

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	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
AUTHORS	Zulyniak, Michael; de Souza, Russell; Shaikh, Mateen; Desai, Dipika; Lefebvre, Diana; Gupta, M; Wilson, Julie; Wahi, Gita; Subbarao, Padmaja; Becker, Allan; Mandhane, Piush; Turvey, Stuart; Beyene, Joseph; Atkinson, S; Morrison, Katherine; McDonald, Sarah; Teo, Koon; Sears, Malcolm; Anand, Sonia

VERSION 1 – REVIEW

REVIEWER	S. Zhu UMB, USA No Competing Interest
REVIEW RETURNED	08-Jun-2017

GENERAL COMMENTS	Well written manuscript that focuses on the race/ethnic differences of plant-based diet in pregnant women using Principal Component Analysis. Methods are clear and statistical analysis is well done. Large sample size and multisite nature of the study helps with generalizability.
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REVIEWER	Anne Lise Brantsæter Norwegian Institute of Public Health, Norway
REVIEW RETURNED	12-Jun-2017

GENERAL COMMENTS	<p>This is a well-written and interesting manuscript. The main finding is that among women living in a high-income country, a plant-based diet in pregnancy is differentially associated with new born birthweight in white Caucasian women and in South Asian women. In white Caucasian women, consumption of a plant-based diet was associated with lower birthweight, increased risk of SGA infants, and reduced risk of LGA infants, while in South Asian women the plant-based diet was associated with higher birthweight but not with SGA nor LGA infants.</p> <p>Differences in diet composition is an important aspect that may explain this finding. The authors did examined dietary composition and report that the plant based diet in the white Caucasian women was characterized by high intake of healthy (e.g. fruit, nuts and seeds) as well as unhealthy items (convenience foods, sweet drinks and sweets).</p>
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The plant based diet in the South Asian women was characterized by high intake of south Asian breads, rice, legumes, raw vegetables and cooked vegetables, and this dietary pattern seems to include fewer ultra-refined and processed items than the Caucasian plant-based diet.

Overall, the scientific evidence suggests that plant-based diets may help prevent and even reverse chronic diseases 1-5, however, the “healthy” plant-based diets emphasize whole foods with minimally processed and refined items. The obvious differences in the plant-based dietary pattern composition is a challenge with regard to the clinical and public health implications of the current study.

In my opinion, the authors need to add to their discussion a section about clinical and public health implications of their findings. Dietary counselling has low cost and low risk and clinical practitioners should pay more attention to dietary counselling in antenatal care.

1. Aune D, Giovannucci E, Boffetta P, et al. Fruit and vegetable intake and the risk of cardiovascular disease, total cancer and all-cause mortality-a systematic review and dose-response meta-analysis of prospective studies. *Int J Epidemiol* 2017 doi: 10.1093/ije/dyw319 [published Online First: 2017/03/25]

2. Aune D, Keum N, Giovannucci E, et al. Nut consumption and risk of cardiovascular disease, total cancer, all-cause and cause-specific mortality: a systematic review and dose-response meta-analysis of prospective studies. *BMC medicine* 2016;14(1):207. doi: 10.1186/s12916-016-0730-3 [published Online First: 2016/12/06]

3. Rinaldi S, Campbell EE, Fournier J, et al. A Comprehensive Review of the Literature Supporting Recommendations From the Canadian Diabetes Association for the Use of a Plant-Based Diet for Management of Type 2 Diabetes. *Canadian journal of diabetes* 2016;40(5):471-77. doi: 10.1016/j.jcjd.2016.02.011 [published Online First: 2016/08/01]

4. Aune D, Keum N, Giovannucci E, et al. Whole grain consumption and risk of cardiovascular disease, cancer, and all cause and cause specific mortality: systematic review and dose-response meta-analysis of prospective studies. *BMJ* 2016;353:i2716. doi: 10.1136/bmj.i2716 [published Online First: 2016/06/16]

5. Tusso PJ, Ismail MH, Ha BP, et al. Nutritional update for physicians: plant-based diets. *The Permanente journal* 2013;17(2):61-6. doi: 10.7812/tpp/12-085 [published Online First: 2013/05/25]

REVIEWER	Satish Kalhan Cleveland Clinic USA
REVIEW RETURNED	16-Aug-2017

GENERAL COMMENTS	<p>This is an interesting study demonstrating a relationship between plant based dietary pattern during pregnancy and birth weight of the baby in two ethnic groups in Canada.</p> <p>Their data show that while plant based diet had a negative association with birth weight in the "caucasian" group, the relationship was positive in the South Asian population.</p> <p>The study is done well and the data are clearly presented. The discussion is rather long and could be shortened by deleting the unrelated details such as impact of micronutrients etc. The fundamental issue with the study is the concept of relating a qualitative data i.e adherence to plant based diet to an objective quantitative measure i.e. birth weight.</p> <p>Since birth weight is determined by the actual accretion of mass supported by energy intake and metabolism, it is unclear why the investigators wanted to examine the association with qualitative diet pattern. As presented the study lacks a mechanistic question. It could have been strengthened if they had examined the association between plant based diet and energy intake in the two ethnic groups and then related it to birth weight. The authors have collected the data on energy intake and should be able to do such an analysis.</p> <p>Minor: Use of "Caucasian" to describe an ethnic group is incorrect, it would be better to describe them as "European" or simple white. The discussion should be shortened to make it more focussed and related to actual data. Describe how the adjustment for gestational diabetes in South Asian group was done.</p>
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VERSION 1 – AUTHOR RESPONSE

RESPONSE TO REVIEWER 1 COMMENT:

We thank Reviewer 1 for their favourable review and positive feedback.

RESPONSE TO REVIEWER 2 COMMENT:

We thank Reviewer 2 for their feedback and critique of our interpretation of the study results. Their suggestion to present the clinical and public health implications of our findings is a valuable addition and we have added the following information to the discussion section.

[PAGE 19] “Thus, policy recommendation 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.”

41. Aune D, Giovannucci E, Boffetta P, et al. Fruit and vegetable intake and the risk of cardiovascular disease, total cancer and all- cause mortality—a systematic review and dose- response meta-analysis of prospective studies. *Int J Epi* 2017;46:1029–1056. doi:10.1093/ije/dyw319

42. Aune D, Keum N, Giovannucci E, et al. Whole grain consumption and risk of cardiovascular disease, cancer, and all cause and cause specific mortality: systematic review and dose-response meta-analysis of prospective studies. *BMJ* 2016;353:i2716. doi: 10.1136/bmj.i2716

RESPONSE TO REVIEWER 3 COMMENT:

We thank Reviewer 3 for their feedback and critique of our manuscript. Their comments are valuable and well-founded, and we have strived to address them in the revised manuscript in order to improve the reporting, interpretation, and readability, of the manuscript.

MAJOR:

Comment 1. The discussion is rather long and could be shortened by deleting the unrelated details such as impact of micronutrients etc..

Response: This is an important consideration and we have strived to shorten the length of our original discussion, including study details related to the impact of micronutrients. However, information added at the request of other reviewers has replaced its space and resulted in a discussion that is of the same length.

Comment 2. The fundamental issue with the study is the concept of relating a qualitative data i.e., adherence to plant based diet to an objective quantitative measure i.e. birth weight.

Response: Our dietary pattern analysis is data-driven reliant on a quantitative characterization of the clustering of foods into “dietary patterns”, using principal components analysis. Diet patterns are derived using a correlation matrix of quantitative measures of food intake to identify patterns of food consumption that account for the largest amount of variation in diet (Newby et al. *Nutr Rev* 2004). This approach retains the information of the quantitative data from the original datasets but shifts the focus of an investigation from individual food components to food combinations, with empirically derived measures of adherence for each person to each of the dietary patterns.

The derived diet patterns can then be adjusted for energy-intake in order to examine the overall effect of (i) consuming these population-derived diet patterns (i.e., food combinations) and (ii) their combined nutritional value independent of total energy.

To more clearly present the derivation and purpose of PCA-derived diet patterns, the methods section [PAGE 6] now reads: "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., PCA scores) for each person to each of the individual dietary patterns is calculated in the PCA. The PCA scores for each individual were adjusted to the mean total population caloric intake (2500 kcal/day) using the residual method.[19]

Comment 3. Since birth weight is determined by the actual accretion of mass supported by energy intake and metabolism, it is unclear why the investigators wanted to examine the association with qualitative diet pattern.

Response: Dietary pattern, like those presented in our study, differ with respect to amounts of micro- and macronutrients provided. Both of which appear to effect birth weight independent of maternal energy intake.

Concerning macronutrients, a prospective cohort study of 557 women in Australia reported that dietary protein intake during pregnancy positively associated with birth weight and placental weight and that dietary carbohydrate intake negatively associated with Ponderal index, independently of energy intake and after adjustment for weight gain during pregnancy and potential confounders. [Moore Nut Epi 2004] This suggest that macronutrients may effect birth weight in a manner that is independent of energy intake. Regarding micronutrients, a randomized study in Nepal across 426 communities (n=4926 women) reported that women assigned to consume a folic acid-iron supplement were at 34% lower risk of delivering a low birth weight infant than the placebo group [Christian BMJ 2003], while a meta-analysis of 18 cohort studies (n=11,216 participants) reported that serum vitamin B12 associated with birth weight in low- and middle-income countries (0.08 SD [0.03, 0.14] per 1 SD increase in B12) but not in high-income countries (-0.02 SD [-0.05, 0.02] per 1 SD increase in B12).[Rogne BMJ 2017] This suggest that micronutrients may effect birth weight in a manner that is independent of energy intake. As such, by providing a measure of adherence to population-derived diet patterns, dietary pattern analysis can inform our understanding of how diets containing macro and micro nutrient-rich food items (e.g., dark leafy greens) associate with our outcome of interest (e.g., birth weight).

In this manner, we feel that it is a practical method to investigate the association between maternal diet during pregnancy on infant birth weight. It allows us to investigate how distinct combinations of foods consumed in an ethnically diverse population may provide varying quantities of macro and micronutrients, that could explain some of the variance we observe in birth weight between ethnic groups.

Comment 4. As presented the study lacks a mechanistic question.

Response: We thank the reviewer for noting this and have added to the introduction a section [PAGE 4] which presents (i) the mechanistic rationale for studying dietary patterns, and (ii) underscores its potential to capture the complex interplay between foods and nutrients and (iii) evaluate their association with health and disease: “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 or nutrients, and these patterns can be assessed for their associations with health and disease. Using dietary patterns, we investigated the association between maternal diet and birthweight in a multi-ethnic cohort.”

Comment 5. It could have been strengthened if they had examined the association between plant based diet and energy intake in the two ethnic groups and then related it to birth weight. The authors have collected the data on energy intake and should be able to do such an analysis.

Response: The reviewer raises an important point and touches on an area of methodological interest that we have recently investigated and reported [de Souza J Nutr 2016]. The reviewer is correct, we have total energy intake for each participant and have used it to energy-adjust each participant’s PCA score (i.e., measure of adherence) for each of the diet patterns. In our publication, when we regressed the non-adjusted and energy-adjusted PCAs for each pattern against one another, they were well-correlated (r^2) — plant-based = 0.75, $P < 0.001$; Western = 0.47, $P < 0.001$; health-conscious = 0.51, $P < 0.001$). Furthermore, we also tested the effect of including ‘total energy’ intake with the food groups in the PCA model (not published) and found no difference in the foods groups or the loading scores that characterize each diet pattern. Collectively, these findings suggest that ‘total energy’ does not have a large influence on the PCA diet pattern construct.

To test this in the relation to birth weight, as suggested by the reviewer, we have investigated the association between total energy intake and birth weight in our targeted cohort of white Europeans and South Asians -- and then tested the interaction between ethnicity (i.e., white Europeans and South Asians) and ‘total calories’. Without ethnicity in the model, we note 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 (calories*ethnicity) were included, total calories and the interaction term were not significant ($P > 0.05$) but ethnicity was ($P < 0.01$), whereby a South Asian newborn was estimated to weigh 231 g less [-266, -197g] than a white European newborn. Collectively, this suggests that (in general) total maternal energy intake is associated with infant birthweight in our diverse cohort; however, when ‘ethnicity’ is taken into account it appears to be the primary determinant of the variation in birth weight that we observe between white European and South Asian newborns.

While we have not added this additional analysis or description to the paper we are happy to do this if the Editor recommends it. However, we have added a brief note into the discussion: [PAGE 16] “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...”

MINOR:

Comment 6. Use of "Caucasian" to describe an ethnic group is incorrect, it would be better to describe them as "European" or simple white.

Response: We have replaced the word 'Caucasian' with 'European'. [not highlighted]

Comment 7. The discussion should be shortened to make it more focussed and related to actual data.

Response: Addressed above in MAJOR comment #1

Comment 8. Describe how the adjustment for gestational diabetes in South Asian group was done.

Response: We apologize for not being clear. We did not adjust for gestational diabetes in the study, for either ethnic group. However, we did assess it as a potential covariate in a forward step-wise selection procedure to identify predictors of birthweight, where it was input as a dummy variable (i.e., gestational diabetes=1, normal glucose levels = 0). However, because gestational diabetes has been reported to be associated with higher infant birth weight [Casey Obst & Gyn 1997; Kim Obst & Gyn 2014], we performed a sensitivity analysis. Mothers diagnosed with gestational hypertension and/or gestational diabetes were removed from the analysis, and then the analysis was rerun to see if the direction and significance of association shifted. Our results remained consistent after removing this subgroup of women, which suggest that they did not significantly influence our finding.

VERSION 2 – REVIEW

REVIEWER	Anne Lise Brantsæter Norwegian Institute of Public Health
REVIEW RETURNED	20-Sep-2017

GENERAL COMMENTS	The authors have satisfactorily responded to my comments and made the necessary changes to the manuscript.
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REVIEWER	Satish Kalhan Cleveland Clinic Foundation/ Case Western Reserve university Cleveland, Ohio, USA No Competing Interest
REVIEW RETURNED	28-Sep-2017

GENERAL COMMENTS	The authors have responded to the previous critique. Since maternal energy intake has repeatedly been shown to be a key determinant of birth weight, the authors should include their analysis of energy intake by the mother and its relationship with the quality of food and birth weight (Item 5, their response to my previous critique). This would strengthen the manuscript. Otherwise this question will be raised by most readers and would remain unanswered. The relation between micronutrients and fetal growth is lot more complex and cannot be easily answered as presented by the authors. I would suggest not to overemphasize it.
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VERSION 2 – AUTHOR RESPONSE

RESPONSE TO REVIEWER 2 COMMENT:

We thank Reviewer 2 for their support in revising the original manuscript and favourable critique of the revisions.

RESPONSE TO REVIEWER 3 COMMENT:

We thank Reviewer 3 for their feedback and critique of our manuscript. Their comments are valuable and well-founded, and we have strived to address them in the revised manuscript in order to improve the reporting, interpretation, and readability, of the manuscript.

Comment 1. The authors have responded to the previous critique.

We thank the review for favourably reviewing our revisions.

Comment 2. Since maternal energy intake has repeatedly been shown to be a key determinant of birth weight, the authors should include their analysis of energy intake by the mother and its relationship with the quality of food and birth weight (Item 5, their response to my previous critique). This would strengthen the manuscript. Otherwise this question will be raised by most readers and would remain unanswered.

Response: We acknowledge the reviewers focus on providing adequate data to only answer the questions proposed by the authors but also those (most likely) to be raised by the reader. In doing, we agree that the manuscript will be strengthened. As such, we have added the requested information.

The RESULTS section [PAGE 15] now reads:

“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.”

Comment 3. The relation between micronutrients and fetal growth is lot more complex and cannot be easily answered as presented by the authors. I would suggest not to overemphasize it.

Response: We acknowledge that the relationship between micronutrients and fetal growth is very complex. However, with recent evidence emerging of micronutrient deficiency in India and its association with infant birthweight, we felt it was important to inform readers of these findings and put it into context for South Asians in Canada. Nonetheless, as suggested, we have aimed to not overemphasize the evidence from India as being directly relatable to South Asians in Canada where food fortification and multivitamin use are common.