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Ethnic Variations in Consumption of a Plant-Based diet in Pregnancy on Birthweight

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Complete List of Authors:	Zulyniak, Michael; McMaster University, Department of Medicine; University Of Leeds, School of Food Science and Nutrition de Souza, Russell; McMaster University, Department of Health Research Methods, Evidence, and Impact Shaikh, Mateen; McMaster University, Department of Health Research Methods, Evidence, and Impact Desai, Dipika; McMaster University, Department of Medicine Lefebvre, Diana; McMaster University, Department of Medicine Gupta, M; McMaster University, Department of Medicine; Canadian Cardiovascular Research Network Wilson, Julie; Six Nations Health Services Wahi, Gita; McMaster University, Department of Health Research Methods, Evidence, and Impact; McMaster University, Department of Paedeatrics Subbarao, Padmaja; University of Toronto, Department of Paediatrics; Hospital for Sick Children Becker, Allan; University of Manitoba, Department of Immunology Mandhane, Piush; University of Alberta, Department of Pediatrics Turvey, Stuart; University of British Columbia, Department of Paediatrics Beyene, Joseph; McMaster University, Department of Health Research Methods, Evidence, and Impact Atkinson, S; McMaster University, Department of Paediatrics Morrison, Katherine; McMaster University, Department of Pediatrics McDonald, Sarah; McMaster University, Obstetrics/Gynecology Teo, Koon; Population Health Research Institute; McMaster University, Department of Medicine Sears, Malcolm; McMaster University, Department of Medicine Anand, Sonia; McMaster University, Department of Medicine; McMaster University, Department of Health Research Methods, Evidence, and Impact
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Title: Ethnic Variations in Consumption of a Plant-Based diet in Pregnancy on Birthweight

Corresponding Author: Dr. Sonia S. Anand, McMaster University, 1280 Main St. W., MDCL-3204, Hamilton, ON L8S 4K1, Email: anands@mcmaster.ca, Ph. 905.525.9140 x 21523

Authors: Michael A. Zulyniak[1,2]*; Russell J. de Souza[3]*; Mateen Shaikh[3]; Dipika Desai[1,4]; Diana L. Lefebvre[1]; Milan Gupta[1,5]; Julie Wilson[6]; Gita Wahi[3,7]; Padmaja Subbarao[8]; Allan B. Becker[9]; Piush Mandhane[10]; Stuart E. Turvey[11]; Joseph Beyene[3]; Stephanie Atkinson[7]; Katherine Morrison[7]; Sarah McDonald[3]; Koon K. Teo[1,4]; Malcolm R. Sears[1]; Sonia S. Anand[1,3,4] for the *NutriGen* Alliance investigators

Author Affiliations:

[1] Department of Medicine, McMaster University, Hamilton, ON, Canada;

[2] School of Food Science and Nutrition, University of Leeds, Leeds, UK;

[3]Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, ON, Canada;

[4]Population Health Research Institute, Hamilton Health Sciences and McMaster University, Hamilton, ON, Canada;

[5]Canadian Cardiovascular Research Network, Brampton, ON, Canada;

[6]Six Nations Health Services, Ohsweken, ON, Canada;

[7]Department of Paediatrics, McMaster University, Hamilton, ON, Canada;

[8]Hospital for Sick Children & Department of Paediatrics, University of Toronto, Toronto, ON, Canada;

[9]Department of Immunology, Faculty of Medicine, University of Manitoba, Winnipeg, MB, Canada;

[10]Department of Pediatrics, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, AB, Canada;

[11]BC Children's Hospital, Department of Paediatrics, Faculty of Medicine, University of British Columbia, Vancouver, BC, Canada.

*authors contributed equally

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ABSTRACT

OBJECTIVE. Birthweight is an indicator of newborn health and a strong predictor of health outcomes in later life. Significant variation in diet during pregnancy between ethnic groups in high-income countries provides an ideal opportunity to investigate the influence of maternal diet on birthweight.

SETTING. Four multi-ethnic birth cohorts based in Canada (The NutriGen Alliance).

PARTICIPANTS. 3,997 full-term mother-infant pairs of diverse ethnic groups with principal component analysis (PCA)-derived diet pattern — plant-based, Western, health-conscious — and birthweight data.

RESULTS. No associations were identified between the Western and health-conscious diet patterns and birthweight; however, the plant-based dietary pattern was inversely associated with birthweight (β=-67.6g per 1-unit increase; P<0.001) and an interaction with non-white ethnicity and birthweight was present. Ethnically stratified analyses demonstrated that among white Caucasians, maternal consumption of a plant-based diet associated with lower birthweight (β=-65.9g per 1-unit increase; P<0.001), increased risk of small for gestational age (SGA; OR=1.46; 95%CI:1.08-1.54;P=0.005), and reduced risk of large for gestational age (LGA;OR=0.71; 95%CI:0.53-0.95;P=0.02). Among South Asians, maternal consumption of a plant-based diet associated with a higher birthweight (β=+40.5g per 1-unit increase; P=0.01), partially driven by cooked vegetable consumption.

CONCLUSIONS. Maternal adherence to a plant-based diet during pregnancy is associated with birthweight. Among white Caucasians, a plant-based diet is associated with lower birthweight, reduced odds of an infant born LGA, and increased odds of SGA, whereas among South Asians living in Canada, a plant-based diet is associated with increased birthweight.

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'Strengths and limitations of this study'

1. Strengths - Prospective data collection, large sample size, adequate power to allow for ethnic comparisons, and detailed measurement of diet using ethnic-specific FFQs;
2. Limitations - Self-reported retrospective food intake, the inability to adjust for differences in cooking methods, and residual confounding which is a potential bias in all cohort studies;
3. Strength - To minimize potential bias, a sensitivity analysis was conducted, which excluded mothers who may have deliberately altered their diet due to a medical condition.

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INTRODUCTION

Birthweight is an indicator of infant health and a strong predictor of future health outcomes.[1] Infants born small (birthweight<10th%ile) or large (birthweight>90th%ile) for gestational age are at increased risk of future health complications, including asthma,[2] obesity,[3] and cardiovascular disease (CVD).[4] High-income countries generally have similar proportions of babies who weigh <2500g at birth but there is greater variation (up to 10%) in the proportion of infants born >4000g.[5-7] However, such population figures often mask important differences in the distribution of birthweight between ethnic groups. In the United States, white Caucasians have more high- (9.6%) than low-birthweight infants (7.0%); African Americans have more low- (13.1%) than high-birthweight infants (4.3%); and Hispanics have an equal proportion (7.1% high- and 7.1% low-birthweight).[5] Furthermore, we recently reported that newborns in Canada of South Asian ancestry (those who originate from the Indian subcontinent) are of lower birthweight, and that Aboriginal newborns are of higher birthweight compared to full term newborns of white Caucasian ancestry in Canada.[8] This provides additional evidence that among full term newborns, ethnic differences in birthweight distribution exist. Numerous factors influence birthweight, including gestational weight gain, maternal pre-pregnancy weight, maternal height, gestational diabetes, and fetal smoke exposure.[9,10] It has been postulated that maternal dietary intake also influences birthweight.[11,12] The substantial variation in dietary exposures and birthweight between ethnic groups affords an opportunity to investigate the influence of maternal dietary patterns on birthweight in a large multi-ethnic birth cohort alliance (NutriGen Alliance) based in Canada.

METHODS

Study Population. The NutriGen Alliance[13] is a consortium of four birth cohorts in Canada investigating the contribution of nutritional, genetic, and epigenetic factors to the health of pregnant women and their children—(i) Canadian Healthy Infant Longitudinal Development[14] study (CHILD); (ii)

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Family Atherosclerosis Monitoring In earLY life (FAMILY)[15]; (iii) SouTh Asian birth cohoRT (START)[16]; and (iv) Aboriginal Birth Cohort (ABC)[17]. Of these, ABC is still recruiting. To date (October 2016), 5018 pregnant women have provided comprehensive clinical and dietary data and 4556 (≈90.8%) have provided birth data. From this group, 559 women were excluded from the present analysis because they (i)reported an implausible energy intake (<500 or ≥6500kcal/d), (ii)were non-singleton pregnancies, (iii)delivered pre-term (<36 weeks), and/or (iv)reported not knowing their ethnic origin. Pre-term infants were excluded to reduce the risk of confounding of infants born early (and very-low birthweight) due to pregnancy complications (e.g., trauma, stress, infections, or placenta previa).The remaining 3997 full-term infant-mothers represented multiple maternal self-reported ethnicities—White Caucasian (n=2367), South Asian (n=884), East/South East Asian (n=335), Aboriginal (n=190), African (n=60) and women who reported another ethnicity (n=141, e.g.,Egyptian, Haitian, etc.).(eFigure 1) Ethical approval was obtained for each study independently, and informed consent was obtained from all individual participants included in the study.

Dietary Assessment. Dietary information during pregnancy was collected in each cohort 24-28 weeks gestation using a validated semi-quantitative food-frequency questionnaire (FFQ). The CHILD cohort used a version of the Fred Hutchinson Cancer Center tool.[18] The FAMILY, START, and ABC cohorts used ethnic-specific FFQs developed for the Study of Health and Risk in Ethnic Groups (SHARE) study.[13,16,17]

Diet Pattern Analysis. Detailed methods of FFQ harmonization and the derivation of dietary patterns within the NutriGen cohort have been previously described.[13] We performed principal component analysis (PCA) to identify 3 dietary patterns—'plant-based', 'western', and 'health-conscious' (eTable 1)—whereby a higher score reflects greater adherence to the dietary pattern. The PCA loading scores for

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each individual were adjusted to the mean total population caloric intake (2500 kcal/day) using the residual method.[19]

Clinical Parameters: The primary outcome of this analysis was newborn birthweight. Birthweight was collected from the birth chart or measured in duplicate by trained staff perinatally (median<24hrs;95%≤48 hrs). Due to the ethnic-diversity of the study population, sex- and ethnic-specific birthweight cut points were used to define infants born small (SGA<10th%ile) or large (LGA≥90th%ile) for gestational age, which demonstrate greater accuracy to identify risk in multi-ethnic cohorts.[20] Gestational age was determined by ultrasound at the initial visit. Data on all clinical parameters are provided in Table 1.

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Table 1 - Participant characteristics.

Variable	Overall	White Caucasian	South Asian	East/South East Asian	Aboriginal	Other Ethnicity	African	P value*
Number	3997	2367	884	335	190	141	60	
Maternal								
Age at enrollment (years)	31.6 (4.7)	32.1 (4.6)	30.2 (4.0)	33.1 (4.2)	28.0 (6.0)	32.2 (5.1)	31.2 (5.4)	<0.001
Height (cm)	164.4 (6.9)	166.0 (6.5)	162.2 (6.4)	160.2 (6.6)	165.3 (6.9)	161.5 (6.3)	163.7 (7.7)	<0.001
Pre-Pregnancy Weight (kg)	66.8 (13.9)	69.1 (14.1)	62.4 (11.9)	58.7 (9.2)	75.4 (16.9)	64.3 (10.6)	69.7 (14.2)	<0.001
Pre-Pregnancy BMI (kg/m^2)	24.7 (4.8)	25.1 (5.0)	23.7 (4.4)	23.0 (3.3)	27.6 (6.2)	24.8 (4)	26 (4.8)	<0.001
Final Pregnancy Weight (kg)	81.4 (15.7)	84.2 (16.2)	76.5 (12.7)	72.4 (12.5)	91.3 (22.7)	80.1 (14.1)	83.1 (14.8)	<0.001
Primiparous (%)	49.8%	51.3%	41.8%	59.7%	40.8%	58.9%	45.0%	<0.001
Gestational Diabetes (%)	11.3%	7.4%	24.2%	10.8%	4.2%	9.2%	5.0%	<0.001
Years lived in Canada	23.4 (12.2)	29.2 (8.3)	8.4 (7.8)	20.4 (12.5)	28.5 (5.8)	17.2 (12.4)	19.4 (12.6)	<0.001
Post-secondary Education (%)	85.1%	86.8%	84.7%	95.2%	52.9%	82.6%	85.0%	<0.001
Smoking During Pregnancy (%)								
Never Smoked	77.1%	70.4%	99.6%	87.7%	40.6%	71.6%	88.3%	<0.001
Quit Before Pregnancy	16.2%	21.8%	0.2%	9.9%	25.7%	21.3%	5.0%	<0.001

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Quit During Pregnancy	3.6%	4.3%	0.2%	1.8%	15.5%	5.7%	1.7%	<0.001
Currently Smoking	3.1%	3.5%	0.0%	0.6%	18.2%	1.4%	5.0%	<0.001
Household Income (%)								
Total Income ≥ $ 60K	77.2%	88.9%	43.5%	87.2%	48.1%	80.3%	68.3%	<0.001
Multivitamin Use (%)	85.8%	89.3 %	71.8%	95.9 %	91.4 %	87.4 %	83.4 %	<0.001
Vegetarianism (%)	12.3%	3.5%	37.1%	0.0%	0.0%	0.0%	0.0%	<0.001
Newborn								
Sex (% Male)	51.8%	52.3%	49.1%	52.2%	46.8%	58.2%	53.2%	0.42
Gestational Age (weeks)	39.6 (1.1)	39.7 (1.1)[a]	39.4 (1.1)[b]	39.4 (1.1)[bc]	39.6 (1.1)[ac]	39.8 (1)	39.5 (1.1)	<0.001
Birthweight (g)	3432 (466)	3493 (457)[a]	3265 (438)[b]	3330 (448)[c]	3567 (469)[d]	3456 (481)	3347 (468)	<0.001
Birth length (cm)	51.3 (2.5)	51.4 (2.5)[ab]	51.3 (2.5)[ab]	51.0 (2.4)[b]	51.6 (3.2)[a]	51.2 (2.3)	51.4 (2.4)	0.18
LGA (n)	370 (9.8%)	224 (9.9%)	87 (9.9%)	30 (9.2%)	18 (9.6%)	12 (9.0%)	10 (17%)	0.60
SGA (n)	348 (9.2%)	219 (9.6%)	83 (9.4%)	29 (8.9%)	14 (7.5%)	10 (7.4%)	1 (1.7%)	0.36

**Continuous measures (mean and standard deviation) were compared using ANOVA, categorical variables were compared using chi-square. Non-matching superscript letters indicate significant difference (p<0.05) between ethnic groups. Data on parity, pre-pregnancy weight, smoking history, ethnicity, post-graduate education, marital status, employment status, and total household income were self-reported. Maternal age, height, and gestational age of offspring at birth were obtained from participant medical records. Last measured maternal pregnancy weight was*

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obtained from medical records at time of birth (ABC, FAMILY, and START) or using a combination of medical records or maternal recollection (CHILD). Gestational Diabetes was determined either through (i) self-reported by the mother or recorded from the medical chart (CHILD), or (ii) diagnosed using an oral-glucose tolerance test, self-reported by the mother, or recorded from the medical chart (ABC, FAMILY, and START). SGA = ethnic-specific small for gestational age (birthweight < 10^{th} percentile for gestational age and sex); LGA = ethnic-specific large for gestational age (birthweight ≥ 90^{th} percentile for gestational age and sex).

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Statistical Analysis. The distribution of exposures and covariates were summarized using JMP (v.9.0.1)as means (SD) for continuous variables, or counts (%) for categorical variables; between groups, differences were assessed using ANOVA (continuous variables) or chi-square test (categorical variables).

Pre-pregnancy weights from the CHILD cohort were available for ≈73% of women. To impute missing weights, we constructed a multivariable model with white Caucasians recruited in CHILD and FAMILY. The correlation between the value predicted by this equation and observed pre-pregnancy weight was 0.42.

Due to the numerous biological, sociological, and environmental variables that associate with birthweight, we aimed to identify a parsimonious set of covariates. All variables listed in Table 1 significant with birthweight as the response variable in a simple linear regression ($\alpha \leq 0.10$) were entered into a forward step-wise selection procedure. To account for perinatal reductions in weight,[21] timing of birthweight measurement was assessed as a covariate. Covariates significant at $\alpha < 0.05$ in the step-wise multivariable model were retained as covariates in the final model. Multivariable linear regression was used to assess the association between maternal dietary patterns and covariates on infant birthweight. The main effects, ethnicity and each of the dietary patterns, were included in the initial model. Interaction terms between a dietary pattern and ethnicity were added if they were both significant $P<0.05$. To determine which foods contributed to the observed diet and birthweight association, food groups were added one at a time to the full dietary pattern-birthweight multivariable model. If the association between the dietary pattern and birthweight was rendered non-significant by the addition of the food group, we deemed it to be an important explanatory variable.

For ethnic specific analyses, we had adequate power to investigate the association between plant-based diet and birthweight within the two largest ethnic groups—white Caucasians (>95% power) and South Asians (≈80% power) but <40% power to do so in the other ethnic groups. Therefore, stratified analyses by ethnic group were limited to white Caucasians and South Asians.

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RESULTS

Demographic and Clinical Parameters. Maternal demographic and clinical parameters for each of the six ethnic groups are presented in Table 1.

Birthweight. There were significant differences in birthweight by ethnic group (P<0.001). Aboriginal newborns had the highest birthweight, followed by white Caucasians, other ethnicity, African origin, East/South East Asians, and South Asians.(Table 1)

Effect of dietary patterns on birthweight. In the fully-adjusted main-effects multivariable model (Table 2,Model 1), non-white ethnicity and plant-based diet were significantly associated while the Western and Health-Conscious diet patterns were not. After removal of non-significant dietary patterns, an interaction between the plant-based diet and non-white ethnicity was tested and found to be significant (Table 2,Model 2).

Table 2 – Final multivariable regression of the association and interaction between diet patterns in white and non-whites with birthweight (g).

	Model 1		**Model 2**	
Variables	**β**	**P value**	**β**	**P value**
Intercept	-4551.9	<0.001	-4560.8	<0.0001
Pre-Pregnancy Weight (kg)	5.5	<0.001	5.4	<0.001
Maternal Height (cm)	8.4	<0.001	8.5	<0.001
Parity (# of children)	67.6	<0.001	66.0	<0.001
Gestational age (weeks)	158.4	<0.001	158.2	<0.001
Smoking Status	-21.9	0.04	-23.6	0.02

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Infant Sex (Female=1)	-118.6	<0.001	-118.8	<0.001
Non-White Ethnicity	-33.5	0.04	-28.1	0.08
Plant-Based Diet	-34.6	<0.001	-67.6	<0.001
Western Diet	-12.7	0.35	ns	ns
Health-Conscious Diet	6.0	0.56	ns	ns
Plant-Based Diet × non-White	n/a	n/a	40.5	0.03

Model 1 included all covariates, non-White ethnicity indicator, 3 diet patterns identified using PCA: plant-based, Western, and health-conscious diet. Model 2 tests interactions between Non-White ethnicity and significant diet patterns from Model 1. n=3,997. Non-significant variables removed from the model are denoted as 'ns'. Smoking status was ordinal and input as either 0 = never smoked, 1 = quit smoking pre-pregnancy, 2 = quit smoking during pregnancy, or 3 = currently smoking. Parity was ordinal and reported as having 0, 1, 2, 3, 4, 5, or 6 (or more) children. Non-whites included individuals that self-reported as being of South Asian, East/South East Asian, or Aboriginal descent.

Stratified Analyses. Multivariable models, stratified by ethnicity (white Caucasian and South Asian), and adjusted for the same covariates as the main model (except for smoking in South Asians, as its prevalence was <0.5%) were built, treating dietary pattern scores as either continuous (Table 3a) or dichotomous (4^{th} vs 1^{st} quartile) variables (Table 3b). In white Caucasians, an inverse association was observed between plant-based diet and birthweight. Among South Asians, a positive association was observed between the plant-based diet and birthweight.(Figure 1).

Table 3 – Multivariable regression of plant-based diet pattern (as a continuous measure) and birthweight stratified by ethnicity: white Caucasian and South Asians

	White Caucasians		**South Asians**	
Variables	**β**	**P value**	**β**	**P value**

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Intercept	-4723.7	<0.001	-4248.1	<0.001
Pre-Pregnancy Weight (kg)	5.1	<0.001	5.3	<0.001
Maternal Height (cm)	9.3	<0.001	6.0	0.01
Parity (# of children)	73.8	<0.001	43.5	0.01
Gestational age (wks)	159.3	<0.001	155.6	<0.001
Smoking Status	-37.6	0.002	ns	n/a
Infant Sex (Female = 1)	-127.7	<0.001	-98.3	<0.001
Plant-Based (Continuous)	-65.9	<0.001	40.5	0.01

White Caucasian r2 = 0.246, South Asian r2 = 0.178. The same covariates were included for each ethnic-specific model but non-significant covariates (e.g., 'smoking' in South Asians) were removed in the final model (denoted as 'ns'). Smoking status was coded as follows: 0 = never smoked, 1 = quit smoking pre-pregnancy, 2 = quit smoking during pregnancy, or 3 = currently smoking. Parity was reported as having 0, 1, 2, 3, 4, 5, or 6 (or more) children. White Caucasians (n=2367) and South Asians (n=884).

A sensitivity analysis, which excluded mothers who were diagnosed with gestational diabetes and/or hypertension, resulted in dietary associations that were largely unchanged with a negative association remaining in white Caucasians (β=-64.5g per 1-unit increase in score;n=2038;P=0.002) and a positive association in South Asians (β=38.3g per 1-unit increase in score;n=728;P=0.03).

In white Caucasians, a 1-unit increase in plant-based diet score was associated with ≈50% increase in odds of SGA and a ≈30% decrease in odds of LGA (Table 4a). In South Asians, a 1-unit increase in plant-based diet score presented a non-significant reduction in odds of SGA (P=0.428) and non-significant increase in odds of LGA (P=0.249).(Table 4b)

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Table 4 Multivariable regression of plant-based diet pattern (as a categorical measure) and birthweight stratified by ethnicity: white Caucasian and South Asians

	White Caucasians		South Asian	
Variables	**B**	**P value**	**β**	**P value**
Intercept	-5001.5	<0.001	-2482.3	<0.001
Pre-Pregnancy Weight (kg)	4.1	<0.001	6.8	<0.001
Maternal Height (cm)	9.4	<0.001	ns	ns
Parity (# of children)	77.1	<0.001	ns	ns
Gestational age (wks)	168.6	<0.001	135.6	<0.001
Smoking Status	ns	ns	ns	ns
Infant Sex (Female = 1)	-130.4	<0.001	-122.8	0.002
Plant-Based (4^{th} vs 1^{st} quartile)	-81.2	0.002	70.5	0.07

White Caucasian r^2 = 0.246; South Asian r^2 = 0.155. The same covariates were included for each ethnic-specific model but non-significant covariates (e.g., 'smoking' in South Asians) were removed in the final model (denoted as 'ns'). Smoking status was coded as follows: 0 = never smoked, 1 = quit smoking pre-pregnancy, 2 = quit smoking during pregnancy, or 3 = currently smoking. Parity was reported as having 0, 1, 2, 3, 4, 5, or 6 (or more) children. White Caucasians (n=2367) and South Asians (n=884)

Validity of the Plant-Based Diet Score

The classification of individuals as plant-based consumers using the harmonized FFQ/PCA was validated against a classification using pre-harmonization FFQ data. Using the raw number of servings obtained by each study-specific FFQ, the sum of servings for five plant-based foods groups common across all FFQs—i.e., total dairy, vegetables, legumes, fruit, and breads and rice—was calculated. There was a high-degree of agreement between pre- and post-harmonized scores with

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>90% of the same plant-based consumers being classified in the 4th quartile using either metric (P<0.001).

Diet Comparison

The food groups among individuals in the 4th quartile of the plant-based diet were compared between white Caucasians and South Asians to understand the ethnic-specific structure of plant-based diets. For white Caucasians, the plant-based diet was characterized by high intakes of fruit, nuts and seeds, convenience foods, sweet drinks, sweets, eggs, and moderate intakes of fish, poultry, red meat, while the South Asian plant-based diet was characterized by higher intakes of South Asian breads (e.g., roti, naan), rice, legumes, raw vegetables, and cooked vegetables.(eTable 2) The use of multivitamins was comparable amongst high consumers of the plant-based diet in white Caucasians (79%) and South Asians (78%), but differed in the low consumers of the plant-based diet with white Caucasians (94%) consuming significantly more multivitamins than South Asians (66%).

Among white Caucasians, higher levels of post-secondary education, employment and marriage were observed in the 4th versus the 1st quartile of the plant-based diet, while South Asians in the 4th quartile were more likely to have recently immigrated to Canada, live with extended family in their household, and were less likely to have post-secondary education compared to quartile 1.(eTable 2)

Food Groups. *Post hoc* analyses were conducted separately in white Caucasians and South Asians, and used 15 mutually exclusive food groups (eTable 2) that showed a high-degree of variance between the individuals in the 1st and 4th quartiles of the plant-based diet. Only the addition of "cooked vegetables" to the model reduced the magnitude of the plant-based dietary pattern association in South Asians (β=37.9g;P=0.041)(eTable 3). No other foods influenced the association of plant-based diet and birthweight in either ethnic group. Multivitamin use had no influence on the association.

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DISCUSSION

Among women living in a high-income country, a plant-based diet in pregnancy is associated with newborn birthweight, the effects of which are moderated by ethnicity. In white Caucasian women, consumption of a plant-based diet is associated with lower birthweight, an increased risk of SGA infants, and a reduced risk of LGA infants, while in South Asian women the plant-based diet is associated with higher birthweight but had no significant effect on SGA nor LGA infants.

Our findings are consistent with a recent systematic review which found differences in the direction of association between maternal plant-based/vegetarian diet patterns and infant birthweight across 13 observational studies.[22] The interpretation of the studies was complicated by (i) the numerous ethnic groups investigated, (ii) the foods that characterized the vegetarian and non-vegetarian (i.e., control) groups within each of the reported studies, and (iii) the socio-economic status of individuals on a vegetarian diet. This is compatible with our finding that birthweight was not associated with self-reported vegetarianism (although a high plant-based diet score associated with increased odds of self-reported vegetarianism), which may be partly explained by the high degree of variability in the foods that comprise a plant-based diet across ethnic groups, even between those that reside in a similar geographic region. This suggests that 'vegetarianism' may be too crude a descriptor of diet to allow for discovery of true associations with birthweight, especially between ethnic groups.

Studies investigating the effect of a plant-based diet in ethnically homogenous populations are sparse. No study in pregnant South Asian women living in a high-income country has yet reported on dietary patterns and birthweight. However, our findings in white Caucasians are consistent with previous work indicating that smoking is associated with reduced birthweight [23], an increased risk of SGA[24], reduced risk of LGA[25], and that increased parity, maternal weight and height are associated with a reduced risk of SGA[26] and increased risk of LGA[25]. Concerning diet, a previous study in white Caucasians (n=38)[27] reported that infants born to mothers classified as 'plant-based' were lighter (3310g;95%CI:3080-3350g) than infants born to 'omnivore' mothers

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(3480g;95%CI:3350-3620g). The Danish National Birth Cohort (n=44612), reported that mothers adhering to a plant-based dietary pattern were at reduced risk of having an SGA infant (OR=0.74;95%CI:0.64–0.86) compared to mothers adhering to a Western diet pattern.[28] However, this observation may be confounded as there was a high prevalence of smoking during pregnancy in the Western diet (38%) vs plant-based diet group (14%).

Our investigation to determine which of the individual food groups comprising the plant-based diet may be driving the association revealed that cooked vegetables reduced the strength and significance of the association between the plant-based diet and birthweight in South Asians but not among white Caucasians. In South Asians, cooked vegetables were also independently associated with birthweight after removing plant-based dietary pattern from the model, whereas multivitamin use was not. This suggests that consumption of 'cooked vegetables' may be a driver of the observed association between the plant-based diet and increased birthweight in South Asians. Prior studies from India have shown that lower levels of serum vitamin B12[29] and folate in pregnancy are associated with low-birthweight.[30] Furthermore, a randomized controlled trial conducted (RCT) in Bangladesh among 28516 mother-infant pairs demonstrated that a prenatal micronutrient supplement containing vitamins A, D, E, C, and B-vitamins, as well as iron, zinc, copper, selenium, and iodine reduced the risk of low-birthweight by 12% (RR=0.88;95%CI:0.85-0.91).[31] Another RCT, the Mumbai Maternal Nutrition Project conducted in the slum-dwelling population in Mumbai, India, reported that women assigned a daily micronutrient-rich snack (green leafy vegetables, fruit, and milk) before or during their pregnancy delivered children who were 48g heavier (95%CI:1-96g) compared to women assigned a low-micronutrient snack (potato and onion).[32] However, the dietary context in Canada differs substantially from that of low income countries. Since 1998 flour and cereals have been fortified with folate,[33] and this coupled with relatively high rates of multivitamin supplementation in pregnancy makes folate and vitamin B12 deficiency in pregnancy unlikely among South Asians in Canada. In addition, women who avoid meat products yet consume milk, yoghurt, cheese, and eggs usually attain adequate vitamin B12. Thus, even in the context of

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virtually no dietary folate and vitamin B12 deficiency, high consumption of cooked vegetables as part of a traditional Indian diet is associated with higher birthweight compared to a lower plant-based/higher animal protein diet.

In our study, South Asian women reported consuming a higher percentage of energy from fat than did white Caucasians; however, we did not collect detailed information on cooking methods. Differences in food preparation methods can significantly alter the chemical and nutritional composition of dishes.[34] This was recently examined using spectrophotometry to determine the chemical composition of fresh and fried portions of ovo-vegetarian dishes.[35] The fried ovo-vegetarian prepared in oil were lower in protein, fibre, and carbohydrate content but higher in caloric and lipid content per 100g serving, compared to fresh dishes[35]. This agrees with previous work in pregnant South Asian women as a higher proportion of energy from fat (40% energy) was observed, compared to other ethnic groups (Caucasian, African, and African-Caribbean) residing in East London (UK).[36] Further, a prospective birth study of 797 rural Indian women, reported that, although protein and carbohydrate intake at 18 weeks of gestation were unrelated to birth measurements, fat intake was associated with newborn length and adiposity.[37] This suggests that South Asian cooking methods may alter the macronutrient composition of food by increasing the proportion of total fat relative to other nutrients, and offers a possible explanation regarding the difference in the association between the plant-based diet and birthweight in South Asians and white Caucasians.

Although markers of socio-economic status (SES) were not significantly associated with birthweight, understanding differences in sociodemographic factors between high and low consumers of the plant-based diet is informative to understand the context in which these diets are consumed. In the ALSPAC birth cohort (n=11833), SES was not associated with birthweight but was associated with food choices whereby women of high SES consumed more healthy foods and less processed foods than women of a lower SES.[23] In the present study, white Caucasian women who adhered most strongly to the plant-based diet represented the highest socioeconomic group compared to less

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adherent white Caucasian women. Interestingly this group consumed fewer multivitamin supplements and it is possible they perceived their "healthy diet consumption" negated the need for the recommended daily supplement in pregnancy. In contrast, South Asian women who adhered most strongly to the plant-based diet were more recent immigrants to Canada, had lower income, and were living with more extended family members, indicating more traditional cultural practices compared to the low adherers to the plant-based diet. Interestingly the more recent immigrants with a high adherence to a plant-based diet also had greater multivitamin use compared to South Asians who were longer settled in Canada. The relationship between immigration and diet is complex due to the numerous and varied factors that influence acculturation within each ethnic group and country.[38-40] Our observations taken together with the socioeconomic profile between and within ethnic groups are important to consider if using these data to shape policy.

Our study has several strengths including prospective data collection, large sample size, adequate power to allow for ethnic comparisons, and detailed measurement of diet using ethnic-specific FFQs. There are some limitations of our analysis including self-reported retrospective food intake, the inability to adjust for differences in cooking methods, and residual confounding which is a potential bias in all cohort studies. To minimize this potential bias, we conducted a sensitivity analysis and excluded mothers who may have deliberately altered their diet due to a medical condition such as diagnosed gestational diabetes or hypertension in pregnancy. After these exclusions, our results remained consistent.

CONCLUSION

Maternal adherence to a plant-based diet during pregnancy is associated with infant birthweight in a high-income country. Among the white Caucasians a plant-based diet is associated with lower birthweight, reduced odds of LGA and increased odds of SGA babies, whereas among South Asians, a plant-based diet is associated with higher birthweight. Future studies are necessary to replicate

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these results and to elucidate potential mechanisms which underlie these ethnic-specific associations.

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FIGURE LEGENDS

Figure 1 - Multivariable regression of plant-based diet pattern and birthweight stratified by ethnicity.

Association between maternal adherence to a plant-based diet, whereby a higher score reflects greater adherence to the dietary pattern, and birthweight in white Caucasians (dashed line; n=2,367) and South Asians (solid line; n=884) after accounting for covariates: pre-pregnancy weight, maternal height, maternal smoking status, number of children, and infant gestational age and sex. Dotted line = 95% confidence interval.

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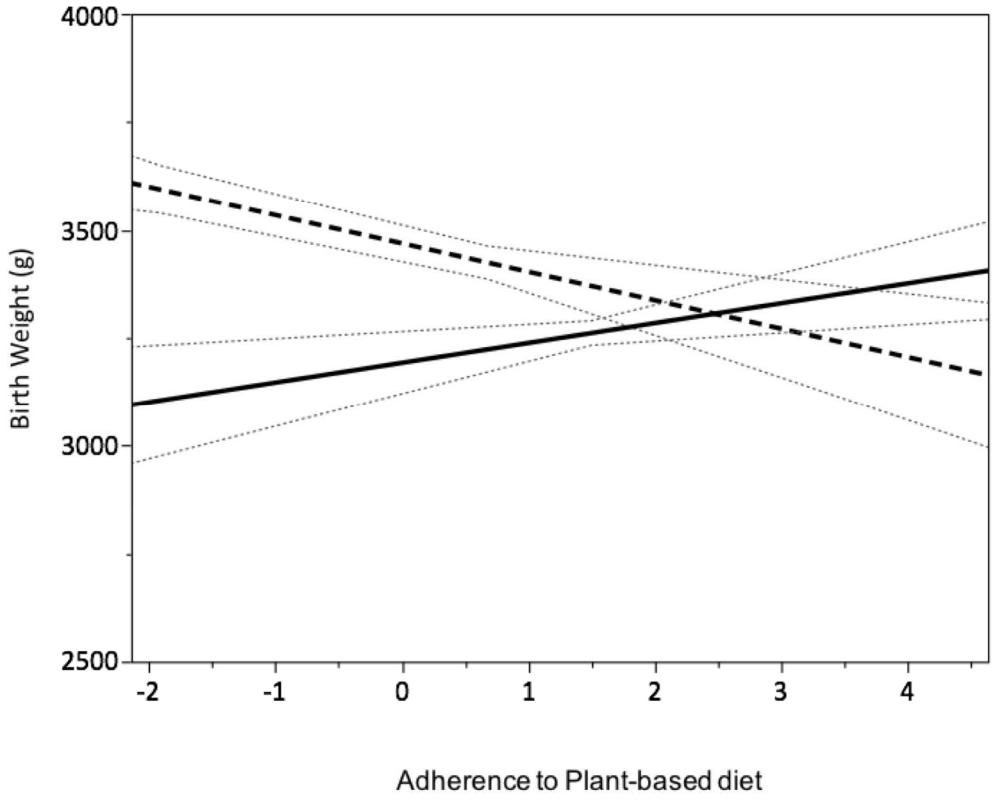

Figure 1 - Multivariable regression of plant-based diet pattern and birthweight stratified by ethnicity.

Association between maternal adherence to a plant-based diet, whereby a higher score reflects greater adherence to the dietary pattern, and birthweight in white Caucasians (dashed line; n=2,367) and South Asians (solid line; n=884) after accounting for covariates: pre-pregnancy weight, maternal height, maternal smoking status, number of children, and infant gestational age and sex. Dotted line = 95% confidence interval.

93x75mm (600 x 600 DPI)

Supplemental Digital Content

eTable 1 - Food groups with a loading ≥ |0.30| whose presence or absence characterize each of the three dietary patterns.

Food Group	Plant-based	Western	Health Conscious
Fats		0.55	
Full Fat Dairy			
Low Fat Dairy	0.39	0.42	
Fermented Dairy	0.61		
Meat	(-0.35)	0.43	0.34
Eggs			0.36
Organ Meats			
Fish and Seafood			0.50
Processed Meats		0.55	
Meat Dishes			0.49
Poultry and Waterfowl			0.36
Fried Foods			
Leafy Greens			0.38
Cruciferous Vegetables			0.56
Legumes	0.62		
Fresh Seasonings	0.72		
Starchy Vegetables		0.43	
Vegetable Medley	0.42		0.47
Other Vegetables	0.70		0.32
Tofu			
Fruits			0.53
Whole Grains	0.71		
Refined Grains			0.35
Pasta		0.54	
Pizza		0.32	
French Fries		0.47	
Non-Meat Dishes	0.63		
Stir-Fried Dishes			0.47
Snacks		0.42	
Nuts and Seeds			0.34
Sweets		0.46	
Condiments		0.47	0.41
Tea	0.56		
Coffee		0.34	
Sweet Drinks		0.56	
Artificial Sweets			
Eigenvalue	4.05	3.18	3.06
Cumulative Variation	0.11	0.20	0.29

[1]Proportion of the total dietary variation in the dataset that is explained by considering 1, 2, or 3 underlying dietary patterns.

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eTable 2– Comparison of reported daily consumption frequencies (servings/d) of common food groups by White Caucasian and South Asian women, divided by 1st and 4th quartile.

	Plant-Based Diet Adherence					
	White Caucasian		South Asian		White Caucasian vs South Asian	
Food	Quartile 1	Quartile 4	Quartile 1	Quartile 4	Quartile 1	Quartile 4
Dairy	3.4 (2.6)	3.9 (2.1)	2.5 (1.7)	3.3 (2.3)*	0.306	<0.001
Eggs	0.1 (0.1)	0.3 (0.3)*	0.6 (0.6)	0.2 (0.3)*	<0.001	0.002
Fish	0.1 (0.1)	0.2 (0.2)*	0.1 (0.3)	0.0 (0.1)*	0.03	<0.001
Poultry	0.3 (0.2)	0.2 (0.2)	0.3 (0.3)	0.1 (0.2)*	0.948	<0.001
Red Meat	0.6 (0.3)	0.4 (0.2)*	0.4 (0.4)	0.0 (0.1)*	0.013	<0.001
Breads and Rice	2.7 (2.7)	1.9 (1.1)	3.0 (3.3)	3.8 (1.5)*	0.73	<0.001
Legumes	0.1 (0.1)	0.2 (0.2)*	0.4 (0.4)	0.8 (0.7)*	<0.001	<0.001
Fruit	2.5 (2.5)	2.6 (1.5)	2.5 (2.4)	2.1 (1.4)*	0.97	<0.001
Raw Vegetables	0.8 (0.8)	1.3 (0.9)	1.4 (4.2)	2.7 (1.6)*	0.10	<0.001
Cooked Vegetables	1.3 (0.9)	2.3 (1.3)*	2.2 (1.5)	4.3 (2.2)*	0.01	<0.001
Fried Foods	1.2 (1.0)	0.2 (0.2)	0.4 (0.4)	0.2 (0.2)*	0.02	0.421
Nuts and Seeds	0.4 (0.5)	0.6 (0.6)*	0.3 (0.6)	0.2 (0.3)*	0.57	<0.001
Convenience Foods	1.7 (0.8)	1.3 (0.9)	0.3 (0.7)	0.2 (0.4)*	<0.001	<0.001
Sweet Drinks	4.3 (2.5)	2.2 (1.7)*	0.8 (1.0)	0.5 (0.7)*	<0.00	<0.001
Sweets	2.2 (1.7)	2.1 (1.5)	1.4 (1.3)	1.1 (0.9)	0.15	<0.001
Multivitamin (%)	94.0%	79.3%*	66.3%	78.1%*	<0.001	0.72
Married (%)	93.0%	95.8%*	100.0%	100.0%	<0.001	0.002
Years in Canada (yrs)	28.8 (7.4)	29.5 (8.8)	11.3 (10.3)	7.0 (5.5)*	<0.001	<0.001
Adults living in household (n)	2.2 (0.6)	2.1 (0.7)	3.0 (1.5)	3.5 (1.7)*	<0.001	<0.001
Any Post-Secondary Education (%)	74.1%	93.4%*	87.3%	75.4%*	<0.001	<0.001
Currently Employed (%)	80.2%	88.2%*	55.1%	53.7%	<0.001	<0.001
Household Income ≥ *$ 60K/yr (%)*	85.5%	88.6%	55.9%	33.5%*	<0.001	<0.001

Consumption of foods were compared using t-tests. Data are reported as mean servings per day and standard deviation. Quartiles are in white Caucasians (n=2367) and South Asians (n=884). *p<0.05 between Q1 vs Q4.

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eTable 3— Multivariable regression in South Asians (n=884) of the role of 'cooked vegetables' in the association between the plant-based diet pattern and birthweight.

	With Plant-based diet		Without Plant-based diet	
Variables	β	P value	β	P value
Intercept	-4188.2	<0.001	-4136.4	<0.001
Pre-Pregnancy Weight (kg)	5.1	<0.001	5.1	<0.001
Maternal Height (cm)	5.9	0.007	5.9	0.008
Parity (# of children)	44.1	0.009	46.2	0.006
Gestational age (wks)	154.5	<0.001	154.8	<0.001
Infant Sex (Female = 1)	-93.9	<0.001	-93.5	<0.001
Plant-Based	37.9	0.041	ns	ns
Cooked Vegetables	7.4	0.376	15.6	0.034

The same covariates were included for each ethnic-specific model but non-significant covariates (e.g., 'smoking' in South Asians) were removed in the final model (denoted as 'ns'). Parity was reported as having 0, 1, 2, 3, 4, 5, or 6 (or more) children. The consumption of 'cooked vegetables' includes all vegetables asked within the food frequency questionnaire that were not stated as 'raw'. The consumption of 'cooked vegetables' includes all vegetables asked within the food frequency questionnaire that were not stated as 'raw'.

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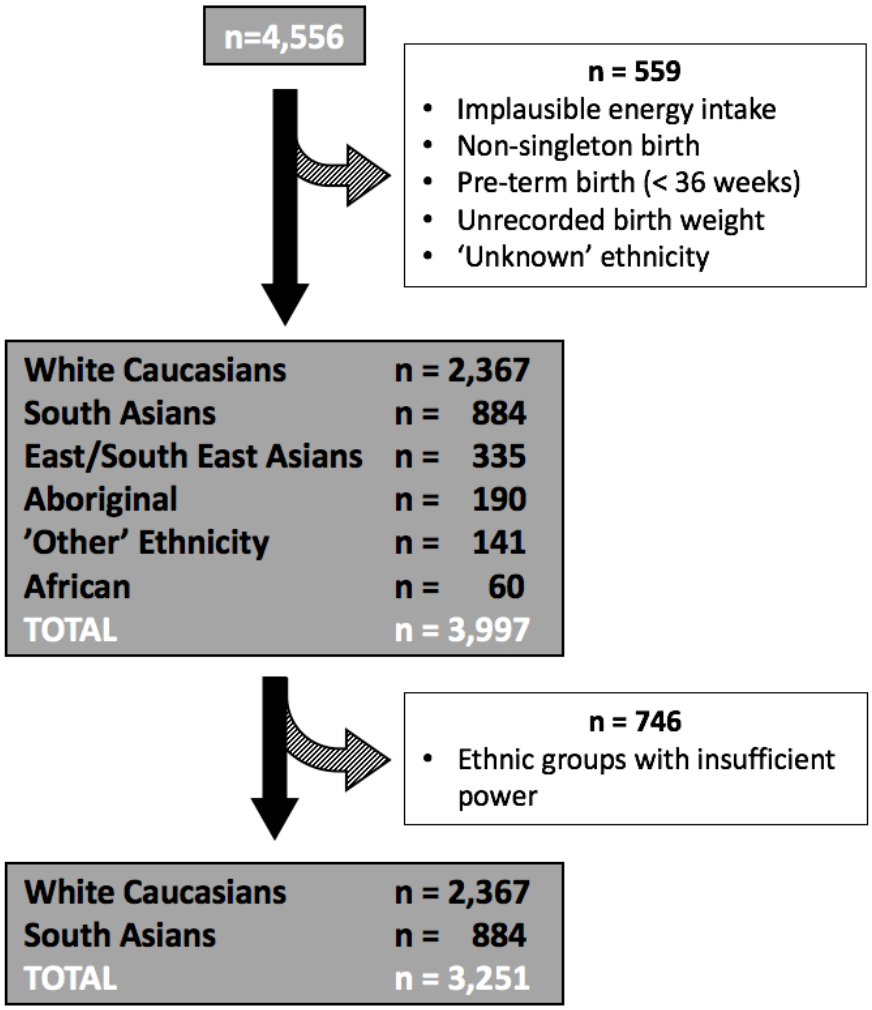
eFigure 1 – Schema of participant inclusion and exclusion



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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (PAGE 2)
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found (PAGE 2)
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported (PAGE 4)
Objectives	3	State specific objectives, including any prespecified hypotheses (PAGE 4)
Methods		
Study design	4	Present key elements of study design early in the paper (PAGES 4 - 5)
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection (PAGES 4 - 5)
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (PAGE 5 and eFigure1) ~~*Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls~~ ~~*Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants~~
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed (PAGE 15) ~~*Case-control study*—For matched studies, give matching criteria and the number of controls per case~~
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable (PAGE 5, 6, AND 10)
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group (PAGE 5 AND 6)
Bias	9	Describe any efforts to address potential sources of bias (PAGE 13)
Study size	10	Explain how the study size was arrived at (PAGE 4,5 AND eFigure1)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why (PAGE 10)
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (PAGE 10)
		(*b*) Describe any methods used to examine subgroups and interactions (PAGE 10 AND 15)
		(*c*) Explain how missing data were addressed (PAGE 5)
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed (N/A) ~~*Case-control study*—If applicable, explain how matching of cases and controls was addressed~~ ~~*Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy~~
		(*e*) Describe any sensitivity analyses (PAGE 13)

Continued on next page

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Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (PAGE 4,5 AND eFigure1)
		(b) Give reasons for non-participation at each stage (PAGE 4,5 AND eFigure1)
		(c) Consider use of a flow diagram (eFigure1)
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (Table 1)
		(b) Indicate number of participants with missing data for each variable of interest (PAGE 10)
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount) (PAGE 6)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time (TABLE 1)
		~~*Case-control study*—Report numbers in each exposure category, or summary measures of exposure~~
		~~*Cross-sectional study*—Report numbers of outcome events or summary measures~~
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (PAGE 10)
		(*b*) Report category boundaries when continuous variables were categorized (PAGE 15)
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period (N/A)
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses (PAGE 13)
Discussion		
Key results	18	Summarise key results with reference to study objectives (PAGE 15)
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias (PAGE 19)
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence (PAGE 19)
Generalisability	21	Discuss the generalisability (external validity) of the study results (PAGE 19)
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based (PAGE 20)

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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The impact of a plant-based diet during pregnancy on birthweight differs by ethnicity: a dietary pattern analysis from a prospective Canadian birth cohort Alliance

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Complete List of Authors:	Zulyniak, Michael; McMaster University, Department of Medicine; University Of Leeds, School of Food Science and Nutrition de Souza, Russell; McMaster University, Department of Health Research Methods, Evidence, and Impact Shaikh, Mateen; McMaster University, Department of Health Research Methods, Evidence, and Impact Desai, Dipika; McMaster University, Department of Medicine Lefebvre, Diana; McMaster University, Department of Medicine Gupta, M; McMaster University, Department of Medicine; Canadian Cardiovascular Research Network Wilson, Julie; Six Nations Health Services Wahi, Gita; McMaster University, Department of Health Research Methods, Evidence, and Impact; McMaster University, Department of Paedeatrics Subbarao, Padmaja; University of Toronto, Department of Paediatrics; Hospital for Sick Children Becker, Allan; University of Manitoba, Department of Immunology Mandhane, Piush; University of Alberta, Department of Pediatrics Turvey, Stuart; University of British Columbia, Department of Paediatrics Beyene, Joseph; McMaster University, Department of Health Research Methods, Evidence, and Impact Atkinson, S; McMaster University, Department of Paediatrics Morrison, Katherine; McMaster University, Department of Pediatrics McDonald, Sarah; McMaster University, Obstetrics/Gynecology Teo, Koon; Population Health Research Institute; McMaster University, Department of Medicine Sears, Malcolm; McMaster University, Department of Medicine Anand, Sonia; McMaster University, Department of Medicine; McMaster University, Department of Health Research Methods, Evidence, and Impact
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Title: The impact of a plant-based diet during pregnancy on birthweight differs by ethnicity: a dietary pattern analysis from a prospective Canadian birth cohort Alliance

Corresponding Author: Dr. Sonia S. Anand, McMaster University, 1280 Main St. W., MDCL-3204, Hamilton, ON L8S 4K1, Email: anands@mcmaster.ca, Ph. 905.525.9140 x 21523

Authors: Michael A. Zulyniak[1,2]*; Russell J. de Souza[3]*; Mateen Shaikh[3]; Dipika Desai[1,4]; Diana L. Lefebvre[1]; Milan Gupta[1,5]; Julie Wilson[6]; Gita Wahi[3,7]; Padmaja Subbarao[8]; Allan B. Becker[9]; Piush Mandhane[10]; Stuart E. Turvey[11]; Joseph Beyene[3]; Stephanie Atkinson[7]; Katherine Morrison[7]; Sarah McDonald[3]; Koon K. Teo[1,4]; Malcolm R. Sears[1]; Sonia S. Anand[1,3,4] for the *NutriGen* Alliance investigators

Author Affiliations:

[1] Department of Medicine, McMaster University, Hamilton, ON, Canada;

[2] School of Food Science and Nutrition, University of Leeds, Leeds, UK;

[3]Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, ON, Canada;

[4]Population Health Research Institute, Hamilton Health Sciences and McMaster University, Hamilton, ON, Canada;

[5]Canadian Cardiovascular Research Network, Brampton, ON, Canada;

[6]Six Nations Health Services, Ohsweken, ON, Canada;

[7]Department of Paediatrics, McMaster University, Hamilton, ON, Canada;

[8]Hospital for Sick Children & Department of Paediatrics, University of Toronto, Toronto, ON, Canada;

[9]Department of Immunology, Faculty of Medicine, University of Manitoba, Winnipeg, MB, Canada;

[10]Department of Pediatrics, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, AB, Canada;

[11]BC Children's Hospital, Department of Paediatrics, Faculty of Medicine, University of British Columbia, Vancouver, BC, Canada.

*authors contributed equally

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ABSTRACT

OBJECTIVE. Birthweight is an indicator of newborn health and a strong predictor of health outcomes in later life. Significant variation in diet during pregnancy between ethnic groups in high-income countries provides an ideal opportunity to investigate the influence of maternal diet on birthweight.

SETTING. Four multi-ethnic birth cohorts based in Canada (The NutriGen Alliance).

PARTICIPANTS. 3,997 full-term mother-infant pairs of diverse ethnic groups with principal component analysis (PCA)-derived diet pattern — plant-based, Western, health-conscious — and birthweight data.

RESULTS. No associations were identified between the Western and health-conscious diet patterns and birthweight; however, the plant-based dietary pattern was inversely associated with birthweight (β=-67.6g per 1-unit increase; P<0.001) and an interaction with non-white ethnicity and birthweight was present. Ethnically stratified analyses demonstrated that among white Europeans, maternal consumption of a plant-based diet associated with lower birthweight (β=-65.9g per 1-unit increase; P<0.001), increased risk of small for gestational age (SGA; OR=1.46; 95%CI:1.08-1.54;P=0.005), and reduced risk of large for gestational age (LGA;OR=0.71; 95%CI:0.53-0.95;P=0.02). Among South Asians, maternal consumption of a plant-based diet associated with a higher birthweight (β=+40.5g per 1-unit increase; P=0.01), partially driven by cooked vegetable consumption.

CONCLUSIONS. Maternal consumption of a plant-based diet during pregnancy is associated with birthweight. Among white Europeans, a plant-based diet is associated with lower birthweight, reduced odds of an infant born LGA, and increased odds of SGA, whereas among South Asians living in Canada, a plant-based diet is associated with increased birthweight.

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'Strengths and limitations of this study'

1. Strengths - Prospective data collection, large sample size, adequate power to allow for ethnic comparisons, and detailed measurement of diet using ethnic-specific FFQs;
2. Limitations - Self-reported retrospective food intake, the inability to adjust for differences in cooking methods, and residual confounding which is a potential bias in all cohort studies;
3. Strength - To minimize potential bias, a sensitivity analysis was conducted, which excluded mothers who may have deliberately altered their diet due to a medical condition.

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INTRODUCTION

Birthweight is an indicator of infant health and a strong predictor of future health outcomes.[1] Infants born small (birthweight<10th%ile) or large (birthweight>90th%ile) for gestational age are at increased risk of future health complications, including asthma,[2] obesity,[3] and cardiovascular disease (CVD).[4] High-income countries generally have similar proportions of babies who weigh <2500g at birth but there is greater variation (up to 10%) in the proportion of infants born >4000g.[5-7] However, such population figures often mask important differences in the distribution of birthweight between ethnic groups. In the United States, white Europeans have more high- (9.6%) than low-birthweight infants (7.0%); African Americans have more low- (13.1%) than high-birthweight infants (4.3%); and Hispanics have an equal proportion (7.1% high- and 7.1% low-birthweight).[5] Furthermore, we recently reported that newborns in Canada of South Asian ancestry (those who originate from the Indian subcontinent) are of lower birthweight, and that Aboriginal newborns are of higher birthweight compared to full term newborns of white European ancestry in Canada.[8] This provides additional evidence that among full term newborns, ethnic differences in birthweight distribution exist. Numerous factors influence birthweight, including gestational weight gain, maternal pre-pregnancy weight, maternal height, gestational diabetes, and fetal smoke exposure.[9,10] It has been postulated that maternal dietary intake also influences birthweight.[11,12] The investigation of specific food items and nutrients has advanced our understanding of specific nutrient deficiency syndromes (e.g. neural tube defects) and facilitated the identification of particularly harmful food components (e.g., trans-fats). However, single-nutrient studies may be misleading because they fail to capture the complex interplay between foods and nutrients consumed as meals over long periods of time. To overcome this, the empirical derivation of dietary patterns[13] has been proposed as a method to characterize diet that more accurately reflects how we consume foods and nutrients, and these patterns can be assessed for their associations with health and disease.

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Using dietary patterns, we investigated the association between maternal diet and birthweight in a multi-ethnic cohort.

METHODS

Study Population. The NutriGen Alliance[13] is a consortium of four birth cohorts in Canada investigating the contribution of nutritional, genetic, and epigenetic factors to the health of pregnant women and their children—(i) Canadian Healthy Infant Longitudinal Development[14] study (CHILD); (ii) Family Atherosclerosis Monitoring In earLY life (FAMILY)[15]; (iii) SouTh Asian birth cohoRT (START)[16]; and (iv) Aboriginal Birth Cohort (ABC)[17]. Of these, ABC is still recruiting. To date (October 2016), 5018 pregnant women have provided comprehensive clinical and dietary data and 4556 (≈90.8%) have provided birth data. From this group, 559 women were excluded from the present analysis because they (i)reported an implausible energy intake (<500 or ≥6500kcal/d), (ii)were non-singleton pregnancies, (iii)delivered pre-term (<36 weeks), and/or (iv)reported not knowing their ethnic origin. Pre-term infants were excluded to reduce the risk of confounding of infants born early (and very-low birthweight) due to pregnancy complications (e.g., trauma, stress, infections, or placenta previa).The remaining 3997 full-term infant-mothers represented multiple maternal self-reported ethnicities—White European (n=2367), South Asian (n=884), East/South East Asian (n=335), Aboriginal (n=190), African (n=60) and women who reported another ethnicity (n=141, e.g.,Egyptian, Haitian, etc.).(eFigure 1) Ethical approval was obtained independently for all studies from the Hamilton Integrated Research Ethics Board — CHILD (REB 07-2929), FAMILY (REB 02-060), START (REB 10-640), and ABC (REB 12- 152). Additional approval for ABC was obtained from the Six Nations Band Council. Informed written consent was obtained from each participant within each study. Data sharing is currently not available for most data due to ethnical restrictions.

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Dietary Assessment. Dietary information during pregnancy was collected in each cohort 24-28 weeks gestation using a validated semi-quantitative food-frequency questionnaire (FFQ). The CHILD cohort used a version of the Fred Hutchinson Cancer Center tool.[18] The FAMILY, START, and ABC cohorts used ethnic-specific FFQs developed for the Study of Health and Risk in Ethnic Groups (SHARE) study.[13,16,17]

Diet Pattern Analysis. Detailed methods of FFQ harmonization and the statistical derivation of dietary patterns within the NutriGen cohort have been previously described.[13] We performed principal component analysis (PCA) to identify 3 orthogonal dietary patterns—'plant-based', 'western', and 'health-conscious' (eTable 1).This approach retains the information of the quantitative data from the original FFQ but shifts the focus from individual food components to food combinations. An empirically derived measure of adherence (i.e., loading scores) for each person to each of the individual dietary patterns is calculated in the PCA. The PCA loading scores for each individual were adjusted to the mean total population caloric intake (2500 kcal/day) using the residual method.[19]

Clinical Parameters: The primary outcome of this analysis was newborn birthweight. Birthweight was collected from the birth chart or measured in duplicate by trained staff perinatally (median<24hrs;95%≤48 hrs). Due to the ethnic-diversity of the study population, sex- and ethnic-specific birthweight cut points were used to define infants born small (SGA<10th%ile) or large (LGA≥90th%ile) for gestational age, which demonstrate greater accuracy to identify risk in multi-ethnic cohorts.[20] Gestational age was determined by ultrasound at the initial visit. Data on all clinical parameters are provided in Table 1.

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Table 1 - Participant characteristics.

Variable	Overall	White European	South Asian	East/South East Asian	Aboriginal	Other Ethnicity	African	P value*
Number	3997	2367	884	335	190	141	60	
Maternal								
Age at enrollment (years)	31.6 (4.7)	32.1 (4.6)	30.2 (4.0)	33.1 (4.2)	28.0 (6.0)	32.2 (5.1)	31.2 (5.4)	<0.001
Height (cm)	164.4 (6.9)	166.0 (6.5)	162.2 (6.4)	160.2 (6.6)	165.3 (6.9)	161.5 (6.3)	163.7 (7.7)	<0.001
Pre-Pregnancy Weight (kg)	66.8 (13.9)	69.1 (14.1)	62.4 (11.9)	58.7 (9.2)	75.4 (16.9)	64.3 (10.6)	69.7 (14.2)	<0.001
Pre-Pregnancy BMI (kg/m^2)	24.7 (4.8)	25.1 (5.0)	23.7 (4.4)	23.0 (3.3)	27.6 (6.2)	24.8 (4)	26 (4.8)	<0.001
Final Pregnancy Weight (kg)	81.4 (15.7)	84.2 (16.2)	76.5 (12.7)	72.4 (12.5)	91.3 (22.7)	80.1 (14.1)	83.1 (14.8)	<0.001
Primiparous (%)	49.8%	51.3%	41.8%	59.7%	40.8%	58.9%	45.0%	<0.001
Gestational Diabetes (%)	11.3%	7.4%	24.2%	10.8%	4.2%	9.2%	5.0%	<0.001
Years lived in Canada	23.4 (12.2)	29.2 (8.3)	8.4 (7.8)	20.4 (12.5)	28.5 (5.8)	17.2 (12.4)	19.4 (12.6)	<0.001
Post-secondary Education (%)	85.1%	86.8%	84.7%	95.2%	52.9%	82.6%	85.0%	<0.001
Smoking During Pregnancy (%)								
Never Smoked	77.1%	70.4%	99.6%	87.7%	40.6%	71.6%	88.3%	<0.001
Quit Before Pregnancy	16.2%	21.8%	0.2%	9.9%	25.7%	21.3%	5.0%	<0.001

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Quit During Pregnancy	3.6%	4.3%	0.2%	1.8%	15.5%	5.7%	1.7%	<0.001
Currently Smoking	3.1%	3.5%	0.0%	0.6%	18.2%	1.4%	5.0%	<0.001
Household Income (%)								
Total Income ≥ $ 60K	77.2%	88.9%	43.5%	87.2%	48.1%	80.3%	68.3%	<0.001
Multivitamin Use (%)	85.8%	89.3 %	71.8%	95.9 %	91.4 %	87.4 %	83.4 %	<0.001
Vegetarianism (%)	12.3%	3.5%	37.1%	0.0%	0.0%	0.0%	0.0%	<0.001
Newborn								
Sex (% Male)	51.8%	52.3%	49.1%	52.2%	46.8%	58.2%	53.2%	0.42
Gestational Age (weeks)	39.6 (1.1)	39.7 (1.1)[a]	39.4 (1.1)[b]	39.4 (1.1)[bc]	39.6 (1.1)[ac]	39.8 (1)	39.5 (1.1)	<0.001
Birthweight (g)	3432 (466)	3493 (457)[a]	3265 (438)[b]	3330 (448)[c]	3567 (469)[d]	3456 (481)	3347 (468)	<0.001
Birth length (cm)	51.3 (2.5)	51.4 (2.5)[ab]	51.3 (2.5)[ab]	51.0 (2.4)[b]	51.6 (3.2)[a]	51.2 (2.3)	51.4 (2.4)	0.18
LGA (n)	370 (9.8%)	224 (9.9%)	87 (9.9%)	30 (9.2%)	18 (9.6%)	12 (9.0%)	10 (17%)	0.60
SGA (n)	348 (9.2%)	219 (9.6%)	83 (9.4%)	29 (8.9%)	14 (7.5%)	10 (7.4%)	1 (1.7%)	0.36

**Continuous measures (mean and standard deviation) were compared using ANOVA, categorical variables were compared using chi-square. Non-matching superscript letters indicate significant difference (p<0.05) between ethnic groups. Data on parity, pre-pregnancy weight, smoking history, ethnicity, post-graduate education, marital status, employment status, and total household income were self-reported. Maternal age, height, and gestational age of offspring at birth were obtained from participant medical records. Last measured maternal pregnancy weight was*

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obtained from medical records at time of birth (ABC, FAMILY, and START) or using a combination of medical records or maternal recollection (CHILD). Gestational Diabetes was determined either through (i) self-reported by the mother or recorded from the medical chart (CHILD), or (ii) diagnosed using an oral-glucose tolerance test, self-reported by the mother, or recorded from the medical chart (ABC, FAMILY, and START). SGA = ethnic-specific small for gestational age (birthweight < 10^{th} percentile for gestational age and sex); LGA = ethnic-specific large for gestational age (birthweight ≥ 90^{th} percentile for gestational age and sex).

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Statistical Analysis. The distribution of exposures and covariates were summarized using JMP (v.9.0.1)as means (SD) for continuous variables, or counts (%) for categorical variables; between groups, differences were assessed using ANOVA (continuous variables) or chi-square test (categorical variables).

Pre-pregnancy weights from the CHILD cohort were available for ≈73% of women. To impute missing weights, we constructed a multivariable model with white Europeans recruited in CHILD and FAMILY. The correlation between the value predicted by this equation and observed pre-pregnancy weight was 0.42.

Due to the numerous biological, sociological, and environmental variables that associate with birthweight, we aimed to identify a parsimonious set of covariates. All variables listed in Table 1 significant with birthweight as the response variable in a simple linear regression ($\alpha \leq 0.10$) were entered into a forward step-wise selection procedure. To account for perinatal reductions in weight,[21] timing of birthweight measurement was assessed as a covariate. Covariates significant at $\alpha < 0.05$ in the step-wise multivariable model were retained as covariates in the final model.

Multivariable linear regression was used to assess the association between maternal dietary patterns and covariates on infant birthweight. The main effects, ethnicity and each of the dietary patterns, were included in the initial model. Interaction terms between a dietary pattern and ethnicity were added if they were both significant $P<0.05$. To determine which foods contributed to the observed diet and birthweight association, food groups were added one at a time to the full dietary pattern-birthweight multivariable model. If the association between the dietary pattern and birthweight was rendered non-significant by the addition of the food group, we deemed it to be an important explanatory variable.

For ethnic specific analyses, we had adequate power to investigate the association between plant-based diet and birthweight within the two largest ethnic groups—white Europeans (>95% power) and South Asians (≈80% power) but <40% power to do so in the other ethnic groups. Therefore, stratified analyses by ethnic group were limited to white Europeans and South Asians.

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RESULTS

Demographic and Clinical Parameters. Maternal demographic and clinical parameters for each of the six ethnic groups are presented in Table 1.

Birthweight. There were significant differences in birthweight by ethnic group (P<0.001). Aboriginal newborns had the highest birthweight, followed by white Europeans, other ethnicity, African origin, East/South East Asians, and South Asians.(Table 1)

Effect of dietary patterns on birthweight. In the fully-adjusted main-effects multivariable model (Table 2,Model 1), non-white ethnicity and plant-based diet were significantly associated while the Western and Health-Conscious diet patterns were not. After removal of non-significant dietary patterns, an interaction between the plant-based diet and non-white ethnicity was tested and found to be significant (Table 2,Model 2).

Table 2 – Final multivariable regression of the association and interaction between diet patterns in white and non-whites with birthweight (g).

	Model 1		**Model 2**	
Variables	**β**	**P value**	**β**	**P value**
Intercept	-4551.9	<0.001	-4560.8	<0.0001
Pre-Pregnancy Weight (kg)	5.5	<0.001	5.4	<0.001
Maternal Height (cm)	8.4	<0.001	8.5	<0.001
Parity (# of children)	67.6	<0.001	66.0	<0.001
Gestational age (weeks)	158.4	<0.001	158.2	<0.001
Smoking Status	-21.9	0.04	-23.6	0.02

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Infant Sex (Female=1)	-118.6	<0.001	-118.8	<0.001
Non-White Ethnicity	-33.5	0.04	-28.1	0.08
Plant-Based Diet	-34.6	<0.001	-67.6	<0.001
Western Diet	-12.7	0.35	ns	ns
Health-Conscious Diet	6.0	0.56	ns	ns
Plant-Based Diet × non-White	n/a	n/a	40.5	0.03

Model 1 included all covariates, non-White ethnicity indicator, 3 diet patterns identified using PCA: plant-based, Western, and health-conscious diet. Model 2 tests interactions between Non-White ethnicity and significant diet patterns after removal of non-significant variables from Model 1. n=3,997. Non-significant variables removed from the model are denoted as 'ns'. Smoking status was ordinal and input as either 0 = never smoked, 1 = quit smoking pre-pregnancy, 2 = quit smoking during pregnancy, or 3 = currently smoking. Parity was ordinal and reported as having 0, 1, 2, 3, 4, 5, or 6 (or more) children. Non-whites included individuals that self-reported as being of South Asian, East/South East Asian, or Aboriginal descent.

Stratified Analyses. Multivariable models, stratified by ethnicity (white European and South Asian), and adjusted for the same covariates as the main model (except for smoking in South Asians, as its prevalence was <0.5%) were built, treating dietary pattern scores as either continuous (Table 3a) or dichotomous (4^{th} vs 1^{st} quartile) variables (Table 3b). In white Europeans, an inverse association was observed between plant-based diet and birthweight. Among South Asians, a positive association was observed between the plant-based diet and birthweight.(Figure 1).

Table 3 – Multivariable regression of plant-based diet pattern (as a continuous measure) and birthweight stratified by ethnicity: white European and South Asians

	White Europeans		**South Asians**	
Variables	**β**	**P value**	**β**	**P value**

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Intercept	-4723.7	<0.001	-4248.1	<0.001
Pre-Pregnancy Weight (kg)	5.1	<0.001	5.3	<0.001
Maternal Height (cm)	9.3	<0.001	6.0	0.01
Parity (# of children)	73.8	<0.001	43.5	0.01
Gestational age (wks)	159.3	<0.001	155.6	<0.001
Smoking Status	-37.6	0.002	ns	n/a
Infant Sex (Female = 1)	-127.7	<0.001	-98.3	<0.001
Plant-Based (Continuous)	-65.9	<0.001	40.5	0.01

White European r2 = 0.246, South Asian r2 = 0.178. The same covariates were included for each ethnic-specific model but non-significant covariates (e.g., 'smoking' in South Asians) were removed in the final model (denoted as 'ns'). Smoking status was coded as follows: 0 = never smoked, 1 = quit smoking pre-pregnancy, 2 = quit smoking during pregnancy, or 3 = currently smoking. Parity was reported as having 0, 1, 2, 3, 4, 5, or 6 (or more) children. White Europeans (n=2367) and South Asians (n=884).

A sensitivity analysis, which excluded mothers who were diagnosed with gestational diabetes and/or hypertension, resulted in dietary associations that were largely unchanged with a negative association remaining in white Europeans (β=-64.5g per 1-unit increase in score;n=2038;P=0.002) and a positive association in South Asians (β=38.3g per 1-unit increase in score;n=728;P=0.03).

In white Europeans, a 1-unit increase in plant-based diet score was associated with ≈50% increase in odds of SGA and a ≈30% decrease in odds of LGA (Table 4a). In South Asians, a 1-unit increase in plant-based diet score presented a non-significant reduction in odds of SGA (P=0.428) and non-significant increase in odds of LGA (P=0.249).(Table 4b)

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Table 4 Multivariable regression of plant-based diet pattern (as a categorical measure) and birthweight stratified by ethnicity: white European and South Asians

	White Europeans		South Asian	
Variables	**B**	**P value**	**β**	**P value**
Intercept	-5001.5	<0.001	-2482.3	<0.001
Pre-Pregnancy Weight (kg)	4.1	<0.001	6.8	<0.001
Maternal Height (cm)	9.4	<0.001	ns	ns
Parity (# of children)	77.1	<0.001	ns	ns
Gestational age (wks)	168.6	<0.001	135.6	<0.001
Smoking Status	ns	ns	ns	ns
Infant Sex (Female = 1)	-130.4	<0.001	-122.8	0.002
Plant-Based (4^{th} vs 1^{st} quartile)	-81.2	0.002	70.5	0.07

White European r^2 = 0.246; South Asian r^2 = 0.155. The same covariates were included for each ethnic-specific model but non-significant covariates (e.g., 'smoking' in South Asians) were removed in the final model (denoted as 'ns'). Smoking status was coded as follows: 0 = never smoked, 1 = quit smoking pre-pregnancy, 2 = quit smoking during pregnancy, or 3 = currently smoking. Parity was reported as having 0, 1, 2, 3, 4, 5, or 6 (or more) children. White Europeans (n=2367) and South Asians (n=884)

Validity of the Plant-Based Diet Score

The classification of individuals as plant-based consumers using the harmonized FFQ/PCA was validated against a classification using pre-harmonization FFQ data. Using the raw number of servings obtained by each study-specific FFQ, the sum of servings for five plant-based foods groups common across all FFQs—i.e., total dairy, vegetables, legumes, fruit, and breads and rice—was calculated. There was a high-degree of agreement between pre- and post-harmonized scores with

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>90% of the same plant-based consumers being classified in the 4th quartile using either metric (P<0.001).

Diet Comparison

The food groups among individuals in the 4th quartile of the plant-based diet were compared between white Europeans and South Asians to understand the ethnic-specific structure of plant-based diets. For white Europeans, the plant-based diet was characterized by high intakes of fruit, nuts and seeds, convenience foods, sweet drinks, sweets, eggs, and moderate intakes of fish, poultry, red meat, while the South Asian plant-based diet was characterized by higher intakes of South Asian breads (e.g., roti, naan), rice, legumes, raw vegetables, and cooked vegetables.(eTable 2) The use of multivitamins was comparable amongst high consumers of the plant-based diet in white Europeans (79%) and South Asians (78%), but differed in the low consumers of the plant-based diet with white Europeans (94%) consuming significantly more multivitamins than South Asians (66%).

Among white Europeans, higher levels of post-secondary education, employment and marriage were observed in the 4th versus the 1st quartile of the plant-based diet, while South Asians in the 4th quartile were more likely to have recently immigrated to Canada, live with extended family in their household, and were less likely to have post-secondary education compared to quartile 1.(eTable 2)

Food Groups. *Post hoc* analyses were conducted separately in white Europeans and South Asians, and used 15 mutually exclusive food groups (eTable 2) that showed a high-degree of variance between the individuals in the 1st and 4th quartiles of the plant-based diet. Only the addition of "cooked vegetables" to the model reduced the magnitude of the plant-based dietary pattern association in South Asians (β=37.9g;P=0.041)(eTable 3). No other foods influenced the association of plant-based diet and birthweight in either ethnic group. Multivitamin use had no influence on the association.

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DISCUSSION

Among women living in a high-income country, ethnicity was a predictor of birthweight, independent of caloric intake, in white Europeans and South Asians. Foods and diet differ substantially between ethnic groups, and may contribute to the association. A plant-based diet in pregnancy is associated with newborn birthweight, the effects of which are moderated by ethnicity. In white European women, consumption of a plant-based diet is associated with lower birthweight, an increased risk of a SGA infant, and a reduced risk of a LGA infant, while in South Asian women the plant-based diet is associated with higher birthweight but had no significant effect on the risk of having an SGA or LGA infant.

Our findings are consistent with a recent systematic review which failed to find a consistent association of vegetarian diets on birthweight; five studies reported vegetarian mothers had lower birthweight babies, and two studies reported higher birthweights.[22] The interpretation of the studies was complicated by (i) the numerous ethnic groups investigated, (ii) differences in the foods that characterized the vegetarian and non-vegetarian (i.e., control) groups within each of the reported studies, and (iii) variability in the socio-economic status of individuals on a vegetarian diet. This is compatible with our finding that birthweight was not associated with self-reported vegetarianism, which may be partly explained by the high degree of variability in the foods that comprise a plant-based diet across ethnic groups, which persisted even among those residing in a similar geographic region. This suggests that 'vegetarianism' may be too crude a descriptor of diet to allow for discovery of true associations with birthweight, because the definition of this term is qualitatively different across ethnic groups.

Studies investigating the effect of a plant-based diet in ethnically homogenous populations are sparse. No study in pregnant South Asian women living in a high-income country has reported on dietary patterns and birthweight. However, our findings in white Europeans are consistent with previous work indicating that smoking is associated with reduced birthweight [23], an increased risk

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of SGA[24], reduced risk of LGA[25], and that increased parity, maternal weight and height are associated with a reduced risk of SGA[26] and increased risk of LGA[25]. Concerning diet, a previous study in white Europeans (n=38)[27] reported that infants born to mothers whose diets were classified as 'plant-based' were lighter (3310g;95%CI:3080-3350g) than infants born to 'omnivore' mothers (3480g;95%CI:3350-3620g). The Danish National Birth Cohort (n=44612), reported that mothers adhering to a plant-based dietary pattern were at reduced risk of having an SGA infant (OR=0.74;95%CI:0.64–0.86) compared to mothers adhering to a Western diet pattern.[28] However, this observation may be confounded by the high prevalence of smoking during pregnancy in the Western diet (38%) vs plant-based diet group (14%).

Our investigation to determine which of the individual food groups characteristic of the plant-based diet may be driving the association revealed that controlling for cooked vegetables reduced the strength and significance of the association between the plant-based diet and birthweight in South Asians but not among white Europeans. In South Asians, cooked vegetables were independently associated with birthweight (after removing plant-based dietary pattern from the model), whereas multivitamin use was not. This suggests that consumption of 'cooked vegetables' may be a driver of the observed association between the plant-based diet and increased birthweight in South Asians.

Prior cohort studies from India have shown that lower levels of serum vitamin B12[29] and folate in pregnancy are associated with low-birthweight.[30] In a randomized controlled trial, prenatal supplementation with vitamins A, D, E, C, and B, as well as iron, zinc, copper, selenium, and iodine reduced the risk of low-birthweight (RR=0.88;95%CI:0.85-0.91)[31] . In the slum-dwelling population of Mumbai (India), micronutrient-rich snacks (green leafy vegetables, fruit, and milk) consumed before or during pregnancy increase infant birthweight (+48g; 95%CI:1-96g) compared to a low-micronutrient snack (potato and onion).[32] However, the dietary context in Canada differs substantially from that of low income countries. Since 1998 flour and cereals have been fortified with folate. [33] This, coupled with relatively high rates of multivitamin supplementation in pregnancy, makes folate and vitamin B12 deficiency in pregnancy unlikely among Canadians. In

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addition, women who avoid meat products yet consume milk, yoghurt, cheese, and eggs usually attain adequate vitamin B12. Thus, even in the context of virtually no dietary folate and vitamin B12 deficiency, high consumption of cooked vegetables as part of a traditional Indian diet is associated with higher birthweight compared to a lower plant-based/higher animal protein diet.

We can only speculate about the mechanisms underlying the association with cooked vegetables as we did not collect detailed information on cooking methods. In our study, South Asian women reported consuming a higher percentage of energy from fat than did white Europeans. Differences in food preparation methods can significantly alter the chemical and nutritional composition of dishes.[34] This was recently examined using spectrophotometry to determine the chemical composition of fresh and fried portions of ovo-vegetarian dishes.[35] Fried ovo-vegetarian dishes prepared in oil were lower in protein, fibre, and carbohydrate content but higher in caloric and lipid content per 100g serving, compared to fresh dishes[35]. This aligns with work in pregnant South Asian women residing in East London (UK), who had a higher proportion of energy from fat (40% energy) compared to other ethnic groups (white European, African, and African-Caribbean).[36] Further, a prospective birth study of 797 rural Indian women, reported that, although protein and carbohydrate intake at 18 weeks of gestation were unrelated to birth measurements, fat intake was associated with newborn length and adiposity.[37] This suggests that South Asian cooking methods may alter the macronutrient composition of food by increasing the proportion of total fat relative to other nutrients, and offers a possible explanation regarding the difference in the association between the plant-based diet and birthweight in South Asians and white Europeans.

Although markers of socio-economic status (SES) were not significantly associated with birthweight, understanding differences in sociodemographic factors between high and low consumers of the plant-based diet is informative to understand the context in which these diets are consumed. In the ALSPAC birth cohort (n=11833), SES was not associated with birthweight but was associated with food choices whereby women of high SES consumed more healthy foods and less processed foods

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than women of a lower SES.[23] In the present study, white European women who adhered most strongly to the plant-based diet represented the highest socioeconomic group compared to less adherent white European women. Interestingly this group consumed multivitamin supplements less frequently, and it is possible they perceived their "healthy diet consumption" negated the need for the recommended daily supplement in pregnancy. In contrast, South Asian women who adhered most strongly to the plant-based diet were more recent immigrants to Canada, had lower income, and were living with more extended family members, indicating more traditional cultural practices compared to the South Asian women who were low adherers to the plant-based diet. More recent immigrants with a high adherence to a plant-based diet also had greater multivitamin use compared to South Asians who were longer settled in Canada. The relationship between immigration and diet is complex due to the numerous and varied factors that influence acculturation within each ethnic group and country.[38-40] Thus, policy recommendations for dietary guidelines should consider the socioeconomic profile of the population. Although recent evidence suggests that plant-based diets may improve health and reduce risk of disease,[41,42] our observations suggest that the food composition of the plant-based diets matters. Emphasis should likely be placed on whole foods, minimally processed and non-refined items. In light of this, dietary counselling and antenatal practitioners should tailor dietary guidance to match the socioeconomic status and ethnicity of the patient whenever possible.

Our study has several strengths including prospective data collection, large sample size, adequate power to allow for comparisons between ethnic groups, and detailed measurement of diet using validated, ethnic-specific FFQs. There are some limitations of our analyses including self-reported retrospective food intake, the inability to account for differences in cooking methods, and residual confounding which is a potential bias in all cohort studies. To minimize this potential bias, we conducted a sensitivity analysis and excluded mothers who may have deliberately altered their diet

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due to a medical condition such as diagnosed gestational diabetes or hypertension in pregnancy. After these exclusions, our results remained consistent.

CONCLUSION

Maternal consumption of a plant-based diet during pregnancy is associated with infant birthweight. Among white Europeans a plant-based diet is associated with lower birthweight, reduced odds of LGA and increased odds of SGA babies, whereas among South Asians living in Canada, a plant-based diet is associated with higher birthweight. Future studies are necessary to replicate these results and to elucidate potential mechanisms which underlie these ethnic-specific associations.

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FIGURE LEGENDS

Figure 1 - Multivariable regression of plant-based diet pattern and birthweight stratified by ethnicity.

Association between maternal adherence to a plant-based diet, whereby a higher score reflects greater adherence to the dietary pattern, and birthweight in white Europeans (dashed line; n=2,367) and South Asians (solid line; n=884) after accounting for covariates: pre-pregnancy weight, maternal height, maternal smoking status, number of children, and infant gestational age and sex. Dotted line = 95% confidence interval.

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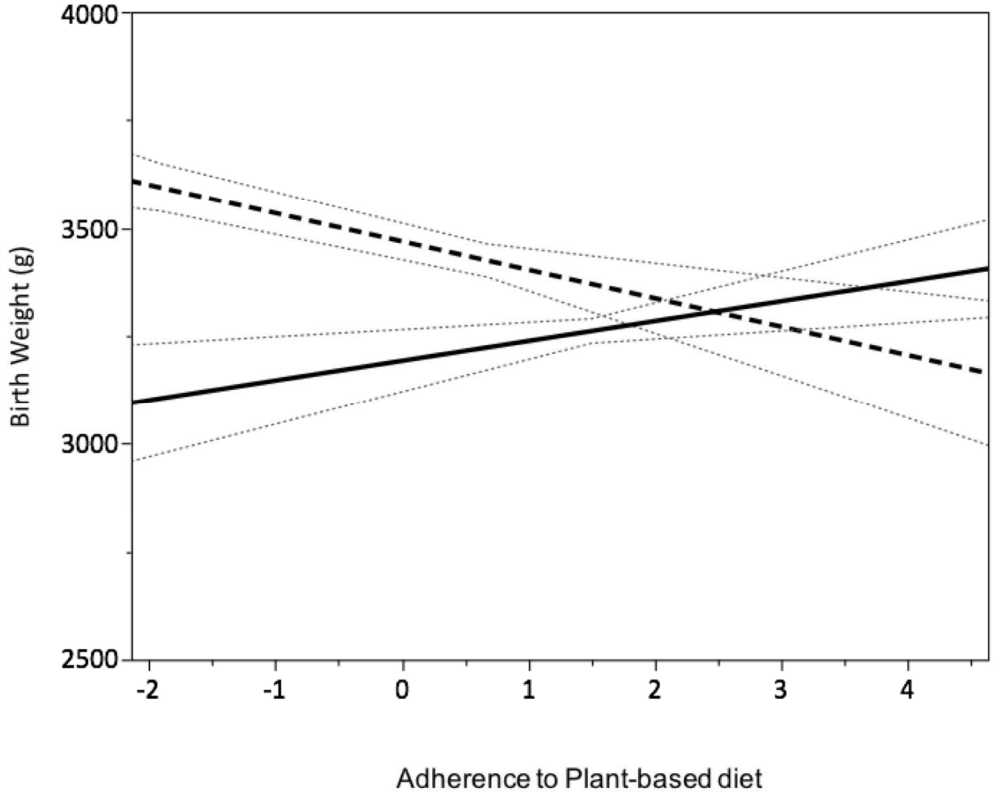

Figure 1 - Multivariable regression of plant-based diet pattern and birthweight stratified by ethnicity.

Association between maternal adherence to a plant-based diet, whereby a higher score reflects greater adherence to the dietary pattern, and birthweight in white Caucasians (dashed line; n=2,367) and South Asians (solid line; n=884) after accounting for covariates: pre-pregnancy weight, maternal height, maternal smoking status, number of children, and infant gestational age and sex. Dotted line = 95% confidence interval.

93x75mm (600 x 600 DPI)

Supplemental Digital Content

eTable 1 - Food groups with a loading ≥ |0.30| whose presence or absence characterize each of the three dietary patterns.

Food Group	Plant-based	Western	Health Conscious
Fats		0.55	
Full Fat Dairy			
Low Fat Dairy	0.39	0.42	
Fermented Dairy	0.61		
Meat	(-0.35)	0.43	0.34
Eggs			0.36
Organ Meats			
Fish and Seafood			0.50
Processed Meats		0.55	
Meat Dishes			0.49
Poultry and Waterfowl			0.36
Fried Foods			
Leafy Greens			0.38
Cruciferous Vegetables			0.56
Legumes	0.62		
Fresh Seasonings	0.72		
Starchy Vegetables		0.43	
Vegetable Medley	0.42		0.47
Other Vegetables	0.70		0.32
Tofu			
Fruits			0.53
Whole Grains	0.71		
Refined Grains			0.35
Pasta		0.54	
Pizza		0.32	
French Fries		0.47	
Non-Meat Dishes	0.63		
Stir-Fried Dishes			0.47
Snacks		0.42	
Nuts and Seeds			0.34
Sweets		0.46	
Condiments		0.47	0.41
Tea	0.56		
Coffee		0.34	
Sweet Drinks		0.56	
Artificial Sweets			
Eigenvalue	4.05	3.18	3.06
Cumulative Variation	0.11	0.20	0.29

[1]Proportion of the total dietary variation in the dataset that is explained by considering 1, 2, or 3 underlying dietary patterns.

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eTable 2– Comparison of reported daily consumption frequencies (servings/d) of common food groups by White Caucasian and South Asian women, divided by 1st and 4th quartile.

	Plant-Based Diet Adherence					
	White Caucasian		South Asian		White Caucasian vs South Asian	
Food	Quartile 1	Quartile 4	Quartile 1	Quartile 4	Quartile 1	Quartile 4
Dairy	3.4 (2.6)	3.9 (2.1)	2.5 (1.7)	3.3 (2.3)*	0.306	<0.001
Eggs	0.1 (0.1)	0.3 (0.3)*	0.6 (0.6)	0.2 (0.3)*	<0.001	0.002
Fish	0.1 (0.1)	0.2 (0.2)*	0.1 (0.3)	0.0 (0.1)*	0.03	<0.001
Poultry	0.3 (0.2)	0.2 (0.2)	0.3 (0.3)	0.1 (0.2)*	0.948	<0.001
Red Meat	0.6 (0.3)	0.4 (0.2)*	0.4 (0.4)	0.0 (0.1)*	0.013	<0.001
Breads and Rice	2.7 (2.7)	1.9 (1.1)	3.0 (3.3)	3.8 (1.5)*	0.73	<0.001
Legumes	0.1 (0.1)	0.2 (0.2)*	0.4 (0.4)	0.8 (0.7)*	<0.001	<0.001
Fruit	2.5 (2.5)	2.6 (1.5)	2.5 (2.4)	2.1 (1.4)*	0.97	<0.001
Raw Vegetables	0.8 (0.8)	1.3 (0.9)	1.4 (4.2)	2.7 (1.6)*	0.10	<0.001
Cooked Vegetables	1.3 (0.9)	2.3 (1.3)*	2.2 (1.5)	4.3 (2.2)*	0.01	<0.001
Fried Foods	1.2 (1.0)	0.2 (0.2)	0.4 (0.4)	0.2 (0.2)*	0.02	0.421
Nuts and Seeds	0.4 (0.5)	0.6 (0.6)*	0.3 (0.6)	0.2 (0.3)*	0.57	<0.001
Convenience Foods	1.7 (0.8)	1.3 (0.9)	0.3 (0.7)	0.2 (0.4)*	<0.001	<0.001
Sweet Drinks	4.3 (2.5)	2.2 (1.7)*	0.8 (1.0)	0.5 (0.7)*	<0.00	<0.001
Sweets	2.2 (1.7)	2.1 (1.5)	1.4 (1.3)	1.1 (0.9)	0.15	<0.001
Multivitamin (%)	94.0%	79.3%*	66.3%	78.1%*	<0.001	0.72
Married (%)	93.0%	95.8%*	100.0%	100.0%	<0.001	0.002
Years in Canada (yrs)	28.8 (7.4)	29.5 (8.8)	11.3 (10.3)	7.0 (5.5)*	<0.001	<0.001
Adults living in household (n)	2.2 (0.6)	2.1 (0.7)	3.0 (1.5)	3.5 (1.7)*	<0.001	<0.001
Any Post-Secondary Education (%)	74.1%	93.4%*	87.3%	75.4%*	<0.001	<0.001
Currently Employed (%)	80.2%	88.2%*	55.1%	53.7%	<0.001	<0.001
Household Income ≥ *$ 60K/yr (%)*	85.5%	88.6%	55.9%	33.5%*	<0.001	<0.001

Consumption of foods were compared using t-tests. Data are reported as mean servings per day and standard deviation. Quartiles are in white Caucasians (n=2367) and South Asians (n=884). *p<0.05 between Q1 vs Q4.

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eTable 3— Multivariable regression in South Asians (n=884) of the role of 'cooked vegetables' in the association between the plant-based diet pattern and birthweight.

	With Plant-based diet		Without Plant-based diet	
Variables	β	P value	β	P value
Intercept	-4188.2	<0.001	-4136.4	<0.001
Pre-Pregnancy Weight (kg)	5.1	<0.001	5.1	<0.001
Maternal Height (cm)	5.9	0.007	5.9	0.008
Parity (# of children)	44.1	0.009	46.2	0.006
Gestational age (wks)	154.5	<0.001	154.8	<0.001
Infant Sex (Female = 1)	-93.9	<0.001	-93.5	<0.001
Plant-Based	37.9	0.041	ns	ns
Cooked Vegetables	7.4	0.376	15.6	0.034

The same covariates were included for each ethnic-specific model but non-significant covariates (e.g., 'smoking' in South Asians) were removed in the final model (denoted as 'ns'). Parity was reported as having 0, 1, 2, 3, 4, 5, or 6 (or more) children. The consumption of 'cooked vegetables' includes all vegetables asked within the food frequency questionnaire that were not stated as 'raw'. The consumption of 'cooked vegetables' includes all vegetables asked within the food frequency questionnaire that were not stated as 'raw'.

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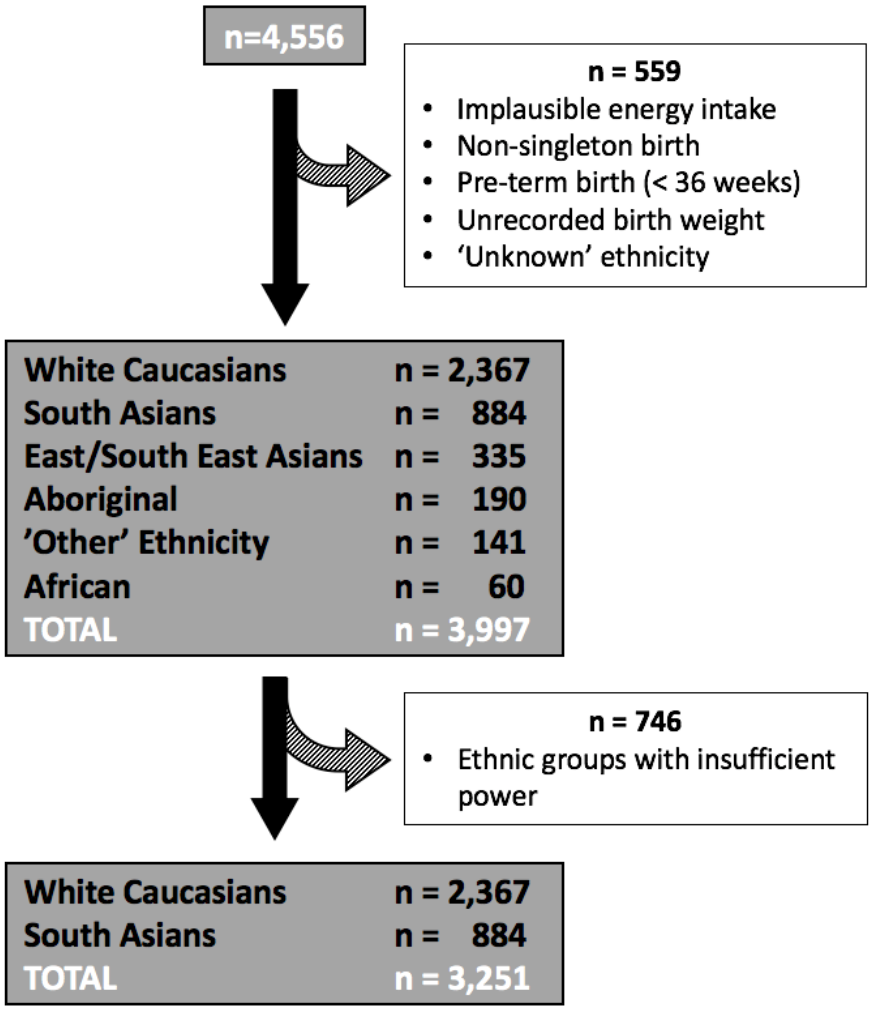
eFigure 1 – Schema of participant inclusion and exclusion



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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (PAGE 2)
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found (PAGE 2)
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported (PAGE 4)
Objectives	3	State specific objectives, including any prespecified hypotheses (PAGE 4)
Methods		
Study design	4	Present key elements of study design early in the paper (PAGES 4 - 5)
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection (PAGES 4 - 5)
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (PAGE 5 and eFigure1) ~~*Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls~~ ~~*Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants~~
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed (PAGE 15) ~~*Case-control study*—For matched studies, give matching criteria and the number of controls per case~~
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable (PAGE 5, 6, AND 10)
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group (PAGE 5 AND 6)
Bias	9	Describe any efforts to address potential sources of bias (PAGE 13)
Study size	10	Explain how the study size was arrived at (PAGE 4,5 AND eFigure1)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why (PAGE 10)
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (PAGE 10)
		(*b*) Describe any methods used to examine subgroups and interactions (PAGE 10 AND 15)
		(*c*) Explain how missing data were addressed (PAGE 5)
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed (N/A) ~~*Case-control study*—If applicable, explain how matching of cases and controls was addressed~~ ~~*Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy~~
		(*e*) Describe any sensitivity analyses (PAGE 13)

Continued on next page

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Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (PAGE 4,5 AND eFigure1)
		(b) Give reasons for non-participation at each stage (PAGE 4,5 AND eFigure1)
		(c) Consider use of a flow diagram (eFigure1)
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (Table 1)
		(b) Indicate number of participants with missing data for each variable of interest (PAGE 10)
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount) (PAGE 6)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time (TABLE 1)
		~~*Case-control study*—Report numbers in each exposure category, or summary measures of exposure~~
		~~*Cross-sectional study*—Report numbers of outcome events or summary measures~~
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (PAGE 10)
		(*b*) Report category boundaries when continuous variables were categorized (PAGE 15)
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period (N/A)
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses (PAGE 13)
Discussion		
Key results	18	Summarise key results with reference to study objectives (PAGE 15)
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias (PAGE 19)
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence (PAGE 19)
Generalisability	21	Discuss the generalisability (external validity) of the study results (PAGE 19)
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based (PAGE 20)

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Does the impact of a plant-based diet during pregnancy on birthweight differ by ethnicity? A dietary pattern analysis from a prospective Canadian birth cohort Alliance

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Complete List of Authors:	Zulyniak, Michael; McMaster University, Department of Medicine; University Of Leeds, School of Food Science and Nutrition de Souza, Russell; McMaster University, Department of Health Research Methods, Evidence, and Impact Shaikh, Mateen; McMaster University, Department of Health Research Methods, Evidence, and Impact Desai, Dipika; McMaster University, Department of Medicine Lefebvre, Diana; McMaster University, Department of Medicine Gupta, M; McMaster University, Department of Medicine; Canadian Cardiovascular Research Network Wilson, Julie; Six Nations Health Services Wahi, Gita; McMaster University, Department of Health Research Methods, Evidence, and Impact; McMaster University, Department of Paedeatrics Subbarao, Padmaja; University of Toronto, Department of Paediatrics; Hospital for Sick Children Becker, Allan; University of Manitoba, Department of Immunology Mandhane, Piush; University of Alberta, Department of Pediatrics Turvey, Stuart; University of British Columbia, Department of Paediatrics Beyene, Joseph; McMaster University, Department of Health Research Methods, Evidence, and Impact Atkinson, S; McMaster University, Department of Paediatrics Morrison, Katherine; McMaster University, Department of Pediatrics McDonald, Sarah; McMaster University, Obstetrics/Gynecology Teo, Koon; Population Health Research Institute; McMaster University, Department of Medicine Sears, Malcolm; McMaster University, Department of Medicine Anand, Sonia; McMaster University, Department of Medicine; McMaster University, Department of Health Research Methods, Evidence, and Impact
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Title: Does the impact of a plant-based diet during pregnancy on birthweight differ by ethnicity? A dietary pattern analysis from a prospective Canadian birth cohort Alliance

Corresponding Author: Dr. Sonia S. Anand, McMaster University, 1280 Main St. W., MDCL-3204, Hamilton, ON L8S 4K1, Email: anands@mcmaster.ca, Ph. 905.525.9140 x 21523

Authors: Michael A. Zulyniak[1,2]*; Russell J. de Souza[3]*; Mateen Shaikh[3]; Dipika Desai[1,4]; Diana L. Lefebvre[1]; Milan Gupta[1,5]; Julie Wilson[6]; Gita Wahi[3,7]; Padmaja Subbarao[8]; Allan B. Becker[9]; Piush Mandhane[10]; Stuart E. Turvey[11]; Joseph Beyene[3]; Stephanie Atkinson[7]; Katherine Morrison[7]; Sarah McDonald[3]; Koon K. Teo[1,4]; Malcolm R. Sears[1]; Sonia S. Anand[1,3,4] for the *NutriGen* Alliance investigators

Author Affiliations:

[1] Department of Medicine, McMaster University, Hamilton, ON, Canada;

[2] School of Food Science and Nutrition, University of Leeds, Leeds, UK;

[3]Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, ON, Canada;

[4]Population Health Research Institute, Hamilton Health Sciences and McMaster University, Hamilton, ON, Canada;

[5]Canadian Cardiovascular Research Network, Brampton, ON, Canada;

[6]Six Nations Health Services, Ohsweken, ON, Canada;

[7]Department of Paediatrics, McMaster University, Hamilton, ON, Canada;

[8]Hospital for Sick Children & Department of Paediatrics, University of Toronto, Toronto, ON, Canada;

[9]Department of Immunology, Faculty of Medicine, University of Manitoba, Winnipeg, MB, Canada;

[10]Department of Pediatrics, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, AB, Canada;

[11]BC Children's Hospital, Department of Paediatrics, Faculty of Medicine, University of British Columbia, Vancouver, BC, Canada.

*authors contributed equally

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ABSTRACT

OBJECTIVE. Birthweight is an indicator of newborn health and a strong predictor of health outcomes in later life. Significant variation in diet during pregnancy between ethnic groups in high-income countries provides an ideal opportunity to investigate the influence of maternal diet on birthweight.

SETTING. Four multi-ethnic birth cohorts based in Canada (The NutriGen Alliance).

PARTICIPANTS. 3,997 full-term mother-infant pairs of diverse ethnic groups with principal component analysis (PCA)-derived diet pattern — plant-based, Western, health-conscious — and birthweight data.

RESULTS. No associations were identified between the Western and health-conscious diet patterns and birthweight; however, the plant-based dietary pattern was inversely associated with birthweight (β=-67.6g per 1-unit increase; P<0.001) and an interaction with non-white ethnicity and birthweight was present. Ethnically stratified analyses demonstrated that among white Europeans, maternal consumption of a plant-based diet associated with lower birthweight (β=-65.9g per 1-unit increase; P<0.001), increased risk of small for gestational age (SGA; OR=1.46; 95%CI:1.08-1.54;P=0.005), and reduced risk of large for gestational age (LGA;OR=0.71; 95%CI:0.53-0.95;P=0.02). Among South Asians, maternal consumption of a plant-based diet associated with a higher birthweight (β=+40.5g per 1-unit increase; P=0.01), partially driven by cooked vegetable consumption.

CONCLUSIONS. Maternal consumption of a plant-based diet during pregnancy is associated with birthweight. Among white Europeans, a plant-based diet is associated with lower birthweight, reduced odds of an infant born LGA, and increased odds of SGA, whereas among South Asians living in Canada, a plant-based diet is associated with increased birthweight.

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'Strengths and limitations of this study'

1. Strengths - Prospective data collection, large sample size, adequate power to allow for ethnic comparisons, and detailed measurement of diet using ethnic-specific FFQs;
2. Limitations - Self-reported retrospective food intake, the inability to adjust for differences in cooking methods, and residual confounding which is a potential bias in all cohort studies;
3. Strength - To minimize potential bias, a sensitivity analysis was conducted, which excluded mothers who may have deliberately altered their diet due to a medical condition.

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INTRODUCTION

Birthweight is an indicator of infant health and a strong predictor of future health outcomes.[1] Infants born small (birthweight<10th%ile) or large (birthweight>90th%ile) for gestational age are at increased risk of future health complications, including asthma,[2] obesity,[3] and cardiovascular disease (CVD).[4] High-income countries generally have similar proportions of babies who weigh <2500g at birth but there is greater variation (up to 10%) in the proportion of infants born >4000g.[5-7] However, such population figures often mask important differences in the distribution of birthweight between ethnic groups. In the United States, white Europeans have more high- (9.6%) than low-birthweight infants (7.0%); African Americans have more low- (13.1%) than high-birthweight infants (4.3%); and Hispanics have an equal proportion (7.1% high- and 7.1% low-birthweight).[5] Furthermore, we recently reported that newborns in Canada of South Asian ancestry (those who originate from the Indian subcontinent) are of lower birthweight, and that Aboriginal newborns are of higher birthweight compared to full term newborns of white European ancestry in Canada.[8] This provides additional evidence that among full term newborns, ethnic differences in birthweight distribution exist. Numerous factors influence birthweight, including gestational weight gain, maternal pre-pregnancy weight, maternal height, gestational diabetes, and fetal smoke exposure.[9,10] It has been postulated that maternal dietary intake also influences birthweight.[11,12] The investigation of specific food items and nutrients has advanced our understanding of specific nutrient deficiency syndromes (e.g. neural tube defects) and facilitated the identification of particularly harmful food components (e.g., trans-fats). However, single-nutrient studies may be misleading because they fail to capture the complex interplay between foods and nutrients consumed as meals over long periods of time. To overcome this, the empirical derivation of dietary patterns[13] has been proposed as a method to characterize diet that more accurately reflects how we consume foods and nutrients, and these patterns can be assessed for their associations with health and disease.

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Using dietary patterns, we investigated the association between maternal diet and birthweight in a multi-ethnic cohort.

METHODS

Study Population. The NutriGen Alliance[13] is a consortium of four birth cohorts in Canada investigating the contribution of nutritional, genetic, and epigenetic factors to the health of pregnant women and their children—(i) Canadian Healthy Infant Longitudinal Development[14] study (CHILD); (ii) Family Atherosclerosis Monitoring In earLY life (FAMILY)[15]; (iii) SouTh Asian birth cohoRT (START)[16]; and (iv) Aboriginal Birth Cohort (ABC)[17]. Of these, ABC is still recruiting. To date (October 2016), 5018 pregnant women have provided comprehensive clinical and dietary data and 4556 (≈90.8%) have provided birth data. From this group, 559 women were excluded from the present analysis because they (i)reported an implausible energy intake (<500 or ≥6500kcal/d), (ii)were non-singleton pregnancies, (iii)delivered pre-term (<36 weeks), and/or (iv)reported not knowing their ethnic origin. Pre-term infants were excluded to reduce the risk of confounding of infants born early (and very-low birthweight) due to pregnancy complications (e.g., trauma, stress, infections, or placenta previa).The remaining 3997 full-term infant-mothers represented multiple maternal self-reported ethnicities—White European (n=2367), South Asian (n=884), East/South East Asian (n=335), Aboriginal (n=190), African (n=60) and women who reported another ethnicity (n=141, e.g.,Egyptian, Haitian, etc.).(eFigure 1) Ethical approval was obtained independently for all studies from the Hamilton Integrated Research Ethics Board — CHILD (REB 07-2929), FAMILY (REB 02-060), START (REB 10-640), and ABC (REB 12- 152). Additional approval for ABC was obtained from the Six Nations Band Council. Informed written consent was obtained from each participant within each study. Data sharing is currently not available for most data due to ethnical restrictions.

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Dietary Assessment. Dietary information during pregnancy was collected in each cohort 24-28 weeks gestation using a validated semi-quantitative food-frequency questionnaire (FFQ). The CHILD cohort used a version of the Fred Hutchinson Cancer Center tool.[18] The FAMILY, START, and ABC cohorts used ethnic-specific FFQs developed for the Study of Health and Risk in Ethnic Groups (SHARE) study.[13,16,17]

Diet Pattern Analysis. Detailed methods of FFQ harmonization and the statistical derivation of dietary patterns within the NutriGen cohort have been previously described.[13] We performed principal component analysis (PCA) to identify 3 orthogonal dietary patterns—'plant-based', 'western', and 'health-conscious' (eTable 1).This approach retains the information of the quantitative data from the original FFQ but shifts the focus from individual food components to food combinations. An empirically derived measure of adherence (i.e., loading scores) for each person to each of the individual dietary patterns is calculated in the PCA. The PCA loading scores for each individual were adjusted to the mean total population caloric intake (2500 kcal/day) using the residual method.[19]

Clinical Parameters: The primary outcome of this analysis was newborn birthweight. Birthweight was collected from the birth chart or measured in duplicate by trained staff perinatally (median<24hrs;95%≤48 hrs). Due to the ethnic-diversity of the study population, sex- and ethnic-specific birthweight cut points were used to define infants born small (SGA<10th%ile) or large (LGA≥90th%ile) for gestational age, which demonstrate greater accuracy to identify risk in multi-ethnic cohorts.[20] Gestational age was determined by ultrasound at the initial visit. Data on all clinical parameters are provided in Table 1.

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Table 1 - Participant characteristics.

Variable	Overall	White European	South Asian	East/South East Asian	Aboriginal	Other Ethnicity	African	P value*
Number	3997	2367	884	335	190	141	60	
Maternal								
Age at enrollment (years)	31.6 (4.7)	32.1 (4.6)	30.2 (4.0)	33.1 (4.2)	28.0 (6.0)	32.2 (5.1)	31.2 (5.4)	<0.001
Height (cm)	164.4 (6.9)	166.0 (6.5)	162.2 (6.4)	160.2 (6.6)	165.3 (6.9)	161.5 (6.3)	163.7 (7.7)	<0.001
Pre-Pregnancy Weight (kg)	66.8 (13.9)	69.1 (14.1)	62.4 (11.9)	58.7 (9.2)	75.4 (16.9)	64.3 (10.6)	69.7 (14.2)	<0.001
Pre-Pregnancy BMI (kg/m^2)	24.7 (4.8)	25.1 (5.0)	23.7 (4.4)	23.0 (3.3)	27.6 (6.2)	24.8 (4)	26 (4.8)	<0.001
Final Pregnancy Weight (kg)	81.4 (15.7)	84.2 (16.2)	76.5 (12.7)	72.4 (12.5)	91.3 (22.7)	80.1 (14.1)	83.1 (14.8)	<0.001
Primiparous (%)	49.8%	51.3%	41.8%	59.7%	40.8%	58.9%	45.0%	<0.001
Gestational Diabetes (%)	11.3%	7.4%	24.2%	10.8%	4.2%	9.2%	5.0%	<0.001
Years lived in Canada	23.4 (12.2)	29.2 (8.3)	8.4 (7.8)	20.4 (12.5)	28.5 (5.8)	17.2 (12.4)	19.4 (12.6)	<0.001
Post-secondary Education (%)	85.1%	86.8%	84.7%	95.2%	52.9%	82.6%	85.0%	<0.001
Smoking During Pregnancy (%)								
Never Smoked	77.1%	70.4%	99.6%	87.7%	40.6%	71.6%	88.3%	<0.001
Quit Before Pregnancy	16.2%	21.8%	0.2%	9.9%	25.7%	21.3%	5.0%	<0.001

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Quit During Pregnancy	3.6%	4.3%	0.2%	1.8%	15.5%	5.7%	1.7%	<0.001
Currently Smoking	3.1%	3.5%	0.0%	0.6%	18.2%	1.4%	5.0%	<0.001
Household Income (%)								
Total Income ≥ $ 60K	77.2%	88.9%	43.5%	87.2%	48.1%	80.3%	68.3%	<0.001
Multivitamin Use (%)	85.8%	89.3 %	71.8%	95.9 %	91.4 %	87.4 %	83.4 %	<0.001
Vegetarianism (%)	12.3%	3.5%	37.1%	0.0%	0.0%	0.0%	0.0%	<0.001
Newborn								
Sex (% Male)	51.8%	52.3%	49.1%	52.2%	46.8%	58.2%	53.2%	0.42
Gestational Age (weeks)	39.6 (1.1)	39.7 (1.1)[a]	39.4 (1.1)[b]	39.4 (1.1)[bc]	39.6 (1.1)[ac]	39.8 (1)	39.5 (1.1)	<0.001
Birthweight (g)	3432 (466)	3493 (457)[a]	3265 (438)[b]	3330 (448)[c]	3567 (469)[d]	3456 (481)	3347 (468)	<0.001
Birth length (cm)	51.3 (2.5)	51.4 (2.5)[ab]	51.3 (2.5)[ab]	51.0 (2.4)[b]	51.6 (3.2)[a]	51.2 (2.3)	51.4 (2.4)	0.18
LGA (n)	370 (9.8%)	224 (9.9%)	87 (9.9%)	30 (9.2%)	18 (9.6%)	12 (9.0%)	10 (17%)	0.60
SGA (n)	348 (9.2%)	219 (9.6%)	83 (9.4%)	29 (8.9%)	14 (7.5%)	10 (7.4%)	1 (1.7%)	0.36

**Continuous measures (mean and standard deviation) were compared using ANOVA, categorical variables were compared using chi-square. Non-matching superscript letters indicate significant difference (p<0.05) between ethnic groups. Data on parity, pre-pregnancy weight, smoking history, ethnicity, post-graduate education, marital status, employment status, and total household income were self-reported. Maternal age, height, and gestational age of offspring at birth were obtained from participant medical records. Last measured maternal pregnancy weight was*

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obtained from medical records at time of birth (ABC, FAMILY, and START) or using a combination of medical records or maternal recollection (CHILD). Gestational Diabetes was determined either through (i) self-reported by the mother or recorded from the medical chart (CHILD), or (ii) diagnosed using an oral-glucose tolerance test, self-reported by the mother, or recorded from the medical chart (ABC, FAMILY, and START). SGA = ethnic-specific small for gestational age (birthweight < 10^{th} percentile for gestational age and sex); LGA = ethnic-specific large for gestational age (birthweight ≥ 90^{th} percentile for gestational age and sex).

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Statistical Analysis. The distribution of exposures and covariates were summarized using JMP (v.9.0.1)as means (SD) for continuous variables, or counts (%) for categorical variables; between groups, differences were assessed using ANOVA (continuous variables) or chi-square test (categorical variables).

Pre-pregnancy weights from the CHILD cohort were available for ≈73% of women. To impute missing weights, we constructed a multivariable model with white Europeans recruited in CHILD and FAMILY. The correlation between the value predicted by this equation and observed pre-pregnancy weight was 0.42.

Due to the numerous biological, sociological, and environmental variables that associate with birthweight, we aimed to identify a parsimonious set of covariates. All variables listed in Table 1 significant with birthweight as the response variable in a simple linear regression ($\alpha \leq 0.10$) were entered into a forward step-wise selection procedure. To account for perinatal reductions in weight,[21] timing of birthweight measurement was assessed as a covariate. Covariates significant at $\alpha < 0.05$ in the step-wise multivariable model were retained as covariates in the final model.

Multivariable linear regression was used to assess the association between maternal dietary patterns and covariates on infant birthweight. The main effects, ethnicity and each of the dietary patterns, were included in the initial model. Interaction terms between a dietary pattern and ethnicity were added if they were both significant $P<0.05$. To determine which foods contributed to the observed diet and birthweight association, food groups were added one at a time to the full dietary pattern-birthweight multivariable model. If the association between the dietary pattern and birthweight was rendered non-significant by the addition of the food group, we deemed it to be an important explanatory variable.

For ethnic specific analyses, we had adequate power to investigate the association between plant-based diet and birthweight within the two largest ethnic groups—white Europeans (>95% power) and South Asians (≈80% power) but <40% power to do so in the other ethnic groups. Therefore, stratified analyses by ethnic group were limited to white Europeans and South Asians.

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RESULTS

Demographic and Clinical Parameters. Maternal demographic and clinical parameters for each of the six ethnic groups are presented in Table 1.

Birthweight. There were significant differences in birthweight by ethnic group (P<0.001). Aboriginal newborns had the highest birthweight, followed by white Europeans, other ethnicity, African origin, East/South East Asians, and South Asians.(Table 1)

Effect of dietary patterns on birthweight. In the fully-adjusted main-effects multivariable model (Table 2,Model 1), non-white ethnicity and plant-based diet were significantly associated while the Western and Health-Conscious diet patterns were not. After removal of non-significant dietary patterns, an interaction between the plant-based diet and non-white ethnicity was tested and found to be significant (Table 2,Model 2).

Table 2 – Final multivariable regression of the association and interaction between diet patterns in white and non-whites with birthweight (g).

	Model 1		**Model 2**	
Variables	**β**	**P value**	**β**	**P value**
Intercept	-4551.9	<0.001	-4560.8	<0.0001
Pre-Pregnancy Weight (kg)	5.5	<0.001	5.4	<0.001
Maternal Height (cm)	8.4	<0.001	8.5	<0.001
Parity (# of children)	67.6	<0.001	66.0	<0.001
Gestational age (weeks)	158.4	<0.001	158.2	<0.001
Smoking Status	-21.9	0.04	-23.6	0.02

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Infant Sex (Female=1)	-118.6	<0.001	-118.8	<0.001
Non-White Ethnicity	-33.5	0.04	-28.1	0.08
Plant-Based Diet	-34.6	<0.001	-67.6	<0.001
Western Diet	-12.7	0.35	ns	ns
Health-Conscious Diet	6.0	0.56	ns	ns
Plant-Based Diet × non-White	n/a	n/a	40.5	0.03

Model 1 included all covariates, non-White ethnicity indicator, 3 diet patterns identified using PCA: plant-based, Western, and health-conscious diet. Model 2 tests interactions between Non-White ethnicity and significant diet patterns after removal of non-significant variables from Model 1. n=3,997. Non-significant variables removed from the model are denoted as 'ns'. Smoking status was ordinal and input as either 0 = never smoked, 1 = quit smoking pre-pregnancy, 2 = quit smoking during pregnancy, or 3 = currently smoking. Parity was ordinal and reported as having 0, 1, 2, 3, 4, 5, or 6 (or more) children. Non-whites included individuals that self-reported as being of South Asian, East/South East Asian, or Aboriginal descent.

Stratified Analyses. Multivariable models, stratified by ethnicity (white European and South Asian), and adjusted for the same covariates as the main model (except for smoking in South Asians, as its prevalence was <0.5%) were built, treating dietary pattern scores as either continuous (Table 3a) or dichotomous (4^{th} vs 1^{st} quartile) variables (Table 3b). In white Europeans, an inverse association was observed between plant-based diet and birthweight. Among South Asians, a positive association was observed between the plant-based diet and birthweight.(Figure 1).

Table 3 – Multivariable regression of plant-based diet pattern (as a continuous measure) and birthweight stratified by ethnicity: white European and South Asians

	White Europeans		**South Asians**	
Variables	**β**	**P value**	**β**	**P value**

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Intercept	-4723.7	<0.001	-4248.1	<0.001
Pre-Pregnancy Weight (kg)	5.1	<0.001	5.3	<0.001
Maternal Height (cm)	9.3	<0.001	6.0	0.01
Parity (# of children)	73.8	<0.001	43.5	0.01
Gestational age (wks)	159.3	<0.001	155.6	<0.001
Smoking Status	-37.6	0.002	ns	n/a
Infant Sex (Female = 1)	-127.7	<0.001	-98.3	<0.001
Plant-Based (Continuous)	-65.9	<0.001	40.5	0.01

White European r2 = 0.246, South Asian r2 = 0.178. The same covariates were included for each ethnic-specific model but non-significant covariates (e.g., 'smoking' in South Asians) were removed in the final model (denoted as 'ns'). Smoking status was coded as follows: 0 = never smoked, 1 = quit smoking pre-pregnancy, 2 = quit smoking during pregnancy, or 3 = currently smoking. Parity was reported as having 0, 1, 2, 3, 4, 5, or 6 (or more) children. White Europeans (n=2367) and South Asians (n=884).

A sensitivity analysis, which excluded mothers who were diagnosed with gestational diabetes and/or hypertension, resulted in dietary associations that were largely unchanged with a negative association remaining in white Europeans (β=-64.5g per 1-unit increase in score;n=2038;P=0.002) and a positive association in South Asians (β=38.3g per 1-unit increase in score;n=728;P=0.03).

In white Europeans, a 1-unit increase in plant-based diet score was associated with ≈50% increase in odds of SGA and a ≈30% decrease in odds of LGA (Table 4a). In South Asians, a 1-unit increase in plant-based diet score presented a non-significant reduction in odds of SGA (P=0.428) and non-significant increase in odds of LGA (P=0.249).(Table 4b)

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Table 4 Multivariable regression of plant-based diet pattern (as a categorical measure) and birthweight stratified by ethnicity: white European and South Asians

	White Europeans		South Asian	
Variables	**B**	**P value**	**β**	**P value**
Intercept	-5001.5	<0.001	-2482.3	<0.001
Pre-Pregnancy Weight (kg)	4.1	<0.001	6.8	<0.001
Maternal Height (cm)	9.4	<0.001	ns	ns
Parity (# of children)	77.1	<0.001	ns	ns
Gestational age (wks)	168.6	<0.001	135.6	<0.001
Smoking Status	ns	ns	ns	ns
Infant Sex (Female = 1)	-130.4	<0.001	-122.8	0.002
Plant-Based (4^{th} vs 1^{st} quartile)	-81.2	0.002	70.5	0.07

White European r^2 = 0.246; South Asian r^2 = 0.155. The same covariates were included for each ethnic-specific model but non-significant covariates (e.g., 'smoking' in South Asians) were removed in the final model (denoted as 'ns'). Smoking status was coded as follows: 0 = never smoked, 1 = quit smoking pre-pregnancy, 2 = quit smoking during pregnancy, or 3 = currently smoking. Parity was reported as having 0, 1, 2, 3, 4, 5, or 6 (or more) children. White Europeans (n=2367) and South Asians (n=884)

Validity of the Plant-Based Diet Score

The classification of individuals as plant-based consumers using the harmonized FFQ/PCA was validated against a classification using pre-harmonization FFQ data. Using the raw number of servings obtained by each study-specific FFQ, the sum of servings for five plant-based foods groups common across all FFQs—i.e., total dairy, vegetables, legumes, fruit, and breads and rice—was calculated. There was a high-degree of agreement between pre- and post-harmonized scores with

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>90% of the same plant-based consumers being classified in the 4th quartile using either metric (P<0.001).

Diet Comparison

The food groups among individuals in the 4th quartile of the plant-based diet were compared between white Europeans and South Asians to understand the ethnic-specific structure of plant-based diets. For white Europeans, the plant-based diet was characterized by high intakes of fruit, nuts and seeds, convenience foods, sweet drinks, sweets, eggs, and moderate intakes of fish, poultry, red meat, while the South Asian plant-based diet was characterized by higher intakes of South Asian breads (e.g., roti, naan), rice, legumes, raw vegetables, and cooked vegetables.(eTable 2) The use of multivitamins was comparable amongst high consumers of the plant-based diet in white Europeans (79%) and South Asians (78%), but differed in the low consumers of the plant-based diet with white Europeans (94%) consuming significantly more multivitamins than South Asians (66%).

Among white Europeans, higher levels of post-secondary education, employment and marriage were observed in the 4th versus the 1st quartile of the plant-based diet, while South Asians in the 4th quartile were more likely to have recently immigrated to Canada, live with extended family in their household, and were less likely to have post-secondary education compared to quartile 1.(eTable 2)

Food Groups. *Post hoc* analyses were conducted separately in white Europeans and South Asians, and used 15 mutually exclusive food groups (eTable 2) that showed a high-degree of variance between the individuals in the 1st and 4th quartiles of the plant-based diet. Only the addition of "cooked vegetables" to the model reduced the magnitude of the plant-based dietary pattern association in South Asians (β=37.9g;P=0.041)(eTable 3). No other foods influenced the association of plant-based diet and birthweight in either ethnic group. Multivitamin use had no influence on the association.

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Effect of Total Energy intake on Birthweight. To investigate the effect of maternal energy intake on birthweight, we evaluated the association between total energy intake and birthweight in our population of white Europeans and South Asians with and without an interaction term for non-white ethnicity. Without ethnicity or its interaction term, we note there is a significant association between total maternal energy intake and infant birth weight, whereby a 100 calorie increase in total energy associated with 4g [2, 7g] increase in birthweight (P<0.01). When ethnicity and its interaction term (energy intake*non-white ethnicity) were included in the model, total energy intake and the interaction term were no longer significant (P>0.05), whereas ethnicity remained so (P<0.01), indicating that a South Asian newborn was estimated to weigh 231 g less [-266, -197g] than a white European newborn.

DISCUSSION

Among women living in a high-income country, ethnicity was a predictor of birthweight, independent of caloric intake, in white Europeans and South Asians. Foods and diet differ substantially between ethnic groups, and may contribute to the association. A plant-based diet in pregnancy is associated with newborn birthweight, the effects of which are moderated by ethnicity. In white European women, consumption of a plant-based diet is associated with lower birthweight, an increased risk of a SGA infant, and a reduced risk of a LGA infant, while in South Asian women the plant-based diet is associated with higher birthweight but had no significant effect on the risk of having an SGA or LGA infant.

Our findings are consistent with a recent systematic review which failed to find a consistent association of vegetarian diets on birthweight; five studies reported vegetarian mothers had lower birthweight babies, and two studies reported higher birthweights.[22] The interpretation of the studies was complicated by (i) the numerous ethnic groups investigated, (ii) differences in the foods that characterized the vegetarian and non-vegetarian (i.e., control) groups within each of the

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reported studies, and (iii) variability in the socio-economic status of individuals on a vegetarian diet. This is compatible with our finding that birthweight was not associated with self-reported vegetarianism, which may be partly explained by the high degree of variability in the foods that comprise a plant-based diet across ethnic groups, which persisted even among those residing in a similar geographic region. This suggests that 'vegetarianism' may be too crude a descriptor of diet to allow for discovery of true associations with birthweight, because the definition of this term is qualitatively different across ethnic groups.

Studies investigating the effect of a plant-based diet in ethnically homogenous populations are sparse. No study in pregnant South Asian women living in a high-income country has reported on dietary patterns and birthweight. However, our findings in white Europeans are consistent with previous work indicating that smoking is associated with reduced birthweight [23], an increased risk of SGA[24], reduced risk of LGA[25], and that increased parity, maternal weight and height are associated with a reduced risk of SGA[26] and increased risk of LGA[25]. Concerning diet, a previous study in white Europeans (n=38)[27] reported that infants born to mothers whose diets were classified as 'plant-based' were lighter (3310g;95%CI:3080-3350g) than infants born to 'omnivore' mothers (3480g;95%CI:3350-3620g). The Danish National Birth Cohort (n=44612), reported that mothers adhering to a plant-based dietary pattern were at reduced risk of having an SGA infant (OR=0.74;95%CI:0.64–0.86) compared to mothers adhering to a Western diet pattern.[28] However, this observation may be confounded by the high prevalence of smoking during pregnancy in the Western diet (38%) vs plant-based diet group (14%).

Our investigation to determine which of the individual food groups characteristic of the plant-based diet may be driving the association revealed that controlling for cooked vegetables reduced the strength and significance of the association between the plant-based diet and birthweight in South Asians but not among white Europeans. In South Asians, cooked vegetables were independently associated with birthweight (after removing plant-based dietary pattern from the model), whereas

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multivitamin use was not. This suggests that consumption of 'cooked vegetables' may be a driver of the observed association between the plant-based diet and increased birthweight in South Asians. Prior cohort studies from India have shown that lower levels of serum vitamin B12[29] and folate in pregnancy are associated with low-birthweight.[30] In a randomized controlled trial, prenatal supplementation with vitamins A, D, E, C, and B, as well as iron, zinc, copper, selenium, and iodine reduced the risk of low-birthweight (RR=0.88;95%CI:0.85-0.91)[31] . In the slum-dwelling population of Mumbai (India), micronutrient-rich snacks (green leafy vegetables, fruit, and milk) consumed before or during pregnancy increase infant birthweight (+48g; 95%CI:1-96g) compared to a low-micronutrient snack (potato and onion).[32] However, the dietary context in Canada differs substantially from that of low income countries. Since 1998 flour and cereals have been fortified with folate. [33] This, coupled with relatively high rates of multivitamin supplementation in pregnancy, makes folate and vitamin B12 deficiency in pregnancy unlikely among Canadians. In addition, women who avoid meat products yet consume milk, yoghurt, cheese, and eggs usually attain adequate vitamin B12. Thus, even in the context of virtually no dietary folate and vitamin B12 deficiency, high consumption of cooked vegetables as part of a traditional Indian diet is associated with higher birthweight compared to a lower plant-based/higher animal protein diet.

We can only speculate about the mechanisms underlying the association with cooked vegetables as we did not collect detailed information on cooking methods. In our study, South Asian women reported consuming a higher percentage of energy from fat than did white Europeans. Differences in food preparation methods can significantly alter the chemical and nutritional composition of dishes.[34] This was recently examined using spectrophotometry to determine the chemical composition of fresh and fried portions of ovo-vegetarian dishes.[35] Fried ovo-vegetarian dishes prepared in oil were lower in protein, fibre, and carbohydrate content but higher in caloric and lipid content per 100g serving, compared to fresh dishes[35]. This aligns with work in pregnant South Asian women residing in East London (UK), who had a higher proportion of energy from fat (40% energy) compared to other ethnic groups (white European, African, and African-Caribbean).[36]

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Further, a prospective birth study of 797 rural Indian women, reported that, although protein and carbohydrate intake at 18 weeks of gestation were unrelated to birth measurements, fat intake was associated with newborn length and adiposity.[37] This suggests that South Asian cooking methods may alter the macronutrient composition of food by increasing the proportion of total fat relative to other nutrients, and offers a possible explanation regarding the difference in the association between the plant-based diet and birthweight in South Asians and white Europeans.

Although markers of socio-economic status (SES) were not significantly associated with birthweight, understanding differences in sociodemographic factors between high and low consumers of the plant-based diet is informative to understand the context in which these diets are consumed. In the ALSPAC birth cohort (n=11833), SES was not associated with birthweight but was associated with food choices whereby women of high SES consumed more healthy foods and less processed foods than women of a lower SES.[23] In the present study, white European women who adhered most strongly to the plant-based diet represented the highest socioeconomic group compared to less adherent white European women. Interestingly this group consumed multivitamin supplements less frequently, and it is possible they perceived their "healthy diet consumption" negated the need for the recommended daily supplement in pregnancy. In contrast, South Asian women who adhered most strongly to the plant-based diet were more recent immigrants to Canada, had lower income, and were living with more extended family members, indicating more traditional cultural practices compared to the South Asian women who were low adherers to the plant-based diet. More recent immigrants with a high adherence to a plant-based diet also had greater multivitamin use compared to South Asians who were longer settled in Canada. The relationship between immigration and diet is complex due to the numerous and varied factors that influence acculturation within each ethnic group and country.[38-40] Thus, policy recommendations for dietary guidelines should consider the socioeconomic profile of the population. Although recent evidence suggests that plant-based diets may improve health and reduce risk of disease,[41,42] our observations suggest that the food

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composition of the plant-based diets matters. Emphasis should likely be placed on whole foods, minimally processed and non-refined items. In light of this, dietary counselling and antenatal practitioners should tailor dietary guidance to match the socioeconomic status and ethnicity of the patient whenever possible.

Our study has several strengths including prospective data collection, large sample size, adequate power to allow for comparisons between ethnic groups, and detailed measurement of diet using validated, ethnic-specific FFQs. There are some limitations of our analyses including self-reported retrospective food intake, the inability to account for differences in cooking methods, and residual confounding which is a potential bias in all cohort studies. To minimize this potential bias, we conducted a sensitivity analysis and excluded mothers who may have deliberately altered their diet due to a medical condition such as diagnosed gestational diabetes or hypertension in pregnancy. After these exclusions, our results remained consistent.

CONCLUSION

Maternal consumption of a plant-based diet during pregnancy is associated with infant birthweight. Among white Europeans a plant-based diet is associated with lower birthweight, reduced odds of LGA and increased odds of SGA babies, whereas among South Asians living in Canada, a plant-based diet is associated with higher birthweight. Future studies are necessary to replicate these results and to elucidate potential mechanisms which underlie these ethnic-specific associations.

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FIGURE LEGENDS

Figure 1 - Multivariable regression of plant-based diet pattern and birthweight stratified by ethnicity.

Association between maternal adherence to a plant-based diet, whereby a higher score reflects greater adherence to the dietary pattern, and birthweight in white Europeans (dashed line; n=2,367) and South Asians (solid line; n=884) after accounting for covariates: pre-pregnancy weight, maternal height, maternal smoking status, number of children, and infant gestational age and sex. Dotted line = 95% confidence interval.

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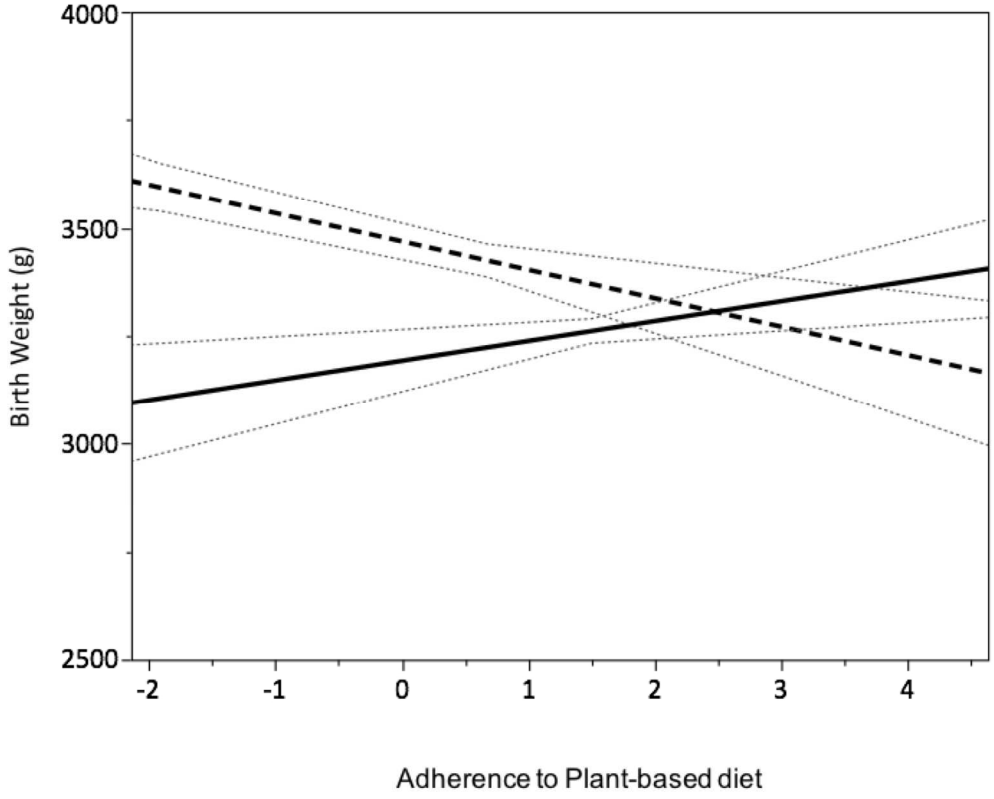

Figure 1 - Multivariable regression of plant-based diet pattern and birthweight stratified by ethnicity.

Association between maternal adherence to a plant-based diet, whereby a higher score reflects greater adherence to the dietary pattern, and birthweight in white Caucasians (dashed line; n=2,367) and South Asians (solid line; n=884) after accounting for covariates: pre-pregnancy weight, maternal height, maternal smoking status, number of children, and infant gestational age and sex. Dotted line = 95% confidence interval.

93x75mm (600 x 600 DPI)

Supplemental Digital Content

eTable 1 - Food groups with a loading ≥ |0.30| whose presence or absence characterize each of the three dietary patterns.

Food Group	Plant-based	Western	Health Conscious
Fats		0.55	
Full Fat Dairy			
Low Fat Dairy	0.39	0.42	
Fermented Dairy	0.61		
Meat	(-0.35)	0.43	0.34
Eggs			0.36
Organ Meats			
Fish and Seafood			0.50
Processed Meats		0.55	
Meat Dishes			0.49
Poultry and Waterfowl			0.36
Fried Foods			
Leafy Greens			0.38
Cruciferous Vegetables			0.56
Legumes	0.62		
Fresh Seasonings	0.72		
Starchy Vegetables		0.43	
Vegetable Medley	0.42		0.47
Other Vegetables	0.70		0.32
Tofu			
Fruits			0.53
Whole Grains	0.71		
Refined Grains			0.35
Pasta		0.54	
Pizza		0.32	
French Fries		0.47	
Non-Meat Dishes	0.63		
Stir-Fried Dishes			0.47
Snacks		0.42	
Nuts and Seeds			0.34
Sweets		0.46	
Condiments		0.47	0.41
Tea	0.56		
Coffee		0.34	
Sweet Drinks		0.56	
Artificial Sweets			
Eigenvalue	4.05	3.18	3.06
Cumulative Variation	0.11	0.20	0.29

[1]Proportion of the total dietary variation in the dataset that is explained by considering 1, 2, or 3 underlying dietary patterns.

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eTable 2– Comparison of reported daily consumption frequencies (servings/d) of common food groups by White Caucasian and South Asian women, divided by 1st and 4th quartile.

	Plant-Based Diet Adherence					
	White Caucasian		South Asian		White Caucasian vs South Asian	
Food	Quartile 1	Quartile 4	Quartile 1	Quartile 4	Quartile 1	Quartile 4
Dairy	3.4 (2.6)	3.9 (2.1)	2.5 (1.7)	3.3 (2.3)*	0.306	<0.001
Eggs	0.1 (0.1)	0.3 (0.3)*	0.6 (0.6)	0.2 (0.3)*	<0.001	0.002
Fish	0.1 (0.1)	0.2 (0.2)*	0.1 (0.3)	0.0 (0.1)*	0.03	<0.001
Poultry	0.3 (0.2)	0.2 (0.2)	0.3 (0.3)	0.1 (0.2)*	0.948	<0.001
Red Meat	0.6 (0.3)	0.4 (0.2)*	0.4 (0.4)	0.0 (0.1)*	0.013	<0.001
Breads and Rice	2.7 (2.7)	1.9 (1.1)	3.0 (3.3)	3.8 (1.5)*	0.73	<0.001
Legumes	0.1 (0.1)	0.2 (0.2)*	0.4 (0.4)	0.8 (0.7)*	<0.001	<0.001
Fruit	2.5 (2.5)	2.6 (1.5)	2.5 (2.4)	2.1 (1.4)*	0.97	<0.001
Raw Vegetables	0.8 (0.8)	1.3 (0.9)	1.4 (4.2)	2.7 (1.6)*	0.10	<0.001
Cooked Vegetables	1.3 (0.9)	2.3 (1.3)*	2.2 (1.5)	4.3 (2.2)*	0.01	<0.001
Fried Foods	1.2 (1.0)	0.2 (0.2)	0.4 (0.4)	0.2 (0.2)*	0.02	0.421
Nuts and Seeds	0.4 (0.5)	0.6 (0.6)*	0.3 (0.6)	0.2 (0.3)*	0.57	<0.001
Convenience Foods	1.7 (0.8)	1.3 (0.9)	0.3 (0.7)	0.2 (0.4)*	<0.001	<0.001
Sweet Drinks	4.3 (2.5)	2.2 (1.7)*	0.8 (1.0)	0.5 (0.7)*	<0.00	<0.001
Sweets	2.2 (1.7)	2.1 (1.5)	1.4 (1.3)	1.1 (0.9)	0.15	<0.001
Multivitamin (%)	94.0%	79.3%*	66.3%	78.1%*	<0.001	0.72
Married (%)	93.0%	95.8%*	100.0%	100.0%	<0.001	0.002
Years in Canada (yrs)	28.8 (7.4)	29.5 (8.8)	11.3 (10.3)	7.0 (5.5)*	<0.001	<0.001
Adults living in household (n)	2.2 (0.6)	2.1 (0.7)	3.0 (1.5)	3.5 (1.7)*	<0.001	<0.001
Any Post-Secondary Education (%)	74.1%	93.4%*	87.3%	75.4%*	<0.001	<0.001
Currently Employed (%)	80.2%	88.2%*	55.1%	53.7%	<0.001	<0.001
Household Income ≥ *$ 60K/yr (%)*	85.5%	88.6%	55.9%	33.5%*	<0.001	<0.001

Consumption of foods were compared using t-tests. Data are reported as mean servings per day and standard deviation. Quartiles are in white Caucasians (n=2367) and South Asians (n=884). *p<0.05 between Q1 vs Q4.

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eTable 3— Multivariable regression in South Asians (n=884) of the role of 'cooked vegetables' in the association between the plant-based diet pattern and birthweight.

	With Plant-based diet		Without Plant-based diet	
Variables	β	P value	β	P value
Intercept	-4188.2	<0.001	-4136.4	<0.001
Pre-Pregnancy Weight (kg)	5.1	<0.001	5.1	<0.001
Maternal Height (cm)	5.9	0.007	5.9	0.008
Parity (# of children)	44.1	0.009	46.2	0.006
Gestational age (wks)	154.5	<0.001	154.8	<0.001
Infant Sex (Female = 1)	-93.9	<0.001	-93.5	<0.001
Plant-Based	37.9	0.041	ns	ns
Cooked Vegetables	7.4	0.376	15.6	0.034

The same covariates were included for each ethnic-specific model but non-significant covariates (e.g., 'smoking' in South Asians) were removed in the final model (denoted as 'ns'). Parity was reported as having 0, 1, 2, 3, 4, 5, or 6 (or more) children. The consumption of 'cooked vegetables' includes all vegetables asked within the food frequency questionnaire that were not stated as 'raw'. The consumption of 'cooked vegetables' includes all vegetables asked within the food frequency questionnaire that were not stated as 'raw'.

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (PAGE 1 AND 2)
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found (PAGE 2)
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported (PAGE 4)
Objectives	3	State specific objectives, including any prespecified hypotheses (PAGE 4)
Methods		
Study design	4	Present key elements of study design early in the paper (PAGE 4 - 5)
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection (PAGES 4 - 5)
Participants	6	(a) Cohort study—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (PAGE 5 and eFigure 1) ~~Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and con~~ ~~Cross-sectional study—Give the eligibilty criteria, and the sources and methods of selecti~~ ~~of participants~~
		(b) Cohort study—For matched studies, give matching criteria and number of exposed and unexposed (PAGE 15) ~~Case-control study—For matched studies, give matching criteria and the number of controls per case~~
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable (PAGE 5, 6, AND 10)
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group (PAGE 5 AND 6)
Bias	9	Describe any efforts to address potential sources of bias (PAGE 13)
Study size	10	Explain how the study size was arrived at (PAGE 4, 5 AND eFigure 1)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why (PAGE 10)
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (PAGE 10)
		(b) Describe any methods used to examine subgroups and interactions (PAGE 10 AND 15)
		(c) Explain how missing data were addressed (PAGE 5)
		(d) Cohort study—If applicable, explain how loss to follow-up was addressed (N/A) ~~Case-control study—If applicable, explain how matching of cases and controls was addresse~~ ~~Cross-sectional study—If applicable, describe analytical methods taking account of samp~~ ~~strategy~~
		(e) Describe any sensitivity analyses (PAGE 13)

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (PAGE 4, 5 AND eFigure 1)
		(b) Give reasons for non-participation at each stage (PAGE 4, 5 AND eFigure 1)
		(c) Consider use of a flow diagram (eFigure 1)
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (Table 1)
		(b) Indicate number of participants with missing data for each variable of interest (PAGE 10)
		(c) Cohort study—Summarise follow-up time (eg, average and total amount) (PAGE 6)
Outcome data	15*	Cohort study—Report numbers of outcome events or summary measures over time (TABLE 1)
		~~Case-control study—Report numbers in each exposure category, or summary measures of exposure~~
		~~Cross-sectional study—Report numbers of outcome events or summary measures~~
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were inclu (PAGE 10)
		(b) Report category boundaries when continuous variables were categorized (PAGE 15)
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time p (N/A)
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses (PAGE 13)
Discussion		
Key results	18	Summarise key results with reference to study objectives (PAGE 15)
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss b direction and magnitude of any potential bias (PAGE 19)
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence (PAGE 19)
Generalisability	21	Discuss the generalisability (external validity) of the study results (PAGE 19)
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based (PAGE 20)

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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