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Title	Causes and consequences of gestational diabetes in South Asians living in Canada: results from a prospective cohort study
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Reviewer 1	Dr. Jennifer L. Kuk
Institution	York University, School of Kinesiology and Health Science
General comments (author response in bold)	The authors investigate correlates of GDM in South Asian women. The topic is of interest but the methods need clarification and justification. 1. How physical activity was assessed is not described. Sedentary and exercisers are not mutually exclusive groups. Individuals can be both sedentary and exercise. **We thank the reviewer for asking this question: Participants were asked to answer the question: "On an average day considering your work and leisure activities, how active have you been during this pregnancy?" with the following options: "a. Mainly sedentary (using computer, answering telephones), b. Mainly walking on one level, or other mild exercise, c. Mainly walking, including climbing stairs, walking uphill or lifting heavy objects or d. Heavy physical labour or moderate/strenuous exercise." We combined the latter two groups into moderate activity, as there were only 2 participants who selected d. Thus in summary participants self-reported their daily lives (work and leisure time) as mainly sedentary, mainly mild activity or mainly moderate (or strenuous) activity. We have clarified this in the Methods Section page 7. We have added the reference 27 to this combination index which we have used in previously publications. (Merchant AT, Anand SS, Vuksan V et al. Protein intake is inversely associated with abdominal obesity in a multi-ethnic population. J Nutr2005;135:1196–201).** 2. To lump all meats (processed, fatty or lean meats) into one group and to categorize them as a 'bad' food does not really seem fair or appropriate. Further, given that vegetarianism did not differ between the 2 groups, then it would imply that meat per say is not a risk factor for GDM. Currently, the discussion is a bit biased. **Thank you. We appreciate your concern that this broad categorization of meats may be problematic. Low diet quality was defined as a higher consumption of meat which includes red meat, chicken, and processed meats, rice, fried foods, and was lower in raw or cooked foods. This score was developed and shown to be predictive of myocardial infarction in the Interheart case control study (Ref 29 Iqbal R, Anand S, Ounpuu S, Islam S, Zhang X, Rangarajan S, Chifamba J, Al-Hinai A, Keltai M, Yusuf S: INTERHEART Investigators. Dietary patterns and the risk of acute myocardial infarction in 52 countries: results of the INTERHEART study. Circulation 2008 Nov 4 118(19):1929 – 37. reference 29 in revised manuscript Page 6). It is also highly correlated at (R=0.45) with the modified alternative healthy eating index developed and validated by researchers in the United States. The literature with respect to processed and red meat is consistent in their association with an increase in chronic disease. We agree that chicken and fish may be different and in fact the latest data shows that they are neutral with respect to cardiovascular disease. (Anand JACC 2016) However, we use the simple index of diet quality, and found that it was predictive versus gestational diabetes. We then went back to the food frequency questionnaires completed by participants defined as low quality diet and high quality diet, and characterized the dietary patterns. Dietary patterns is a more optimal way of describing dietary differences because it provides more information than just a static category of "a meat eater versus not", or, in this case, vegetarian versus not. We have modified the discussion somewhat to minimize any impression that the discussion is biased as raised by the reviewer.** 3. Table 4 is a bit misleading. Given that vegetables and fruits were used to define a high quality diet and meat intake a low quality diet then it would be no surprise that these would appear in a higher frequency. Is there any ability to assess macronutrient intake, total energy intake, vitamin? **In Table 4 we classified the common foods and low quality diet participants versus high quality diet participants. As mentioned above, we wanted to provide context for the other foods such as, in addition to vegetables and meat, the other foods that complement the diet in these participants. Participants did complete a food frequency questionnaire and macro nutrient intake, total energy intake, and vitamin micronutrient are available. However, the majority of individuals in the diet and chronic disease field are now embracing dietary patterns as a more reflective way of communicating dietary advice because an individual who, for example, is shown to have a high percentage of calories from carbohydrates could have consumed these very different types of carbohydrates. For example, fruits and vegetables consumption versus highly process refined carbohydrates. The macronutrient assessment fails to reflect the dietary context. (de Souza RJ, Zulyniak MA, Desai D, Shaikh MR, Campbell NC, Lefebvre DL, Gupta M, Wilson J, Wahi G, Atkinson SA, Teo KK, Subbarao P, Becker AB, Mandhane PJ, Turvey SE, Sears MR, Anand SS; NutriGen Alliance Investigators.. Harmonization of Food-Frequency Questionnaires and Dietary Pattern Analysis in 4 Ethnically Diverse Birth Cohorts. J Nutr. 2016 Nov;146(11):2343-2350. Epub 2016 Oct 5.)** **In Table 4 we have classified the common foods in the "low quality diet" participants versus "high quality diet" participants. For the reviewers information we have added to this table mean intakes of macronutrients, select vitamins (C, E) and minerals (sodium, potassium, magnesium, phosphorus), and total energy intake. As expected, the high-quality diet was reflective of a plant-based diet, and was lower in cholesterol, higher in fiber, vitamin C, folate, and potassium. We have not added this to the Table 4 of the revised paper but would be pleased to do so if the Editor requests.** Low Quality Diet High Quality Diet Most common foods Meat, Meat dishes, processed meats, organ meats, poultry, fish and seafood, rice, fried foods, refined grains (breads and cereals), fast foods, eggs Vegetables (raw and cooked), legumes (daals), nuts and seeds, low-fat dairy (milk and fermented products), whole grains (breads and cereals), sweets, fruits Energy (kcal) 1651 (683) 1960 (753) Carbohydrate (%) 56.7 59.3 Carbohydrate (g)* 256 (26) 267 (25) Fiber (g)* 19 (5) 24 (5) Protein (%) 16.0 16.0 Protein (g)* 72 (10) 72 (11) Fat (%) 30.0 28.2 Fat (g)* 60 (8) 56 (8) Sat (%) 10.1 10.1 Sat (g)* 20 (4) 20 (5)

	Mono (%) 11.1 10.1 Mono (g)* 22 (4) 20 (4) Poly (%) 5.7 5.2 Poly (g)* 11 (2) 11 (2) Trans (%) 0.13 0.12 Trans (g)* 0.26 (0.28) 0.25 (0.30) Cholesterol (mg)* 217 (119) 134 (72) Iron (mg) 12.1 (5.4) 15.5 (7.4) Folate (mcg) 311 (139) 439 (200) Vitamin C (mg) 194 (102) 263 (113) Vitamin E (mg) 5.0 (2.6) 6.1 (2.7) Sodium (mg) 2485 (1202) 3126 (1346) Potassium (mg) 3149 (1420) 4308 (1682) * Energy-adjusted 3. Were underweight women included in the comparison group for the PAR for BMI > 23 kg/m2? That would unfairly inflate the risk estimate. **The lower limit of the normal weight range in South Asian women is 18.5. There are 75 (7.5%/1004) mothers who had a BMI of less than 18.5. Removing the underweight group does not change the population attributable risk calculation.** **As a sensitivity analysis, we recreated the multivariate model and PAR estimates, after removing all women with a pre-pregnancy BMI of <18.5 (n=75). This sensitivity analysis did not show any concerning change to our main analysis.** 5. To describe the cohort as 'women of South Asian origin living in Canada' is a bit misleading as they are really only from 2 cities in the GTA. Thus, to imply that these results apply a given risk reduction in Canada is a bit of an overstatement. **We have revised this to reflect Ontario, Canada throughout the paper.**
Reviewer 2	Dr. Lawrence Svenson
Institution	Alberta Health and Wellness, Surveillance & Environmental Health
General comments (author response in bold)	The authors present findings on the risk of gestational diabetes (GDM) among pregnant women with. The study is a prospective cohort following roughly a 1,000 women. Overall, the paper provides interesting findings. On a general note, there are some areas for improvement in writing style. There are some issues with grammar, punctuation, and some awkward wording. 1. There are a few areas that require some clarification. It is not clear if the scoring used for the food frequency question was derived from other studies or validated. While it appears to be a reasonable approach, it would be good to know if the authors chose the scoring, or based it on other studies. **The score which we used to define a "low quality" diet was developed using data from the Interheart case-control study (n=27,000 MI cases/controls from 52 countries), and shown to be predictive of myocardial infarction (Reference 29: Iqbal et al,. 2008). We defined a Low diet quality as one with higher consumption of meat (which includes red meat, chicken, and processed meats), rice, fried foods, and was low in raw or cooked foods. In unpublished data, we have found it to be well-correlated at (R=0.45) with the modified alternative healthy eating index developed and validated by researchers in the United States. We have referenced this in our Methods section.** 2. It is unclear why the authors opted to age-standardized the incidence of GDM. It would be better to present age-specific rates as age-standardization can obscure information. **Thank you for your comment. We acknowledge that our choice to age-standardize may obscure potentially important information about the age distribution of the population under study. However, the primary aim of this study was not to assess the association of maternal age with GDM, as age is a well-established risk factor for GDM. We suspected that the age distribution in START may not be representative of the Canadian population, and thus elected to age-standardize to improve generalizability. Age-standardizing our estimate to these reference populations yielded an age-standardized prevalence of 36.2 to 44.6%. However, because the Maternity Experience study (MES) was the only study that used a stratified random sample of Census 2016 delivering births), we elected to age standardize to this population (age-standardized prevalence = 36.2%)** Table. Age-distribution of South Asian cohort participants and other reference populations, by age-groups of population under study Age group South Asian study population (START) Census 2011 (Female population)1 Representative Canadian Pregnant Population (MES stratified random sample, from Census 2006)2,3 % n % n % n 20-24 6.97 70 19.37 1,078,675 13.47 835 25-29 37.55 377 19.62 1,092,310 34.29 2125 30-34 41.24 414 19.83 1,104,090 34.10 2113 35-39 13.05 131 19.93 1,109,735 15.02 931 40-44 1.20 12 21.25 1,183,160 3.11 193 Total 1004 5,571,000 6197 Notes: 1 Age-standardized prevalence reported in paper is directly age standardized to the Census 2011, female population aged 20-44 years old 2 The Maternity Experience Survey (MES) is a national survey of Canadian women's experiences, perceptions, knowledge, and practices before conception and during pregnancy, birth and early months of parenthood and was carried out by the Canadian Perinatal Surveillance System (CPSS) branch of the Public Health Agency of Canada (PHAC) and Statistics Canada. Using the 2006 Canadian Census, a stratified random sample of 8,244 women was selected as eligible (target response=75%) without replacement. The eligible MES population included birth mothers, aged 15 years or older, who had a singleton live birth in Canada during the three-month period preceding the 2006 Census. Of the eligible women, 6421 (78%) completed the survey. 3 Not included for age-standardization reference are: 15-19 y.o. (3%) and age missing (0.6%)

	3. The rationale for only selecting one variable where there was high correlation is not clear. How was the variable selected? How did you ensure you weren't excluding a variable that had a potentially causal relationship? Why was stepwise regression performed? Stepwise may lead to reasonable model fits, but can generate overly simplified models and may result in dropping important variables. Given this, did the authors consider other statistical methods, such as structural equation modeling. This would have allow for the development of a conceptual model that may provide more robust results. It appears that age was used as a categorical variable. Was it evaluated in earlier models as a continuous variable? Displaying as a categorical is fine as it can make it easier for the reader to interpret, but the authors need to ensure the groupings don't inadvertently hide information about age effects. **We have provided a detailed explanation above in terms of the selection of variables and the reason we chose step wise over Lasso.** **Collinearity was considered by reviewing the variance inflation factor for each variable added to the model. VIF values for all variables failed to suggest any serious collinearity (all VIF were <1.2). However, we acknowledge that we may have overstated the degree to which collinearity was an issue. This was only noted for the set of variables that best captured "pre-pregnancy adiposity": a) pre-pregnancy weight along with height as independent predictors or b) pre-pregnancy BMI which combines the weight and height. We chose to use the two independent variables for our original MV model as we felt the audience may appreciate pre-pregnancy weight as modifiable; for our PAR calculation, we changed to the combined variable, BMI, as this simplified the mechanics of the PAR calculation and subsequent interpretation. Similarly we used age as a continuous variable in the original MV model, and categorized age for the PAR calculation.** **A backward stepwise model selection program was used to verify/support the analyst driven model selection. We developed the model using backward stepwise regression, but also then subjected the same variable list to forward and stepwise selection methods. All methods yielded the same final set of predictors. For the purposes of this multivariate model, the list of included variables was short (maternal age, multiparous, diet quality, family history of diabetes, pre-pregnancy weight and height) and the final reduced model only removed 1 variable (multiparous). We acknowledge the need for improved variable selection methods, and look forward to the development and validation of these methods for logistic regression models in SAS, as already available for models with continuous outcomes.** **We understand that variable selection procedures have advanced considerably beyond simple stepwise regression approaches. While we appreciate the value of LASSO, we were concerned about the choice of tuning parameter. Although cross-validation is often used as an automated means of picking the tuning parameter, this is typically used to prevent overfitting in a prediction problem, not to address our goal of feature selection. Further, in a variety of situations, cross-validation with the lasso has been shown to result in an unacceptable solution set, often with no or extreme sparsity leading investigators to subjectively choose the number of variables manually. Finally, the audience we intended to read this article would appreciate and are accustomed to classical inferential measures such as p-values and confidence intervals. These quantities are inappropriate with the lasso and levels of significance are lost entirely.** The conclusions appear to be fine given the results presented. **Thank you.**
Reviewer 3	Dr. Susan Baxter
Institution	Simon Fraser Univ. Faculty of Health Science
General comments (author response in bold)	You've done an enormous amount of work gathering and assembling data though I'm not strictly sure the world really needs another article on South Asians' greater risk of diabetes and GDM. Really, what's needed is basic research into cause, not more correlations derived from observational research. In this context the newborn statistics you collected might be useful - perhaps. 1. Your only genuine point (which is not especially startling) is that health messaging ought to be targeted better and South Asian women contemplating pregnancy should be told to modify the two risk factors you found to be important: their weight and diet. **We agree with the reviewer, is for women to be aware of their risk of being overweight before pregnancy and also the risks of a low quality diet.** 2. Also, your newborn data should also be mentioned in the abstract (as it is the part most people will actually read). **The newborn data is added to the abstract. Specifically, we show the newborn of GDM mothers higher birth weight, higher skin fold thickness, and lower insulin sensitivity compared to infants of non-GDM mothers.** 3. There are nonetheless some concerns with your basic data around diet, which, as you write, were based on self-reports. While I did glance at your previous article on "FFQ data" it is not clear why this particular acronym makes self-reports any more reliable. People forget, dissemble and generally fudge on self-reports; to rely on those exclusively is .problematic. Limitations and questions would need to be clarified and expanded upon. **Dietary acquisition in epidemiological studies, gold standard metric is the food frequency questionnaire. We acknowledge that these too rely on self-report and are validated against self-reported dietary records. We acknowledge the limitation of food-frequency questionnaires with respect to measurement of dietary intake. The FFQs that were used in this study have been validated against 7-day food records (Reference 28 in revised manuscript: Kelemen et al., 2003), which is the standard validation method in the field. FFQs and prospectively collected food diaries typically do not share two major and common sources of error: i.e. memory and portion size estimation. We acknowledge that such self-reports are still subject to "desirability bias". For the purpose of dietary scoring and pattern characterization, however, relative amounts of food consumed were used (i.e. more vs. fewer servings), which serves to minimize the impact of misclassification of diet. Nevertheless, we take your point and have added this as a limitation in the Limitations section on Page 13.** 4. This article generally needs editing and tightening. As it stands it is too long. And frankly a bit boring. Your tables and figures are good; but the methods section is hard to read; far too many long sentences and parenthetical notes. **We have made some additions as requested by the editor and the reviewer, but also edited out some sentences which were too long and redundant. We have now maintained the word count as 2,200.** 5. Finally, I am not sure that I would agree with your contention that clinicians don't counsel South Asian women to lose weight and eat better before and during pregnancy as several of your own references suggest that they do know this. Of course the other issue is whether stressing women by telling them they need to lose weight (otherwise they could suffer from GDM and other complications) really is a good idea. **We have modified the wording to reflect that the important of public health messaging to South Asian women**

	who are contemplating pregnancy, does not mean messaging only from family physicians or specialists, but also through public health programs and other healthy babies healthy moms organizations, and health and wellness organizations. We have added a reference to the recent paper in Lancet Diabetes and Endocrinology which calls for multisector strategy to improve mothers pre-conception health including weight using both a bottom up (individual) and top down (policy) approach. (ref #40 Hanson M, Barker M, Dodd JM, Kumanyika S, Norris S, Steegers E, Stephenson J, Thangaratinam S, Yang H. Interventions to prevent maternal obesity before conception, during pregnancy, and post partum. Lancet Diabetes Endocrinol. 2017 Jan;5(1):65-76.)