON families to when children reach age 12 to address the impact of medical, biological, and environmental factors on children's development, behavior and mental health [3]. Data collection for the five-year follow-up questionnaire is complete, eight-year follow-up is ongoing and a 12-year follow-up will start in 2021. The objective of this paper is to describe key findings on maternal and paternal mental health outcomes and maternal nutrient intake and status of APrON participants from pregnancy to three years after delivery.

COHORT DESCRIPTION

Women were recruited into the cohort if they were 16 years of age or older, able to speak and read English, < 27 weeks gestation and willing to come for on-site visits at the University of Calgary, Calgary or University of Alberta, Edmonton, Alberta. Men were eligible if they were cohabitating with the participating woman. Participants were excluded if they planned to move out of the region during the on-site visit timeframe (pregnancy to 3 months postpartum) of the study. A total of 2189 pregnant women (aged 16 to 44) and 1325 men (aged 18 to 52), residing around Calgary or Edmonton, were enrolled in the study between May 2009 and June 2012. The APrON study was approved by the University of Calgary Health Research Ethics Board (REB14-1702) and University of Alberta Health Research Ethics Biomedical Panel (00002954). Full details on how women and their partners were recruited are provided by Kaplan et al. (2014) and in previous publications describing the APrON cohort [4, 5]. To assess the representativeness of the APrON cohort (see Table 1), socio-demographic characteristics of participants at the time of

recruitment were compared to characteristics of women with children in Calgary, Alberta, and

Category	Maternal (n / %)	Paternal (n / %)
Demographics		
Age (years)		
16 – 24	100 (4.6)	19 (1.4)
25 – 29	481 (22.0)	216 (15.4)
30 -34	980 (44.78)	493 (35.2)
35 -39	512 (23.4)	329 (23.5)
≥ 40	105 (4.8)	162 (11.6)
Missing age information	11 (0.5)	181 (12.9)
Marital status		
Married/common-law	2035 (93.0)	1275 (91.1)
Single/divorced/separated	97 (4.4)	27 (1.9)
Missing marital information	57 (2.6)	98 (7.0)
Education		
Less than a high school diploma	59 (2.7)	31 (2.2)
Completed high school diploma	202 (9.2)	147 (10.5)
Completed trade, technical	404 (18.5)	376 (26.9)
Completed university or more	1442 (66.8)	746 (53.3)
Missing education information	83 (3.7)	100 (7.1)
Ethnicity		
White	1693 (77.3)	1082 (77.3)
Non-white	485 (22.2)	206 (14.7)
Missing ethnic information	11 (0.5)	112 (8.0)
Mothers' Report on total household income		
< $40,000	190 (8.7)	-
$40,000 - $69,999	279 (12.7)	-
$70,000 - $99,9999	464(21.2)	-
>$100,000	1146 (52.3)	-
Missing household income information	110 (5.0)	-
Born in Canada		
Yes	1618 (73.9)	1024 (73.1)
No	481 (22.0)	277 (19.8)
Missing country of birth	90 (4.1)	99 (7.1)
Gravidity		
Multigravida	1107 (51.6)	n/a
Primigravida	996 (46.4)	n/a
Missing gravidity information	42 (2.0)	n/a
Parity		
0	1222 (55.8)	n/a
1	732 (33.4)	n/a

Canada [3, 5, 6].

2	181 (8.3)	n/a
≥3	37 (1.7)	n/a
Missing parity information	17 (0.8)	n/a

Table 1. *Participant Intake Characteristics (N = 3514)*

A greater proportion of women in the cohort (28.0%) were over 34 years old compared with women in Calgary (20.0%), Alberta (16.0%), and Canada (18.0%). More APrON women were married (95%) compared with women in Calgary (73.0%), Alberta (70.0%), and Canada (60.0%). A greater proportion of women had household income of $70,000 or more (77.0%) compared to Calgary (65.0%), Alberta (61.0%), and Canada (58.0%). More APrON women completed post-secondary education (87.0%) compared to women in Calgary (69.0%), Alberta (70.0%), and Canada (72.0%). The proportion of APrON women who were born outside of Canada (23.0%) was similar to the proportions in Calgary (25.0%), Alberta (22%), and Canada (20.0%) (Figure 1).

How Often Have They Been Followed Up?

Between 2009 and 2012 the initial cohort completed questionnaires and clinical assessments three times during pregnancy, and at 3 months postpartum. Follow-up questionnaires were provided when their child was 6 months, and 1-, 2- and 3- years of age (see Figure 2).

In total, 2189 women and 1325 men completed at least one questionnaire. Of these, 1945 (88.8%), are continuing participants, who were defined as those who did not become ineligible or lost to follow-up. Participants who discontinued the study included women who miscarried, had a stillbirth, lost custody of their child, or for whom a maternal/child death was reported (n = 52, 2.4%); moved out of Calgary or Edmonton before three months postpartum (n = 43, 2.0%); or withdrew from the study citing loss of interest (n = 147; 6.7%). The demographic characteristics

of participants who continued in APrON compared with those that discontinued are provided in Table 2.

Table 2. *Comparison of Demographic Characteristics of Continuing and Discontinued Participants*

Characteristic	Continuing participants	Discontinuing participants			*P*-value*
	n (%)	Become ineligible n (%)	Lost to follow-up n (%)	Dropped out n (%)	
Maternal age					
16 – 24	71 (3.6)	8 (18.6)	15 (34.8)	6 (4.1)	< 0.001
25 – 29	424 (16.2)	7 (16.2)	7 (16.2)	43 (29.2)	
30 – 34	899 (46.2)	15 (34.8)	14 (32.5)	51 (34.7)	
35 – 39	454 (23.3)	9 (20.9)	7 (16.2)	41 (27.9)	
≥40	95 (4.8)	4 (9.3)	0 (0.0)	6 (4.1)	
Marital status					
Single	72 (3.8)	12 (24.5)	8 (21.1)	5 (3.8)	0.007
Married	1838 (96.2)	37 (75.5)	30 (78.9)	128 (96.2)	
Maternal education					
Less than a high school diploma	41 (2.2)	6 (16.2)	8 (20.5)	4 (3.01)	<0.001
Completed high school diploma	164 (8.6)	9 (24.3)	9 (23.1)	20 (15.0)	
Completed trade, technical diploma	362 (19.1)	5 (13.5)	10 (25.6)	26 (19.5)	
Completed university or more	1329 (70.1)	17 (45.9)	12 (30.6)	83 (62.4)	
Household income					
< $40,000	151 (8.1)	12 (30.8)	19 (54.3)	8 (6.15)	<0.001
$40,000-$60,000	252 (13.4)	6 (15.4)	5 (14.3)	16 (12.31)	
$70,000-$99,9999	428 (22.8)	7 (17.9)	4 (11.4)	24 (18.46)	
≥ $100,000	1042 (55.6)	14 (35.9)	7 (20.0)	82 (63.08)	
Born in Canada					

No	425 (22.5)	13 (32.5)	14(37.8)	28 (21.2)	0.186
Yes	1463 (77.5)	27 (67.5)	23 (62.2)	104 (78.8)	

Note. Assessing the null hypothesis that there is no difference in distributions between those participants who continued and those who did not continue in the study; chi-square test

Continuing participants were more likely older, married, and had higher education and household income (all *p*s < 0.05). The proportion of continuing participants born in Canada was similar to discontinuing participants. When mothers were lost to follow-up, so too were fathers and children.

What Has Been Measured?

Women were asked to complete questionnaires three times during pregnancy (<14, 14-26, and 27-40 weeks gestation, number of scales administered at this time was 37) and six times postnatally (3 and 6 months, 1, 2, 3, and 5 years, number of scales administered at this time was 65). Fathers were asked to complete questionnaires when the women were 14-26 weeks gestational age (number of scales administered at this time was 16), and twice postnatally (3 months and 5 years, number of scales administered at this time were 14). Questionnaires administered during pregnancy measured previous and current mental and physical health status, nutritional, medication and supplement intake, lifestyle choices, healthcare services used, social support, attitudes towards breastfeeding, and sociodemographic variables. The follow-up postpartum questionnaires collected information about labor and delivery; postpartum medical problems; maternal mental health; nutritional, medication and supplement intake; lifestyle choices; food security; and socio-demographics (see Figure 2). A detailed list of data collected, including measures used if applicable, is provided in Table 3.1 for mothers and Table 3.2 for fathers.

Table 3.1. *Maternal Variables and Biological Specimens Collected in All Questionnaires and Clinical Visits*

Variables	<14 weeks	14-26 weeks	27-40 weeks	3 months postpartum	6 months postpartum	1 year	2 years	3 years
Socio-demographics								
Household income	X							
Education	X							
Marital status	X							
Age	X							
Primary language	X							
Born in Canada	X							
Family background		X	X	X	X	X	X	X
Family history		X						
Health and lifestyle								
General health				SF-8	SF-8	SF-8	SF-8	SF-8
Current medical conditions and medications	X	X	X	X	X	X	X	X
Substance use	X	X	X	X	X	X	X	X
Pregnancy history								
Pre-pregnancy physical activity	X	X	X	X	X	X	X	X
Physical activity	GLTE	GLTE	GLTE	GLTE	GLTE	GLTE	GLTE	GLTE
Dental care	X	X	X					
Dietary changes since pregnancy	X							
Food security			CCHSC		CCHSC			
Nutrition counselling information				X				
Diet history pre-pregnancy		FFQ						
Nausea and vomiting	PUQUE	PUQUE	PUQUE					
Breastfeeding information				X	X	X	X	X
24-hour recall of foods consumed	X	X	X	X	X	X	X	X
Psychosocial health								
Depression	EDS	EDS	EDS	EDS	EDS	EDS	EDS	EDS
Stress	SLEQ		SLEQ	SLEQ		SLEQ	SLEQ	SLEQ
Social support	SSQ	SSQ	SSQ	SSQ	SSQ	SSQ	SSQ	SSQ

DSM-IV Axis I disorders		PDSQ		PDSQ				
Anxiety	SCL-90-R	SCL-90-R	SCL-90-R	SCL-90-R	SCL-90-R	SCL-90-R	SCL-90-R	SCL-90-R
Adverse childhood events	ACEs X	X	X	X		X	X	X
History of mental health		X	X					
Anthropometrics (BMI/height/weight)								
Biological specimens								
Urine		X		X				
Venous blood	X	X	X	X				
Breast milk				X				

Note. X refers to investigator-developed measures. SCL-90-R, Symptom Checklist-90-Revised; EDS, Edinburgh Depression Scale; PUQE, Pregnancy-Unique Quantification of Emesis and Nausea questionnaire; SLEQ, Stressful Life Events Questionnaire ; SSQ, Social Support Questionnaire; PDSQ, Psychiatric Diagnostic Screening Questionnaire; ACEs, Adverse Childhood Experiences Questionnaire; SF-8, Short Form Health Survey-8; CCHSC, Canadian Community Health Survey Cycle 2.2, modified; GLTE, Godin Leisure-Time Exercise Questionnaire; FFQ, Food Frequency Questionnaire, adapted from the Canadian version of the Diet History Questionnaire.*Breastfeeding mothers only.

Table 3.2. *Paternal Variables and Biological Specimens Collected in All Questionnaires and Clinical Visits*

Variables	<14 weeks gestation	14-26 weeks	27-40 weeks	3 months postpartum
Socio-demographics				
Household income			X	
Education			X	
Marital status			X	
Age			X	
Primary language			X	
Born in Canada			X	
Family background			X	
Family history*			X	
Health and lifestyle		X	X	
General health				
Current medical conditions and medications		X	X	X
Substance use		X	X	X
Physical Activity Anthropometrics		GLTE	GLTE	GLTE
(BMI/height/weight)		X	X	X
Psychosocial health				
Depression		EDS	EDS	EDS
Social support		SSQ	SSQ	SSQ
Stress			SLEQ	
Biological specimens*				
Buccal cell swab			X	
DNA from blood			X	

Maternal anthropometric measurements were collected at each visit during pregnancy and three months postpartum. These measures included height, pre-pregnancy and current weight, highest weight during pregnancy; circumference measurements (i.e., mid-upper arm, waist, hip, thigh); and skinfold thickness (i.e., biceps, triceps, subscapular, suprailiac, thigh). Each measurement was taken three times and averages were reported for analyses. Paternal height and weight were collected during the prenatal period. One objective of APrON was to establish a biobank for future research that would allow investigation on genetics, epigenetics [1], nutrient exposures and neurotoxicants. Maternal non-fasting venous blood samples were collected from

mothers at <14, 14-26, and 27-40 weeks gestation, and at three months postpartum. Maternal blood collection provided whole blood, plasma, and serum, which were used for DNA, RNA, cytokines, hematocrit, hemoglobin measures, thyroid hormones and measures of heavy metal (e.g., mercury, lead) and perfluorinated chemical exposure. Buccal cell samples were also collected at 14-26 weeks gestation from fathers for DNA extraction and future genetic and epigenetic studies. Purified DNA is available at the Gene Expression Omnibus data repository (https://www.ncbi.nlm.nih.gov/geo/). Midstream random urine samples (10 mL) were collected from expectant mothers at 14-26 weeks gestation and three months postpartum. Samples have been used in the Neurotoxicant study ($N = 546$) to examine maternal exposure to endocrine-disrupting hormones [2]. A breast milk sample was collected from breastfeeding mothers to determine fatty acids composition.

Patient and Public Involvement

There is an APrON Patient Engagement committee, who advises on research directions, but not design. Findings have been disseminated to participants through newsletters and an online conference.

FINDINGS TO DATE

A complete list of publications from APrON can be found at http://www.apronstudy.ca/research/publications-and-press. Key findings on maternal and paternal mental health and maternal nutrition outcomes have been summarized in Box 1.

Box 1 Key findings

Mental health outcomes

- In partnered couples, both mothers and fathers had depressive symptoms in 2.3% (n = 19) of couples. Low household income and prenatal maternal depression were associated with a higher probability of depressive symptoms in both partners. In 78.5% (n = 664) of couples, neither father nor mother experienced depressive symptoms. Postnatal social support was found to be a protective factor associated with decreased risk of maternal and paternal postpartum depressive symptoms. Risk factors for maternal postpartum depression symptoms included low household income, and prenatal EDS score > 10. For paternal postpartum depression symptoms, risk factors included low household income, prenatal EDS score of > 9, postpartum stressful life events, and smoking.
- Women with EDS score of < 10 were more likely to take micronutrients (e.g., vitamins B6, B9, B12, and E; essential fatty acids; selenium) compared to women with EDS score of < 10.
- One hundred and twenty-two women (13.4 %) had a score of 3 or more ACEs. Maternal exposure to ACEs was positively associated with both prenatal depression and anxiety.

Nutrition outcomes

- Approximately 70% of women who enter pregnancy with a body mass index (BMI) > 25 kg/m^2 were likely to exceed GWG guidelines in the beginning of the second trimester. Women with excessive weight gain also gained higher amounts of body fat and retain higher amounts of fat compared to women who gain within the guidelines. Women who consumed a healthy diet pattern prior to pregnancy were less likely to develop complications such as gestational hypertension.
- The median vitamin D intake from diet and supplements was 600 IU/day during pregnancy, which was not enough to achieve a target circulation 25(OH)D concentration. A significant relationship between maternal reported dietary vitamin D intake and plasma 25(OH)D and 3-epi-25(OH)D3 concentration were identified.
- Only 23% (n= 138) of mothers met the adequate intake (AI) recommendations for choline; the number was even lower (10%) in the postpartum period. Consuming eggs and milk during pregnancy increased mothers' likelihood of meeting choline AI recommendations.

Mental Health Outcomes

Four key papers [7-10] reported on perinatal depression and anxiety prevalence and risk factors, and the impact of adverse childhood experiences (ACEs) on maternal prenatal depression and anxiety. Letourneau et al. [8] reported that 10.7% (n = 68) of mothers experienced depressive symptoms in late pregnancy, defined as a score above the Edinburgh Depression Scale (EDS) cut-off of ≥ 10 for mothers [11]. Similarly, 10.7 % (n = 68) reported depressive symptoms at 3 months postpartum (8). For fathers, cut-off of EDS ≥ 9 was used [12]. Nearly 14.0% of fathers (n = 139) reported depressive symptoms in either first or second trimester, with rates going down to 9.1% (58) at 3 months postpartum (8). Leung et al. [9] examined 846 cohabitating (i.e., married

and common-law) mother-father couples, with 2.3% (n = 19) of couples having both mothers and fathers reporting perinatal depressive symptoms. Neither mother nor father reported depressive symptoms in 78.5% (n = 664) of couples. In 9.5% (n = 80) of couples, only mothers experienced depressive symptoms during postpartum; similarly, in 9.8% (n = 83) of couples only fathers reported depressive symptoms. Low household income and prenatal maternal depression were associated with a higher incidence of depressive postpartum symptoms in both mothers and fathers. Risk factors for maternal postpartum depressive symptoms included the low household income and prenatal depressive symptoms. Risk factors for paternal postpartum depressive symptoms included low household income, prenatal depressive symptoms, postpartum stressful life events, and smoking. Postpartum social support was found to be a protective factor associated with decreased risk of maternal and paternal postpartum depressive symptoms. Additionally, Leung et al. [7] found that mothers who reported no depressive symptoms during the perinatal period were more likely to take micronutrients (e.g., vitamins B6, B9, B12, and E; essential fatty acids; selenium) compared to mothers who experienced perinatal depressive symptoms.

Letourneau et al. [10] reported that the higher ACEs score was positively associated with both prenatal depression and anxiety. ACEs were defined as traumatic events that include physical, sexual, and emotional abuse; household dysfunction; domestic violence; or living with an adult experiencing mental illness, substance use, or incarceration during childhood [13]. Nearly 14% (n = 122) of women reported having experienced 3 or more ACEs (10). This finding is consistent with previous research [14] that suggest about a graded relationship between the number of ACEs and later increased risk for health issues. Routine screening for ACEs may facilitate early identification and preventative interventions; however, this has been recently debated (14). In sum, the identified risks and protective factors provide opportunities for prevention of perinatal depression and anxiety in mothers and fathers.

Nutrition Outcomes

Gestational weight gain and dietary intake, and perinatal nutrient intake and status were examined in 8 key papers (15-18, 20-22, 26).

Gestational Weight Gain and Dietary Intake

Gestational weight gain over or below Health Canada's Gestational Weight Gain (GWG) Guidelines is associated with an increased risk of adverse outcomes for mother and infant [15]. The APrON cohort was the first to provide evidence that more than half of women gain more than Health Canada's Guidelines, using prospectively collected body weights from across pregnancy [16]. Since then, several studies have been completed with body weight or body composition in pregnancy or postpartum as a main outcome. Analysis of the APrON data by Jarman et al. [17] provided a clear picture indicating that ~70% of women who enter pregnancy with a body mass index (BMI) > 25 kg/m^2 are likely to exceed GWG guidelines, by about 19 weeks gestation. Women with excessive weight gain also gain higher amounts of body fat and retain higher amounts of fat compared to women who gain within the guidelines [18]. The detailed dietary intake information that was collected showed that women who consumed a healthy diet pattern prior to pregnancy were less likely to develop complications such as gestational hypertension [19]. An individualized approach to supportive dietary counseling that considers pre-pregnancy BMI in addition to the woman's social and financial context is key to helping women meet national recommendations for both diet and GWG in pregnancy [20].

Nutrient Intake and Status

Vitamin D is critical for a healthy pregnancy [21]. Three studies that included APrON participants examined the role of maternal vitamin D intake during pregnancy [22-24]. Aghajafari et al. [23] reported that the median vitamin D intake from diet and supplements was 600 IU/day during pregnancy, which was not sufficient to achieve a target circulation 25(OH)D

concentration. When the 3-epimer was included in the estimation of vitamin D status, the prevalence of vitamin D insufficiency (<75 nmol/L) was lower (33.0 %) compared to when it was excluded (38.0 %). Vitamin D supplementation (2000 IU/day) was associated with 25(OH)D3 sufficiency [22-24]. A significant relationship between maternal reported dietary vitamin D intake and plasma 25(OH)D and 3-epi-25(OH)D3 concentration were identified.

Choline intake during pregnancy and lactation is critical to the offspring's brain function [25]. Lewis et al.[26] reported that the mean choline intake in pregnant and lactating women ranged between 340 (SD 148) in the second trimester and 346 (SD 151) mg/day at 3 months postpartum. Only 23% (*n* = 138) of mothers met the adequate intake (AI) recommendations for choline; the number was even lower (10%) in the postpartum period [26]. Consuming eggs and milk during pregnancy increased mothers' likelihood of meeting choline AI recommendations. These findings contributed to the European Food Safety Authority (EFSA) dietary reference values for choline guidelines [27]. To conclude, a significant number of women were not meeting recommendations for vitamin D and choline intake during pregnancy and postpartum. Increased consumption of these nutrients may be necessary for pregnant and lactating women to improve the health and development of their infants.

STRENGTHS AND WEAKNESSES

The major strengths of APrON are recruitment and retention of the large community-based cohort during pregnancy, postpartum and early childhood. The APrON study used a detailed array of standardized validated psychological and physiological measures and biospecimens. The prospective data collection and follow-up enabled investigation of a wide range of maternal and paternal health outcomes. The APrON team has been successful in continuously engaging participants, as evidenced by high response rates over the years (see Table 4).

Table 4. *Response Rates for Questionnaires*

Data collection time point	Targeted participants (n)	Participants responded (n)	Response rate (%)
Mothers < 14 weeks gestation	2189	2145	97.9
Mothers at 14-26 weeks gestation			
Mothers at 14-26 weeks gestation and those recruited at < 14 weeks gestation	563	475	84.3
Fathers at 14-26 weeks gestation	1325	1315	99.2
Mothers at 27-40 weeks gestation	1838	1830	99.5
Mothers at 3 months postpartum	2051	1811	88.3
Fathers at 3 months postpartum	1287	1150	89.3
Mothers at 6 months postpartum	1727	1523	88.1
Mothers at 1 year postpartum	1747	1305	74.7
Mothers at 2 year postpartum	1809	1299	71.8
Mothers at 3 year postpartum	1648	1282	77.7

Limitations of this study include the sample characteristics that are skewed toward a high percentage of white, well-educated and married participants. Consequently, generalizability of findings to those with different socio-demographic backgrounds should be made with caution. Another limitation is that selective attrition bias has likely occurred, which may lead to underestimation of the effect of parental mental health and lifestyle choices on the child's development. The study likely included participants with healthier lifestyle behaviors or with

more positive attitudes towards research, because such characteristics are associated with higher socioeconomic status [28]. The differences in the demographic characteristics of the continuing participants compared with discontinuing participants should be considered when interpreting the findings. There were also fewer fathers than mothers in the sample; thus, most developmental and behavioral outcomes were based on maternal reports.

FURTHER DETAILS

Collaboration

Information about the APrON study is available at www.apronstudy.ca. The APrON data is available through SAGE (Secondary Evidence to Generate Evidence; https://policywise.com/sage/). For more information contact Dr. Nicole Letourneau at Nicole.letourneau@ucalgary.ca. Collaboration or data access inquiries will be considered by the APrON study team.

Profile in a nutshell

- The APrON study is a longitudinal cohort of mothers, fathers and their children investigating maternal, parental, birth, and child development outcomes.
- A total of 2189 women (aged 16 to 44) and 1325 fathers (aged 18 to 52), residing around either Calgary or Edmonton, Alberta, enrolled and completed at least one questionnaire between May 2009 and June 2012. The majority were married, educated, had annual household incomes >$70 000 and were born in Canada.
- Mothers completed 18 questionnaires and up to 4 clinic visits spanning pregnancy to three years postpartum and provided access to their medical records as well as three to four blood and two urine samples. To date, 1648 mothers and 1255 fathers remain eligible for follow-up.
- The APrON dataset includes comprehensive socio-demographic and psychological data from pregnancy to three years postpartum, as well as maternal blood and urine samples. The 8-year data collection follow-up is ongoing and 12-year data follow-up will start in 2021.

Requests for data and collaboration are welcomed, contact Dr. Nicole Letourneau at Nicole.letourneau@ucalgary.ca

Data Availability Statement

Data can be collected at the Secondary Analysis to General Evidence (SAGE) data repository or by contacting Dr. Nicole Letourneau (the principal investigator for the APrON Study).

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Conflict of Interest

None declared.

AUTHOR CONTRIBUTORSHIP STATEMENT

1. Elena Ali designed the manuscript, drafted the whole manuscript, analyzed and interpreted statistical data; created data tables; worked with co-authors to facilitate feedback and group work on the manuscripts; incorporated co-authors comments into manuscripts; edited the draft of the whole manuscript for content, grammar, format and style to create a final version for submission to the journal; revised and approved final version of manuscript; and agreed to be accountable for all aspects of the work involved in this manuscript.
2. Nicole Letourneau conceived the APrON study and the idea for manuscript, facilitated involvement with co-authors in creation of manuscript; designed the manuscript; obtained data; revised the whole draft for grammar, content, and style; provided final approval of the final version; agreed to be accountable for all aspects of the work.

3. Fariba Aghajafari analyzed and interpreted data; participated in discussions about design of the manuscript; drafted and revised a Nutrient Intake and Status paragraph in the manuscript; provided approval of final version; agreed to be accountable for all aspects of the work.
4. Rhonda Bell contributed to design of the manuscript by suggesting what data to include in the manuscript; obtained and analyzed data; drafted and revised Gestational Weight Gain paragraph in the manuscript; provided final approval; and agreed to be accountable for all aspects of the work.
5. Andrea Deane obtained and interpreted data; revised draft for statistical content accuracy description of the methods; assisted with creating data tables; provided final approval for the manuscript; and agreed to be accountable for all aspects of the work.
6. Deborah Dewey obtained and interpreted data; contributed to design of the draft by suggesting what to include; revised manuscript for brevity and intellectual content; approved final version; and agreed to be accountable for all aspects of the work.
7. Catherine Field obtained, analyzed and interpreted data; drafted the Nutrient Intake and Status paragraph in the manuscript, and provided comments for the whole draft; provided final approval of the manuscript; and agreed to be accountable for all aspects of the work.
8. Gerald Giesbrecht conceived the APrON study; obtained and analyzed data; revised the draft; provided final approval of the final version; agreed to be accountable for all aspects of the work.
9. Bonnie Kaplan conceived the idea for the APrON study; overseen the obtainment of data; revised the manuscript; provided final approval; and agreed to be accountable for all aspects of the work.
10. Brenda Mun Ying Leung conceived the idea for the APrON study; overseen the obtainment of data; revised the manuscript; provided final approval; and agreed to be accountable for all aspects of the work.
11. Henry Ntanda analyzed and interpreted data; revised the draft for statistical accuracy; approved final version; and agreed to be accountable for all aspects of the work.
12. APrON Team includes a large number of individuals who all had all met the ICMJE criteria for

authorship.

FIGURE LEGENDS

- Figure 1. Socio-demographic characteristics of women in APrON, Calgary, Alberta, and Canada
- Figure 2. Data collection procedures

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Figure 1. Socio-demographic characteristics of women in APrON, Calgary, Alberta, and Canada

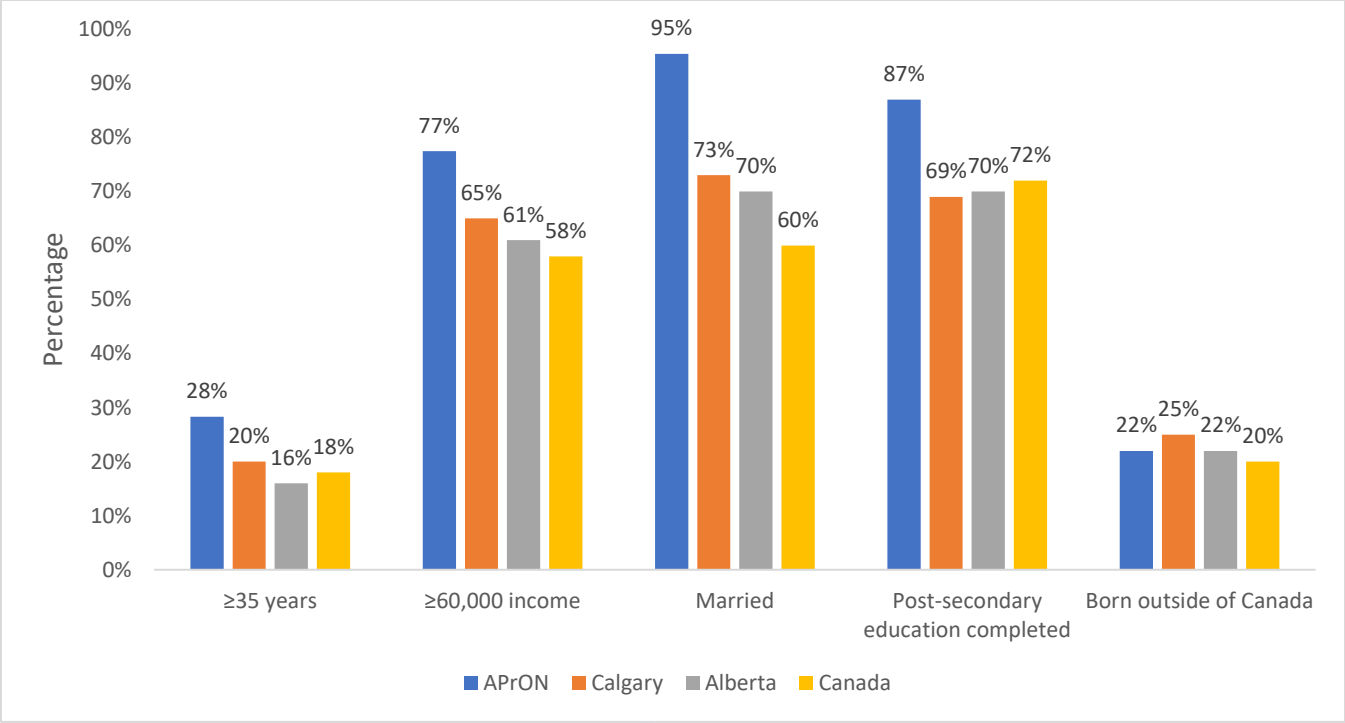
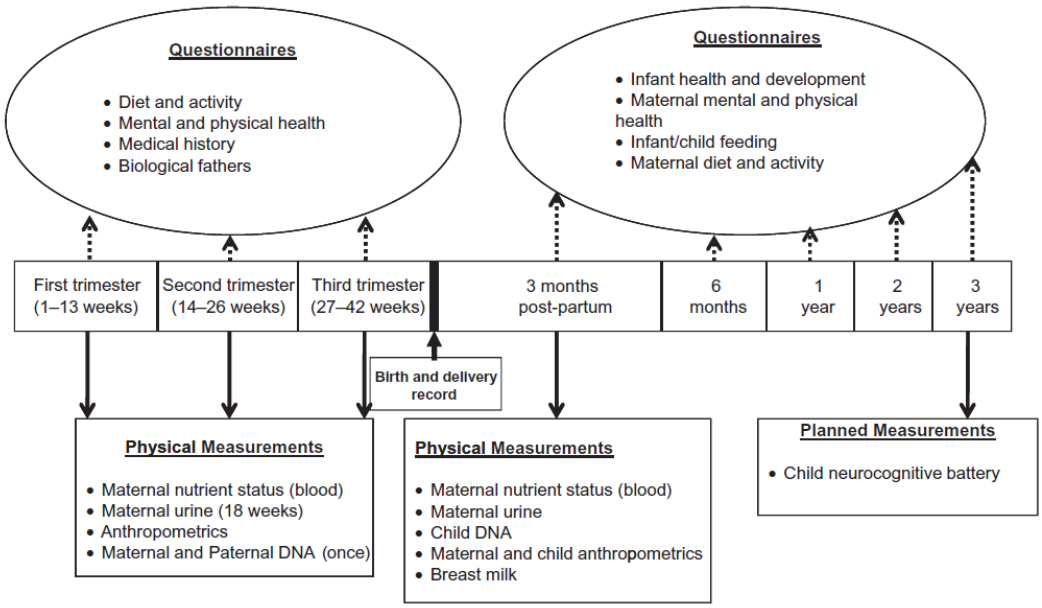


Figure 2. Data collection procedures



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The Alberta Pregnancy Outcomes and Nutrition Cohort (APrON) Study: Cohort Profile and Key Findings from the First Three Years

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Abstract

Objectives. The objectives of the ongoing Canadian longitudinal cohort called the Alberta Pregnancy Outcomes and Nutrition (APrON) Study were to: (1) determine the relationship between maternal nutrient intake and status before, during, after pregnancy, and (a) maternal mental health, (b) pregnancy and birth outcomes, and (c) infant/child neurodevelopment and behavior; (2) identify maternal mental health and nutrient predictors of child behaviour; and (3) establish a DNA biobank to explore genomic predictors of children's neurodevelopment and behavior. Drawn mostly from data collected during the period from pregnancy to when children are 3 years of age, the objectives of this paper are to describe the participants, measures, and key findings on maternal and paternal mental health, maternal nutrition, and child outcomes. However data have been collected to 8 years of age, with planned follow-up at 12 years of age.

Data Collection. Data comprise: questionnaires completed by pregnant women/mothers and their partners (usually fathers) on mothers', fathers' and children's health; dietary interviews; clinical assessments; linkage to hospital obstetrical records; and biological samples such as DNA.

Key Findings. Mental health, nutrition and child outcomes are presented. For example, APrON women who consumed more selenium and omega-3 were less likely to develop symptoms of perinatal depression. Couples in which both mothers and fathers were affected by perinatal depression reported lower incomes and higher maternal prenatal depressive symptoms and lower support from fathers postnatally and their children presented with the most behavioural problems. Higher prenatal consumption of choline rich foods such as eggs and milk were recommended as was vitamin D supplementation for both mothers and children to meet guidelines. Maternal experiences of early adversity predicted increased likelihood of perinatal depression and anxiety and children's behavioural problems.

Conclusion. The APrON cohort offers a unique opportunity to advance understanding of the developmental origins of health and disease.

Strengths and Limitations

1. APrON is a large, ongoing longitudinal study designed to understand the early origins of health and disease;

2. APrON has collected data to eight years of age and has planned follow up at 12 years of age;

3. APrON has retained more than 88% of participants at the 8-year data collection; and

4. A limitation is that the cohort is largely low-risk, limiting generalizability of study findings to higher-risk populations.

The Alberta Pregnancy Outcomes and Nutrition Cohort (APrON) Study: Cohort Profile and Key Findings from the First Three Years

Why was the APrON cohort set up?

The Alberta Pregnancy Outcomes and Nutrition (APrON) study is a longitudinal cohort of pregnant women, their partners[1], and children in Alberta, Canada. The APrON study was designed to investigate the effect of nutrient intake and status during pregnancy on maternal mental health and children's neurodevelopment and behaviour [1, 2]. An original grant of $5 million provided the foundation for the APrON study, which has subsequently expanded its focus and contributed to over 50 additional projects on the psychobiology of stress, parent-child relationships and attachment, neurotoxicant exposure, genetics, epigenetics, inflammation and immune activity, probiotics, the microbiome and children's brain development. To date, the APrON study has received over $15 million in additional funding. This funding enables follow-up of APrON families to when children reach 12 years of age to understand the impact of medical, biological, and environmental factors on children's development, behavior and mental health. Data collection for the five and eight-year follow-up questionnaires is complete, with these data currently being cleaned for analysis and the 12-year follow-up will begin in 2022. Papers have been published detailing how women and their partners were recruited [3, 4] and describing the APrON cohort at enrollment during pregnancy [5, 6] and up to 12 months postpartum [7]; however a summary of key findings has not been reported. Thus, drawn mostly from data collected during the period from pregnancy to when children are 3 years of age, the objectives of this paper are to describe the: (2) participants, (2) measures, and (3) key findings on maternal and paternal mental health, maternal nutrition, and child outcomes.

[1] Women in our study are biological mothers. Partners typically self-identified as fathers of their children, whether biological or not.

Who is in the APrON cohort?

Women were recruited into the cohort if they were 16 years of age or older, able to speak and read English, < 27 weeks gestation and willing to come for on-site clinic visits at the University of Calgary, Calgary or University of Alberta, Edmonton, Alberta. Partners were eligible if they were cohabitating with the participating woman. Participants were excluded if they planned to move out of the region during the clinic visit timeframe of pregnancy to 3 months postpartum. A total of 2189 pregnant women (aged 16 to 44) and 1325 men (aged 18 to 52), residing around Calgary or Edmonton, were enrolled in the study between May 2009 and June 2012. The APrON study was approved by the University of Calgary Health Research Ethics Board (REB14-1702) and University of Alberta Health Research Ethics Biomedical Panel (Pro00002954). To assess the representativeness of the APrON cohort (see Table 1), sociodemographic characteristics of participants at the time of recruitment were compared to characteristics of women with children in Calgary, Alberta, and Canada [6, 8, 9].

Patient and Public Involvement

APrON cohort participants were not involved in the development of the initial study design or in the recruitment of participants. However, APrON established a participant advisory committee (PAC) shortly after recruitment ended in 2012. Over time, 70 parents have participated on the PAC, with approximately 10 to 15 parents taking part in twice yearly meetings to advise the Principal and Co-Investigators on a variety of topics, for example, how to keep participants engaged and interested in APrON research, priorities for future APrON research, and feedback on laymen research summaries posted to APrON's website. APrON has also extensively disseminated knowledge to the public via various modalities including: multiple presentations to various stakeholders, APrON's Newsletter, website (https://apronstudy.ca/) and conferences. Held via Zoom due to COVID-19 on October 29-30th, 2020, APrON hosted an online conference

titled *Celebrating 10 Years: Alberta Pregnancy Outcomes and Nutrition (APrON) Achievements & Evolution Conference,* that attracted over 300 attendees, many who were APrON participants. The APrON cohort PAC members held their own panel session where they spoke to the attendees about their experiences with APrON, why they think the research is so important and how we can continue for years to come.

Table 1. *Participant Intake Characteristics (N = 3514)*

Category	Maternal (n / %)	Paternal (n / %)
Demographics		
Age (years)		
16 – 24	100 (4.6)	19 (1.4)
25 – 29	481 (22.0)	216 (15.4)
30 -34	980 (44.78)	493 (35.2)
35 -39	512 (23.4)	329 (23.5)
≥ 40	105 (4.8)	162 (11.6)
Missing age information	11 (0.5)	181 (12.9)
Marital status		
Married/common-law	2035 (93.0)	1275 (91.1)
Single/divorced/separated	97 (4.4)	27 (1.9)
Missing marital information	57 (2.6)	98 (7.0)
Education		
Less than a high school diploma	59 (2.7)	31 (2.2)
Completed high school diploma	202 (9.2)	147 (10.5)
Completed trade, technical	404 (18.5)	376 (26.9)
Completed university or more	1442 (66.8)	746 (53.3)
Missing education information	83 (3.7)	100 (7.1)
Ethnicity		
White	1693 (77.3)	1082 (77.3)
Non-white	485 (22.2)	206 (14.7)
Missing ethnic information	11 (0.5)	112 (8.0)
Mothers' Report on total household income		
< $40,000	190 (8.7)	-
$40,000 - $69,999	279 (12.7)	-
$70,000 - $99,9999	464(21.2)	-
>$100,000	1146 (52.3)	-
Missing household income information	110 (5.0)	-
Born in Canada		
Yes	1618 (73.9)	1024 (73.1)
No	481 (22.0)	277 (19.8)
Missing country of birth	90 (4.1)	99 (7.1)
Gravidity		
Multigravida	1107 (51.6)	n/a
Primigravida	996 (46.4)	n/a
Missing gravidity information	42 (2.0)	n/a
Parity		
0	1222 (55.8)	n/a
1	732 (33.4)	n/a
2	181 (8.3)	n/a
≥3	37 (1.7)	n/a
Missing parity information	17 (0.8)	n/a

A greater proportion of women in the cohort (28.0%) were over 34 years old compared with women in Calgary (20.0%), Alberta (16.0%), and Canada (18.0%). More APrON women were married (95%) compared with women in Calgary (73.0%), Alberta (70.0%), and Canada (60.0%). A greater proportion of women had household income of $70,000 or more (77.0%) compared to Calgary (65.0%), Alberta (61.0%), and Canada (58.0%). More APrON women completed post-secondary education (87.0%) compared to women in Calgary (69.0%), Alberta (70.0%), and Canada (72.0%). The proportion of APrON women who were born outside of Canada (23.0%) was similar to the proportions in Calgary (25.0%), Alberta (22%), and Canada (20.0%) (see Figure 1).

How often have APrON families been followed up?

Between 2009 and 2012 the initial cohort completed questionnaires and clinical assessments three times during pregnancy, and at 3 months postpartum. Follow-up questionnaires were provided when their child was 6 months, and 1, 2 3, 5 and 8 years of age (see Figure 2). We plan a 12 year follow-up beginning in 2022.

In total, 2189 women and 1325 men completed at least one questionnaire. Of the women, and their children (88.9%) are continuing participants, defined as those who did not become ineligible or were lost to follow-up. Participants who discontinued the study included women who miscarried, had a stillbirth, lost custody of their child, or for whom a maternal/child death was reported (n = 52, 2.4%); moved out of Calgary or Edmonton before three months postpartum (n = 43, 2.0%); or withdrew from the study citing loss of interest (n = 149; 6.8%). The demographic characteristics of participants who continued in APrON compared with those that discontinued are provided in Table 2.

Table 2. *Comparison of Demographic Characteristics of Continuing and Discontinued Participants*

Characteristic	Continuing participants	Discontinuing participants			*P*-value*
	n (%)	Become ineligible n (%)	Lost to follow-up n (%)	Dropped out n (%)	
Maternal age					
16 – 24	71 (3.6)	8 (18.6)	15 (34.8)	6 (4.1)	< 0.001
25 – 29	424 (16.2)	7 (16.2)	7 (16.2)	43 (29.2)	
30 – 34	899 (46.2)	15 (34.8)	14 (32.5)	51 (34.7)	
35 – 39	454 (23.3)	9 (20.9)	7 (16.2)	41 (27.9)	
≥40	95 (4.8)	4 (9.3)	0 (0.0)	6 (4.1)	
Marital status					
Single	72 (3.8)	12 (24.5)	8 (21.1)	5 (3.8)	0.007
Married	1838 (96.2)	37 (75.5)	30 (78.9)	128 (96.2)	
Maternal education					
Less than a high school diploma	41 (2.2)	6 (16.2)	8 (20.5)	4 (3.01)	<0.001
Completed high school diploma	164 (8.6)	9 (24.3)	9 (23.1)	20 (15.0)	
Completed trade, technical diploma	362 (19.1)	5 (13.5)	10 (25.6)	26 (19.5)	
Completed university or more	1329 (70.1)	17 (45.9)	12 (30.6)	83 (62.4)	
Household income					
< $40,000	151 (8.1)	12 (30.8)	19 (54.3)	8 (6.15)	<0.001
$40,000-$60,000	252 (13.4)	6 (15.4)	5 (14.3)	16 (12.31)	
$70,000-$99,9999	428 (22.8)	7 (17.9)	4 (11.4)	24 (18.46)	
≥ $100,000	1042 (55.6)	14 (35.9)	7 (20.0)	82 (63.08)	
Born in Canada					
No	425 (22.5)	13 (32.5)	14 (37.8)	28 (21.2)	0.186
Yes	1463 (77.5)	27 (67.5)	23 (62.2)	104 (78.8)	

Note. Assessing the null hypothesis that there is no difference in distributions between those participants who continued and those who did not continue in the study; chi-square test

Continuing participants were more likely to be older, married, and to have higher education and household incomes (all *p*s < 0.05). The proportion of continuing participants born in Canada was similar to discontinuing participants. When mothers were lost to follow-up, so too were fathers and children.

What has the APrON study measured?

Women were asked to complete questionnaires three times during pregnancy (<14, 14-26, and 27-40 weeks gestation, number of scales administered was 37) and seven times postnatally (3 and 6 months, 1, 2, 3, 5, and 8 years, number of scales administered was 77). Partners (usually self-reported fathers) were asked to complete questionnaires when their partners were 14-26 weeks gestational age (number of scales administered was 16), and twice postnatally (3 months and 5 years, number of scales administered was 14). Questionnaires administered during pregnancy measured previous and current mental and physical health status, nutritional, medication and supplement intake, lifestyle choices, healthcare services used, social support, attitudes towards breastfeeding, and sociodemographic variables. The follow-up postpartum questionnaires collected information about labor and delivery, postpartum medical problems, maternal and paternal mental health and stress, nutritional, medication and supplement intake, lifestyle choices, food security, parenting, experiences in close relationships, and sociodemographics (see Figure 2). Measures were selected based on several synergistic priorities. First, the APrON team had to judge measures to be reliable and valid indicators of the constructs of interest. Second, measures had to minimize burden to participants in terms of time and difficulty of completion, for example measures with fewer items and more accessible language were valued most. Finally, an APrON team member had to express an interest in using the measure. Full details and documentation of all APrON measures is available on request.

Clinic visits were undertaken to gather maternal anthropometric measurements during pregnancy and three months postpartum. These measures included height, pre-pregnancy and current weight, highest weight during pregnancy, circumference measurements (i.e., mid-upper arm, waist, hip, thigh), and skinfold thickness (i.e., biceps, triceps, subscapular, suprailiac, thigh). Each measurement was taken three times and averages were reported for analyses. Paternal height and weight were collected during the prenatal period. One objective of APrON was to

establish a biobank for future research that would allow investigation on genetics, epigenetics [1], nutrient exposures and neurotoxicants. Thus, biosamples were also collected from mothers, their partners and from infants during clinic visits. Midstream random urine samples (10 mL) were collected from expectant mothers at 14-26 weeks gestation and three months postpartum. A breast milk sample was collected from breastfeeding mothers to determine fatty acid composition. Maternal non-fasting venous blood samples were collected from mothers at <14, 14-26, and 27-40 weeks gestation, and at three months postpartum. Maternal blood collection provided whole blood, plasma, and serum, which were used for DNA, RNA, cytokines, hematocrit, hemoglobin measures, thyroid hormones and measures of heavy metals (e.g., mercury, lead) and perfluorinated chemical exposure. Buccal cell samples were also collected at 14-26 weeks gestation from partners for DNA extraction and future genetic and epigenetic studies. From infants, buccal and/or blood samples were collected at 3 months of age for DNA extraction. Purified DNA is available at the Gene Expression Omnibus data repository (https://www.ncbi.nlm.nih.gov/geo/). A detailed list of data collected up to 8 years of age on the full sample is provided in Table 3.1 for mothers, Table 3.2 for fathers and Table 3.3 for children.

Table 3.1. *Maternal Variables and Biological Samples Collected via Questionnaires and Clinic Visits*

Variables	<14 weeks	14-26 weeks	27-40 weeks	3 months postpartum	6 months postpartum	1 year	2 years	3 years	5 years	8 years
Socio-demographics										
Household income	X								X	X
Education	X									
Marital status	X								X	X
Age	X									
Primary language	X									
Born in Canada	X									
Family background		X	X	X	X	X	X	X	X	X
Family history		X								
Health and lifestyle										
General health				SF-8	SF-8	SF-8	SF-8	SF-8		
Current medical conditions and medications	X	X	X	X	X	X	X	X		
Substance use	X	X	X	X	X	X	X	X	X	
Parenting									X	X
Pregnancy history										
Pre-pregnancy physical activity	X	X	X	X	X	X	X	X		
Physical activity	GLTE	GLTE	GLTE	GLTE	GLTE	GLTE	GLTE	GLTE	GLTE	
Dental care	X	X	X							
Dietary changes since pregnancy	X									
Food security			CCHSC		CCHSC					
Nutrition counselling information				X						
Diet history pre-pregnancy		FFQ								
Nausea and vomiting	PUQUE	PUQUE	PUQUE							
Breastfeeding information				X	X	X	X	X		
24-hour recall of foods consumed	X	X	X	X	X	X	X	X		

Psychosocial health										
Depression Stress	EDS SLEQ	EDS	EDS SLEQ	EDS SLEQ	EDS	EDS SLEQ	EDS SLEQ	EDS SLEQ PSS	CESD SLEQ, PSS	CESD SLEQ,
Social support	SSQ	SSQ	SSQ	SSQ	SSQ	SSQ	SSQ	SSQ	SSQ,	SSI,
Attachment									SSI, ECR	ECR
DSM-IV Axis I disorders		PDSQ		PDSQ						
Anxiety	SCL-90-R	SCL-90-R	SCL-90-R	SCL-90-R	SCL-90-R	SCL-90-R	SCL-90-R	SCL-90-R	SCL-90-R	STAI
Adverse childhood events							X			
History of mental health	X	X	X	X		X	X	X		
Anthropometrics (BMI/height/weight)	X	X	X							
Personality traits										
Personality traits										TIPI
Biological specimens										
Urine	X	X	X	X						
Venous blood		X		X						
Breast milk				X						

Note. X refers to investigator-developed measures. SCL-90-R, Symptom Checklist-90-Revised; EDS, Edinburgh Depression Scale; PUQE, Pregnancy-Unique Quantification of Emesis and Nausea questionnaire; SLEQ, Stressful Life Events Questionnaire ; SSQ, Social Support Questionnaire; PDSQ, Psychiatric Diagnostic Screening Questionnaire; ACEs, Adverse Childhood Experiences Questionnaire; SF-8, Short Form Health Survey-8; CCHSC, Canadian Community Health Survey Cycle 2.2, modified; GLTE, Godin Leisure-Time Exercise Questionnaire; FFQ, Food Frequency Questionnaire, adapted from the Canadian version of the Diet History Questionnaire; SSI, Social Support Index; ECR, Experiences in Close Relationship Scale; PSS, Perceived Stress, CES-D, Centre for Epidemiologic Studies Depression Scale; OECD, Organization for Economic Cooperation and Development Guidelines on Measuring Subjective Wellbeing; STAI, State-Trait Anxiety Inventory; TIPI, Ten-Item Personality Inventory. *Breastfeeding mothers only.

Table 3.2. *Paternal Variables and Biological Specimens Collected via Questionnaires and Clinic Visits*

Variables	<14 weeks gestation	14-26 weeks	27-40 weeks	3 months postpartum	5 years postpartum
Socio-demographics					
Household income			X		
Education			X		
Marital status			X		
Age			X		
Primary language			X		
Born in Canada			X		
Family background			X		X
Family history*			X		
Health and lifestyle		X	X		
General health					
Current medical conditions and medications		X	X	X	
Substance use		X	X	X	X
Physical Activity Anthropometrics		GLTE	GLTE	GLTE	GLTE
(BMI/height/weight)		X	X	X	
Psychosocial health					
Depression		EDS	EDS	EDS	EDS
Social support		SSQ	SSQ	SSQ	SSQ
Stress			SLEQ		SLEQ
Anxiety					SCL-90-R
Biological specimens*					
Buccal cell swab			X		
DNA from blood			X		

Note. X refers to investigator-developed measures. EDS, Edinburgh Depression Scale; SLEQ, Stressful Life Events Questionnaire; SSQ, Social Support Questionnaire; GLTE, Godin Leisure-Time Exercise Questionnaire.

Table 3.3. *Child Variables and Biological Specimens Collected in Questionnaires and Clinic Visits*

Variables	3 months	6 months	1 year	2 years	3 years	5 years	8 years
Health and Development		X	X	X	X	X	X
Occupation	X	X	X	X	X	X	
Childcare	X	X	X	X	X	X	
Vaccines						X	
Child food and liquid intake	X	X	X	X	X	X	
Children's eating and drinking behaviours						X	X
Children's activities						X	X
Children's injuries						X	
Community							X
Children's education							X
General infant behaviours							
Infant Behavior Questionnaire (IBQ)	X	X	X	X			
Scales of Independent Behaviors (SIB-R)	X	X	X	X	X	X	
Fussing and Crying	X	X	X	X			
Sleeping		X	X	X	X	X	X
Early Childhood Behavior Questionnaire (ECBQ)				X			
Children's Behavior Questionnaire (CBQ)					X		
Child Behaviour Checklist Ages 1.5 – 5 (CBCL)				X	X		
Behaviour Rating Inventory of Executive Function-Preschool (BRIEF-P)				X	X		
Ages and Stages Questionnaire – Third Edition (ASQ-3)						X	
Children's Communication Checklist – Second Edition (CCC-Q)						X	
Behaviour Assessment System for Children – Second Edition (BASC-2)						X	X
Media use						X	X
Quantitative Checklist for Autism in Toddlers				X	X		
Temper Tantrum Scale – Past 2 Weeks				X	X		
Temper Tantrum Scale – Past 6 Months				X	X		
Parenting						X	X
Biological specimens							
Buccal cells	X						
Venous blood	X						

Numerous sub-studies, employing portions of the APrON sample have employed the originally collected biosamples in related research, for example the Neurotoxicant Study (n=546) that examined maternal exposure to endocrine hormone disrupting chemicals (i.e. bisphenol a and phthalates) on child outcomes [e.g., 10, 11-15] and the Parenting Research on Mental Illness, Stress and Epi/genetics (PROMISE; n=276) Study of gene by environment interactions [e.g., 16, 17-20]. Other sub-studies have collected additional biosamples for related research, for example maternal and infant cortisol and other measures such heart rate variability and parent-child interaction quality observations in the Fetal Programming Study [n=276; e.g., 21, 22-29].

What has APrON found?

A complete list of publications from APrON can be found at http://www.apronstudy.ca/research/publications-and-press. Key findings from the full sample on maternal and paternal mental health, maternal nutrition and child outcomes have been summarized in Box 1 and below.

Box 1 Key findings

Mental health outcomes

Mental health outcomes

- In partnered couples, both mothers and fathers had depressive symptoms in 2.3% of couples. Low household income and prenatal maternal depression were associated with a higher probability of depressive symptoms in both partners. In 78.5% of couples, neither father nor mother experienced depressive symptoms. Postnatal social support was found to be a protective factor associated with decreased risk of maternal and paternal postpartum depressive symptoms. Risk factors for maternal postpartum depression symptoms included low household income, and prenatal EDS score ≥10. For paternal postpartum depression symptoms, risk factors included low household income, prenatal EDS score of <10, postpartum stressful life events, and smoking.
- Women with EDS scores <10 were more likely to take micronutrients (e.g., vitamins B6, B9, B12, and E; essential fatty acids; selenium); however only selenium and omega-3 were significantly different between depressed and non-depressed groups, with non-depressed mothers consuming higher amounts.
- 14% of mothers had a score of three or more adverse childhood experiences. Maternal exposure to early adversities predicted higher reported symptoms of perinatal depression and anxiety.

Nutrition outcomes

- Approximately 70% of women who entered pregnancy with a body mass index (BMI) > 25 kg/m^2 were likely to exceed gestational weight gain guidelines in the beginning of the second trimester. Women with excessive weight gain also gained higher amounts of body fat and retained higher amounts of fat compared to women who gained

within the guidelines. Women who consumed a healthy diet pattern prior to pregnancy were less likely to develop complications such as gestational hypertension.

- The median vitamin D intake from diet and supplements was 600 IU/day during pregnancy, which was not enough to achieve a target plasma circulation 25(OH)D concentration. A significant relationship between maternal reported dietary vitamin D intake and plasma 25(OH)D and 3-epi-25(OH)D3 concentration were identified.
- Only 23% of mothers met the adequate intake (AI) recommendations for choline; the number was even lower (10%) in the postpartum period. Consuming eggs and milk during pregnancy increased mothers' likelihood of meeting choline AI recommendations.

Child Outcomes

- Infants with higher birth weights and at 3 months of age had mothers with a higher pre-pregnancy BMI. Gestational weight gain above recommendations was associated with higher infant weight at birth and three months of age as well as more rapid postnatal growth.
- Infants' vitamin D status increases in direct proportion to mothers' vitamin D intake. Given many mothers are below recommended AI for vitamin D, both infants and breastfeeding mothers require vitamin D supplementation.
- Maternal experience of early adversity associates with maternal symptoms of anxiety and depression during the perinatal period as well as externalizing behavioral problems in their 2-year old children. Boys demonstrate greater vulnerability to the indirect effects of maternal adversity via both depression and anxiety.
- Both mothers' perinatal depressive symptoms and mothers' and fathers' co-occurring perinatal depressive symptoms predicted more problematic emotionally reactive, withdrawn, and total internalizing behaviors in their 2- to 3-year old children. Children's aggression, attention problems and total externalizing behaviors were only predicted by mothers' perinatal depressive symptoms.

Mental health outcomes

Drawn from the full APrON cohort, three key papers [30-32] reported on perinatal depression and anxiety symptom prevalence and risk factors and the impact of adverse childhood experiences on maternal prenatal depression and anxiety. Many more papers report on parental mental health in sub-studies, see APrONstudy.ca for details.

Predictors of Depression

Maternal prenatal depression is known to have negative impacts on pregnancy, maternal postnatal mental health and neonatal outcomes [33, 34], and psychosocial predictors of maternal postpartum depression are well known [35, 36]. However, less well known is whether mothers and fathers in partnered, cohabitating couples (e.g. married, common-law) share common predictors and experiences of depressive symptoms in the perinatal period. Further, whether maternal prenatal nutrition impacts postpartum depressive symptoms is less well studied. Thus,

using APrON data, Leung and colleagues [32] reported on the prevalence of depressive symptoms in couples. For partnered mothers' depressive symptoms, using the recommended Edinburgh Depression Scale (EDS) cut-off score of ≥ 10 [37], findings revealed that 15.2% and 11.18% of mothers had significant symptoms prenatally and at 3 months postpartum, respectively. For fathers in couples, the cut-off of EDS ≥ 9 was used as per recommendations [38] revealing that 14.0% and 12.1% of fathers had significant symptoms prenatally and at 3 months postpartum, respectively. These rates are consistent with other large samples [39, 40]. Further, 2.3% of couples experienced perinatal depressive symptoms in both mothers and fathers, 78.5% of couples did not experience depressive symptoms in either partner, 9.5% of couples experienced depressive symptoms in mothers only, and 9.8% of couples experienced depressive symptoms in fathers only. Leung and colleagues [30] also determined the predictors of depression at 3 months postpartum from second trimester data. Risk factors for maternal postpartum depressive symptoms included low household income, high prenatal depressive symptoms, low postnatal support from fathers, and high stressful life events. Risk factors for paternal postpartum depressive symptoms included low household income, prenatal depressive symptoms, postpartum stressful life events, and smoking. For couples in which both partners were depressed, risk factors included low income, high maternal depressive symptoms and low prenatal social support from fathers. Postpartum social support was found to be a protective factor associated with decreased risk of maternal and paternal postpartum depressive symptoms.

Additionally, Leung and colleagues [30] also examined nutritional predictors of maternal postpartum depression, focusing on APrON mothers' reports of their multivitamin and mineral intake in each trimester of pregnancy. Almost all women (99%) took some type of micronutrient supplement during the prenatal period, with the most commonly consumed being vitamins B6, B9 (folate), B12, and E, with more than 90% of mothers consuming above recommended dietary

allowances. With respect to predictors of postpartum depression, findings revealed that mothers who experienced postpartum depressive symptoms (EDS≥ 10) were statistically more likely to take the supplemental micronutrients selenium and omega-3, compared to mothers who reported no postpartum depressive symptoms (EDS<10). Selenium intake above the recommended dietary allowance appeared to be protective, and other research suggests that this micronutrient has a role in normal brain function and in the pathway between dopamine and the pathophysiology of depression [41]. The supplement taken the least was omega-3; however, 68.5% of women with low depressive symptoms (EDS<10) did not take omega-3, versus 78.0% of women with high depressive symptoms (EDS≥10), a finding consistent with other research [42]. The mean intakes of other nutrients were more likely to be higher in women with low depressive symptoms than those with high symptoms, although not statistically significant. The authors conclude with a call for more study into the value of selenium and omega-3 in the prevention of postpartum depression.

Associations with adverse childhood experiences

Adverse childhood experiences are defined as a set of exposures to personal abuse, neglect and household dysfunction prior 18 years of age that includes physical, sexual, and emotional abuse, domestic violence, and parental mental illness, substance use, and incarceration [43]. A graded relationship has been repeatedly observed between the number of adversities experienced in childhood and later increased risk for poor health, including depression [44, 45]; however whether such adversities affect perinatal mood more broadly including anxiety was less studied. Felitti and colleagues' [43] classic measure of adverse childhood experiences was administered to APrON mothers, revealing that while 55% reported none or one early adversity, 31% reported one or two adversities and nearly 14% reported three or more adverse childhood experiences. Employing data from each trimester of pregnancy and 3, 6 and 12 months

postpartum, more reported early adversities predicted higher reported symptoms of prenatal and postnatal depression and anxiety [31]. Routine screening for maternal childhood adversities may facilitate early identification and preventative interventions for perinatal mood disorders including depression and anxiety; however, this has been recently debated [46]. In sum, the identified risks and protective factors provide opportunities for prevention of perinatal depression and anxiety in mothers and fathers.

Nutrition outcomes

Gestational weight gain and dietary intake, especially perinatal nutrient intake and status focused on vitamin D and choline were examined in eight key papers [47-54].

Gestational weight gain and dietary intake

Gestational weight gain over or below Health Canada's Gestational Weight Gain Guidelines is associated with an increased risk of adverse outcomes for mother and infant [55]. The APrON cohort was the first to provide evidence that more than half of women gain more than Health Canada's Guidelines, using prospectively collected body weights from across pregnancy [47]. Since then, several studies have been completed with body weight or body composition in pregnancy or postpartum as a main outcome. Analysis of the APrON data by Jarman and colleagues [48] provided a clear picture indicating that approximately 70% of women who become pregnant with a body mass index (BMI) > 25 kg/m^2 are likely to exceed gestational weight gain guidelines, by about 19 weeks gestation. Women with excessive weight gain also gain higher amounts of body fat and retain higher amounts of fat compared to women who gain within the guidelines [49]. The detailed dietary intake information that was collected showed that women who consumed a healthy diet pattern prior to pregnancy were less likely to develop complications such as gestational hypertension [50]. An individualized approach to supportive dietary counseling that considers pre-pregnancy BMI in addition to the woman's social and

financial context may be key to helping women meet national recommendations for both diet and gestational weigh gain in pregnancy [56].

Nutrient intake and status

Vitamin D is critical for a healthy pregnancy and the major circulating form of vitamin D is 25-hydroxyvitamin D (25(OH)D); thus, the total serum 25(OH)D level is currently considered the best indicator of vitamin D supply [57]. Three studies that included APrON participants examined the role of maternal vitamin D intake during pregnancy [51-53]. Aghajafari and colleagues [52] reported that the median vitamin D intake from diet and supplements was 600 International Units (IU)/day during pregnancy, which was not sufficient to achieve a target circulation of 25(OH)D) concentration. When the 3-epimer (3-epi-25(OH)D3) was included in the estimation of vitamin D status, the prevalence of vitamin D insufficiency (<75 nmol/L) was lower (33.0 %) compared to when it was excluded (38.0 %). Vitamin D supplementation (2000 IU/day) was associated with 25(OH)D3 sufficiency [51-53]. A significant relationship between maternal reported dietary vitamin D intake and plasma 25(OH)D and 3-epi-25(OH)D3 concentration were identified.

Choline intake during pregnancy and lactation is critical to the offspring's brain function [58]. Lewis and colleagues [54] reported that the mean choline intake in pregnant and lactating women ranged between 340 (SD 148) in the second trimester and 346 (SD 151) mg/day at 3 months postpartum. Only 23% of mothers met the adequate intake (AI) recommendations for choline; the number was even lower (10%) in the postpartum period [54]. Consuming eggs and milk during pregnancy increased mothers' likelihood of meeting choline AI recommendations. These findings contributed to the European Food Safety Authority (EFSA) dietary reference values for choline guidelines [59]. To conclude, a significant number of women were not meeting recommendations for vitamin D and choline intake during pregnancy and postpartum. Increased

consumption of these nutrients may be necessary for pregnant and lactating women to improve the health and development of their infants.

Child outcomes

The impacts of maternal and infant nutrient intake, maternal BMI and gestational weight gain, and perinatal depression and maternal adverse childhood experiences on child outcomes were examined in four key papers [31, 60-62]. Many more papers will emerge as the cohort matures and data become available.

Maternal BMI, gestational weight gain and vitamin D

Subhan and colleagues [60] described the effects of maternal pre-pregnancy BMI and gestational weight gain on infant anthropometrics at birth and three months and infant growth rates between birth and three months. Other research shows that children who are heavier at birth have an increased risk of high BMI in childhood, being overweight or obese as adults [63, 64], a condition linked increased risk for hypertension, type 2 diabetes and cardiovascular diseases [63, 65]. APrON findings revealed that infants with higher weight at birth and at 3 months of age had mothers with a higher pre-pregnancy BMI. Also gestational weight gain above recommendations was associated with higher infant weight at birth and three months of age as well as more rapid postnatal growth. The authors concluded that clinicians and health care professionals should encourage women to enter pregnancy with a healthy BMI and adhere to the current gestational weight gain recommendations. Aghajafari and colleagues [61] examined the association between APrON mothers' vitamin D intake during breastfeeding with their infants' vitamin D status to determine whether infant supplementation was sufficient. Other research reveals that low vitamin D is associated with increased rates of infections, autoimmunity and allergies [66] and poor bone health in children [67]. Using plasma from a subset of breastfed infants, vitamin D status was measured by liquid chromatography-tandem mass spectrometry and maternal and infants' dietary

data were attained from dietary questionnaires. Controlling for race, season, prenatal maternal vitamin D status, infant birth weight, and daily infant vitamin D supplementation, infants vitamin D status increased in direct proportion to mothers' vitamin D intake. Moreover, a quarter of mothers were below recommended AI for vitamin D. The authors concluded that to ensure optimal infant vitamin D status, both infants and breastfeeding mothers require vitamin D supplementation.

Perinatal depression and adverse childhood experiences

Two studies addressed impacts of perinatal depression and adverse childhood experiences on children's behaviour. It is well established that children's internalizing behavioural problems (e.g. emotional reactivity, anxiety, depression, somatic complaints, and social withdrawal) and externalizing behavioral problems (i.e. inattention, hyperactivity and aggression) predict adult mental health problems [68-70]. As indicated above, adverse childhood experiences increased risk for poor health over the lifespan [71-73]; however intergenerational impacts have also been noted [74, 75] with an incomplete understanding of the mechanism of transmission form one generation to the next [31]. In examining intergenerational impacts, Letourneau and colleagues [31] found that APrON mothers' experiences of early adversity were associated with maternal symptoms of anxiety and depression during the perinatal period (discussed earlier) as well as externalizing behavioral problems in their 2-year old children. Indirect associations were observed between maternal adverse childhood experiences and children's internalizing and externalizing problems via maternal anxiety and depression. Sex differences were also observed with boys demonstrating greater vulnerability to the indirect effects of maternal adversity via both depression and anxiety. The authors concluded that interventions may be targeted to women who have multiple adverse childhood experiences as well as mental health problems to prevent behavioral problems in their children. Letourneau and colleagues [62] further examined perinatal

depression in mothers, as well as fathers or both parents and how symptoms in one or both parents predict children's behavioral problems. Other research has shown that fathers may buffer the impacts of maternal depression on children's outcomes and thus this protective factor is likely undermined when fathers are depressed as well as mothers [34, 76]. Mothers' and fathers' depressive symptoms were measured during pregnancy and three months postpartum, and children's behavior was measured at 24 and 36 months of age. Results revealed that both mothers' perinatal depressive symptoms and mothers' and fathers' co-occurring perinatal depressive symptoms predicted more problematic emotionally reactive, withdrawn, and total internalizing behaviors. In contrast, children's aggression, attention problems and toral externalizing behaviors were only predicted by mothers' perinatal depressive symptoms. The authors urge health care providers to consider the whole family, including fathers, when treating maternal symptoms of depression, aligned with review recommendations to also consider fathers [34, 77].

What are the main strengths and weaknesses?

The major strengths of APrON are recruitment and retention of the large community-based cohort during pregnancy, postpartum and early childhood. The APrON study used a detailed array of standardized validated psychological and physiological measures and biospecimens. The prospective data collection and follow-up enabled investigation of a wide range of maternal and paternal health outcomes. The APrON team has been successful in continuously engaging participants, as evidenced by high response rates over the years (see Table 4).

Table 4. *Response Rates for Questionnaires*

Data collection time point	Targeted participants (n)	Participants responded (n)	Response rate (%)
	2189	2145	97.9

Mothers < 14 weeks gestation Mothers at 14-26 weeks gestation			
Mothers at 14-26 weeks gestation and those recruited at < 14 weeks gestation	563	475	84.3
Fathers at 14-26 weeks gestation	1325	1315	99.2
Mothers at 27-40 weeks gestation	1838	1830	99.5
Mothers at 3 months postpartum	2051	1811	88.3
Fathers at 3 months postpartum	1287	1150	89.3
Mothers at 6 months postpartum	1727	1523	88.1
Mothers at 1 year postpartum	1747	1305	74.7
Mothers at 2 years postpartum	1809	1299	71.8
Mothers at 3 years postpartum	1648	1282	77.7

The high response rates over time may be due to the recruitment of a relatively low-risk sample as sociodemographic characteristics are skewed toward a high percentage of well-educated, higher income, married participants. Consequently, generalizability of findings to those with different sociodemographic backgrounds should be made with caution. Further, the study likely included participants with healthier lifestyle behaviors or with more positive attitudes towards research, because such characteristics are associated with higher socioeconomic status [78]. Selective attrition bias is likely operating in the cohort, which may lead to underestimation of the effect of parental mental health and lifestyle choices on children's development. While

attrition has been relatively low over time, differences in the sociodemographic characteristics of the continuing participants compared with discontinuing participants should be considered when interpreting the findings. There were also fewer fathers than mothers in the sample; thus, most developmental and behavioral outcomes are based on maternal reports.

Where can I find out more about APrON research?

Information about the APrON study is available at www.apronstudy.ca. APrON data are available through SAGE (Secondary Evidence to Generate Evidence; https://policywise.com/sage/). For more information contact Dr. Nicole Letourneau at Nicole.letourneau@ucalgary.ca. Collaboration or data access inquiries will be considered by the APrON Study team.

Profile in a nutshell

- The APrON study is a longitudinal cohort of mothers, fathers and their children investigating maternal, parental, birth, and child development outcomes.
- A total of 2189 women (aged 16 to 44) and 1325 fathers (aged 18 to 52), residing around either Calgary or Edmonton, Alberta, enrolled and completed at least one questionnaire between May 2009 and June 2012. The majority were married, educated, had annual household incomes >$70 000 and were born in Canada.
- Mothers completed 18 questionnaires and up to 4 clinic visits spanning pregnancy to eight years postpartum and provided access to their medical records as well as three to four blood and two urine samples. To date, 1648 mothers and 1255 fathers remain eligible for follow-up.
- The APrON dataset includes comprehensive maternal and child sociodemographic data, maternal nutrition and psychological data from pregnancy to eight years postpartum, and infant and child neurodevelopmental and behavioural data to eight years of age. Maternal, paternal and infant biosamples for genetics were also collected. Five and 8-year data collection is complete and 12-year data follow-up will start in 2022.

Requests for data and collaboration are welcomed, contact Dr. Nicole Letourneau at nicole.letourneau@ucalgary.ca

Figure Legends

- *Figure 1.* Socio-demographic characteristics of women in APrON, Calgary, Alberta, Canada.
- *Figure 2.* Data collection to 8 years of child age

Contributorship Statement

Nicole Letourneau (NL) conceived of the idea for the paper, oversees all aspects of the APrON cohort, including the collection, cleaning and analysis of data for reviewed studies, and wrote major sections of the paper, approved the final version of the paper to be published, and agreed to be accountable for all aspects of the work.

Elena Ali (EA) wrote the initial draft of the paper with support from NL, GG, FA, RB, and DD, approved of the final version of the paper to be published, and agreed to be accountable for all aspects of the work.

Fariba Aghajafari (FA) contributed to the collection, cleaning and analysis of data for reviewed studies, critically reviewed the drafts, approved the final version of the paper to be published, and agreed to be accountable for all aspects of the work.

Rhonda Bell (RB) wrote a key section of the paper, contributed to the collection, cleaning and analysis of data for reviewed studies, critically reviewed the drafts, approved the final version of the paper to be published and agreed to be accountable for all aspects of the work.

Andrea J. Deane (AJD) contributed to the collection, cleaning and analysis of data for reviewed studies, critically reviewed the drafts, approved of the final version of the paper to be published, and agreed to be accountable for all aspects of the work.

Deborah Dewey (DD) contributed to the collection, cleaning and analysis of data for reviewed studies, critically reviewed the drafts, approved the final version of the paper to be published, and agreed to be accountable for all aspects of the work.

Catherine Field (CF) contributed to the collection, cleaning and analysis of data for reviewed studies, critically reviewed the drafts, approved the final version of the paper to be published, and agreed to be accountable for all aspects of the work.

Gerald Giesbrecht (GG) contributed to the collection, cleaning and analysis of data for reviewed studies, critically reviewed the drafts, approved the final version of the paper to be published, and agreed to be accountable for all aspects of the work.

Bonnie Kaplan (BK) contributed to the collection, cleaning and analysis of data for reviewed studies, critically reviewed the drafts, approved the final version of the paper to be published, and agreed to be accountable for all aspects of the work.

Brenda Leung (BL) contributed to the collection, cleaning and analysis of data for reviewed studies, critically reviewed the drafts, approved the final version of the paper to be published, and agreed to be accountable for all aspects of the work.

Henry Ntanda (HN) contributed to the cleaning and analysis of data for reviewed studies, critically reviewed the drafts, approved the final version of the paper to be published, and agreed to be accountable for all aspects of the work.

APrON Study Cohort Participants volunteered time and energy to share their individual and family's experiences with us to help improve the long-term health outcomes for future newborns, mother, fathers, and families.

Competing Interest

None declared.

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Data Sharing Statement

Data may be obtained from a third party and are not publicly available and data are available upon reasonable request. Accordingly, data can be collected at the Secondary Analysis to General Evidence (SAGE) data repository or by contacting Dr. Nicole Letourneau (the principal investigator for the APrON study).

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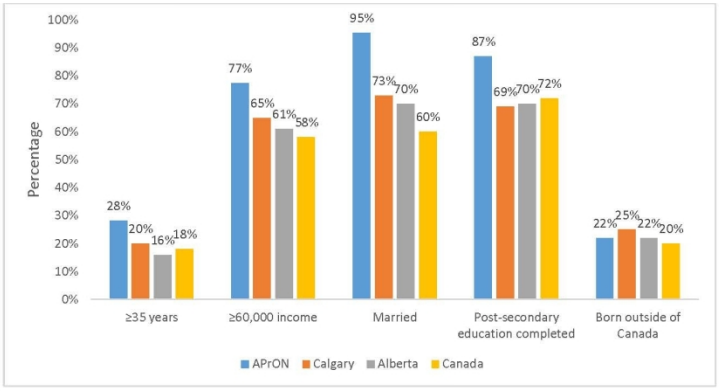

Figure 1. Sociodemographic characteristics of women in APrON, Calgary, Alberta, and Canada.

Sociodemographic characteristics of women in APrON, Calgary, Alberta, and Canada

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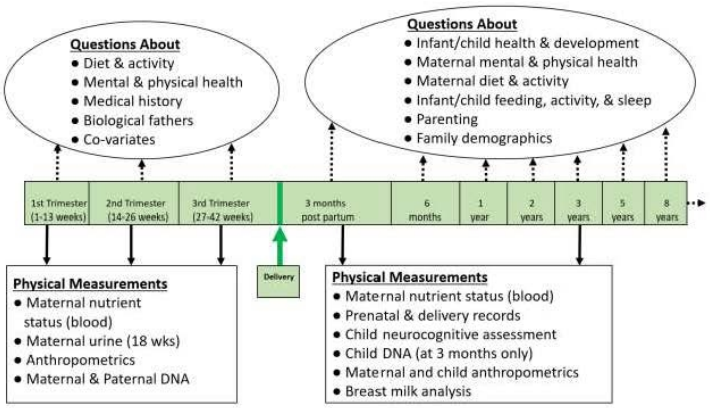

Figure 2. Data collection to 8 years of child age

Data collection to 8 years of child age

215x279mm (96 x 96 DPI)