Article details: 2022-0025
Title: Maternal and neonatal outcomes in pregnancies with type 2 diabetes in First Nation and other Manitoban women: a population-based study
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Reviewer 1: Dr. Maryam Kebbe
Institution: Pennington Biomedical Research Center
General comments (author response in bold)

Very important study and well reported. I offer some comments below that may help to better clarify certain aspects of the paper.

1. Regarding maternal outcomes, how was morbidity defined? Did you have data on pre-eclampsia or other maternal outcomes that may be affected by diabetes?
Thank you for these queries. Maternal morbidity was defined as maternal death or any of the following: eclampsia; rupture of uterus during labour; puerperal sepsis; HIV disease; cardiac arrest; cardiac failure or myocardial infarction; assisted ventilation; hysterectomy, open approach; blood transfusion; repair of bladder, urethra, or intestine; embolization/ligation/suture uterus for postpartum hemorrhage; placenta previa with hemorrhage and blood transfusion; postpartum hemorrhage and blood transfusion; and postpartum hemorrhage and hysterectomy. This was used based on the publication by Heaman et al. (7). We have added this reference to the manuscript and have included the definition in Appendix Table 1.

2. Please elaborate on how the perspectives of First Nation people and communities were included.
First Nation people were included at all steps of this study from inception to manuscript preparation (co-author Lorraine McLeod, First Nations Health and Social Secretariat of Manitoba). The following excerpt is from the Type 2 Diabetes in Manitoba report from which these data arise. "The entire research process, including developing the indicators, selecting the outcomes and interpreting the results, was undertaken in partnership with First Nations Health and Social Secretariat of Manitoba. Our intent was to begin to address the Truth and Reconciliation Commission (TRC) of Canada's Call to Action #19, which calls on governments and research institutions to identify indicators of health and report on the availability of appropriate health services for Indigenous peoples. Additionally, we acknowledge "that the current state of Aboriginal health in Canada is a direct result of previous Canadian government policies, including residential schools". In order to align our research with the TRC's calls to action, this report presents results separately for First Nation populations in Manitoba. This approach is necessary to ensure that the results are interpreted within the proper context and to support planning and appropriate allocation of resources.". Since we do not have space to include those details we have written the following in the manuscript and have referenced the report as follows: "To ensure that this study included the perspective of First Nation people and communities, all study aspects from inception to manuscript preparation were conducted in partnership

between researchers at the Manitoba Centre for Health Policy (MCHP) and the First Nation Health and Social Secretariat of Manitoba (17).” Page 5 line 33

3. Please clarify how you chose your regression model and what preparation steps were taken to address outliers etc. Were all your outcomes count data? Please also comment on any model selections done accounting for AIC levels.
Thank you for these queries. All of our outcomes were dichotomous (yes/no variables). We dealt with outliers as follows: For outcomes involving gestational age, size for gestational age we had prespecified exclusions as follows: records with gestational age <20 or > 50 weeks, or birthweight < 300g or > 9000g were excluded but only where that outcome was relevant. In other words, that record was kept for maternal morbidity, for example, and only excluded for size for gestational age. Unfortunately, the Manitoba Centre for Health Policy does not collect data from outpatient laboratories. Thus, there is a high degree of missing data for HbA1c levels. This has been included as a weakness in the discussion as follows “We had incomplete data for hemoglobin A1c data, so were unable to examine the role of glycemic control in these adverse outcomes.” Page 13 lines 17-19

4. It’s unfortunate that the health records did not capture pre-gravid BMI, smoking, or hbA1c status. Since you are not using conditional logistic regression for matched data, please describe including the matching weights in the estimation and using cluster-robust standard errors with pair membership as the clustering variable.
We agree. Unfortunately, pre-gravid BMI is frequently missing from administrative databases unless they also include clinical databases. We did not include matching weights in the analysis. We should also clarify that we did not use Poisson regression but rather the Modified Poisson methods that addresses the cluster-robust standard errors, which has been clarified in the manuscript. Our apologies for this oversight.

5. I know mode of delivery is one of your outcomes, but did you consider adjusting for it for some of the other outcomes (eg neonatal hospital admission?)
Thank you for this query. While we did match for important clinical factors, we did not perform any adjustments for these analyses. The intent this study was to begin to address the Truth and Reconciliation Commission of Canada’s Call to Action #19, which calls on governments and research institutions to identify “gaps in health incomes between Aboriginal and non-Aboriginal communities”. This approach was necessary to ensure that the results are interpreted within the proper context and to support planning and appropriate allocation of resources. For this reason, we did not adjust for potential confounding factors but rather report the differences in maternal and neonatal outcomes as they exist. Page 7 lines 47-54

6. Please report p-values in table 1 and appendix table 2.
Thank you for suggestion. Because this was a matched cohort and did not represent the entire population of those without type 2 diabetes, we thought it would be misleading to report p-values for Table 1. For Appendix Table 2, we have added the crude rates and 95% confidence intervals to the table as a measure of statistical significance.

Minor:

7. Intro, second para line 33: clarify what type of diabetes.
Thank you for this suggestion. We have clarified the type of diabetes as suggested so the sentence now reads "For First Nation women living in Canada with pre-existing diabetes these include an increased risk of macrosomia, preterm delivery, and neonatal hypoglycemia compared to other individuals with diabetes" Page 4 lines 35-38

Reviewer 2: Dr. Fariba Aghajafari
Institution: University of Calgary
General comments (author response in bold)

This well written manuscript addresses the risk of adverse pregnancy outcomes for women with type 2 diabetes among the cohort of Frist Nation and other women in Manitoba. The authors concluded that the risk of adverse pregnancy outcomes is higher for the First Nation women with Type 2 diabetes compared to other women with Type 2 diabetes in Manitoba.

1. The study is a population-based cohort, and descriptive analysis were used to describe the demographic difference between the 2 groups. However, there have not been any adjusted analysis based on SES factor index level or urban living that could affect the outcome of pregnancy, as it is demonstrated in table 1. The authors could consider an adjusted regression analysis to address the covariates that could affect the pregnancy outcomes.
Thank you for this suggestion. The intent this study was to begin to address the Truth and Reconciliation Commission of Canada's Call to Action #19, which calls on governments and research institutions to identify "gaps in health incomes between Aboriginal and non-Aboriginal communities". This approach was necessary to ensure that the results are interpreted within the proper context and to support planning and appropriate allocation of resources. For this reason, we did not adjust for potential confounding factors but rather report the differences in maternal and neonatal outcomes as they exist.

2. Minor: Table 1. the number in variable Urban in First nation with type 2 diabetes is presented as range.
Thank you for pointing this out. When cells are thought to be too small that patients may be identifiable so that is why the table was displayed like that originally. We were able to locate the exact number, so the table has been updated to give the exact n (Table 1).

Reviewer 3: Prof. Hamideh Bayrampour
Institution: The University of British Columbia Department of Family Practice Midwifery Program, BC Children's Hospital Research Institute
General comments (author response in bold)

Thank you for an opportunity to review this important work.

1. The background section can be presented with more local/national/contextual information for example, please clarify in Line 10 page 2, "in many centres" refers to which centres?

Thank you for this point. Because we are already at our word limit and to improve the clarity as suggested by the reviewer, we have removed reference to "in many centres".

2. This statement needs citation." Pregnancies complicated by type 2 diabetes are associated with a higher risk of maternal and neonatal complications."
Our apologies for this oversight. We have added references here including 2 Canadian studies. Page 4 lines 14-15

3. Please provide an estimate here (line 26): "Indigenous women experience a high prevalence of gestational diabetes."
As requested by the editors, we have removed reference to gestational diabetes in the introduction. We have included an estimate for this risk in those with type 2 diabetes as suggested by the reviewer as follows "First Nation women are more than twice as likely to have type 2 diabetes in pregnancy than others living in Canada". Page 4 lines 26-31

4. Methods sections is relatively brief. Please provide more description for example, please provide a short description for each database, in data sources.
Thank you for this suggestion. Because of the very strict word limit, we are not able to add more descriptors to the methods. We completely agree that this is quite brief. To address this, we have added a table in the appendix with more detail about the data and data sources (Appendix Table 1) as well as a figure with the details of our definition of type 2 diabetes (Appendix Figure 1).

5. Please specify maternal morbidity definition for this study in line 6, page 5.
Maternal morbidity was defined as maternal death or any of the following: eclampsia; rupture of uterus during labour; puerperal sepsis; HIV disease; cardiac arrest; cardiac failure or myocardial infarction; assisted ventilation; hysterectomy, open approach; blood transfusion; repair of bladder, urethra, or intestine; embolization/ligation/suture uterus for postpartum hemorrhage; placenta previa with hemorrhage and blood transfusion; postpartum hemorrhage and blood transfusion; and postpartum hemorrhage and hysterectomy. This was used based on the publication by Heaman et al. (7). Because of the strict word limitation and the length of the detailed definition, we have not explicitly defined it in the manuscript but we have added the reference containing this definition to the manuscript and have included it in Appendix Table 1.

6. This is a retrospective cohort study and use of OR seems more relevant. what is the rational for using RR instead of OR?
The intent this study was to begin to address the Truth and Reconciliation Commission of Canada's Call to Action #19 thus the decision was made in the initial analysis to include RR instead of ORs as it was thought by the committee that RR were easier to interpret and be conveyed to lay people.

7. The interpretation section needs more focused discussion about potential important reasons for increased risk of adverse outcomes among First Nation women compared to other Manitoba women with type 2 diabetes.
Thank you for this comment. Because our study was not designed to address the causes for the increased risk of adverse outcomes among First Nation women

with type 2 diabetes, we thought it would be outside the scope to have a detailed discussion on this. Furthermore, given the limited space, we limited the discussion of this to the following: "We postulate that the higher risk of stillbirth and perinatal death in First Nation women is likely multifactorial and may include factors such as access to care, socioeconomic factor index differences, higher rates of obesity or above target glycemic control, and systemic racism within our healthcare system. Additional research is required to identify modifiable risk factors in this population." (page 11 lines 33-43) and "Additional research is needed to identify potential modifiable risk factors for large-for-gestational-age neonates such as above target glycemic control, maternal weight and excess gestational weight gain in First Nation and all other women with type 2 diabetes, and to improve optimal timing and mode of delivery." (page 12 lines 45-54). We have also highlighted this in our limitations as follows: "Lastly, our study did not examine for or address the complex causes for the differences in pregnancy outcomes in First Nations and all other Manitobans with type 2 diabetes." (page 13 lines26-30).

Reviewer 4: Ms. Shohinee Sarma
Institution: University of Toronto
General comments (author response in bold)

Thank you for the opportunity to review this manuscript titled "Maternal and neonatal outcomes in pregnancies with type 2 diabetes in First Nation and other Manitoban women: a population-based study." The authors conducted a retrospective cohort study of linked administrative data from Manitoba, Canada to compare pregnancy outcomes in Type 2 diabetes between women with First Nations heritage and all other Manitoban women.

Major comments:

[1] This is an important study of Indigenous perinatal and birth outcomes in Type 2 diabetes; however, the authors did not include diabetes severity with HbA1C, which would be a very important factor in assessing differences in birth and neonatal outcomes
We completely agree and this is a limitation of our current manuscript. Unfortunately, the Manitoba Centre for Health Policy only have HbA1c data from the hospital-based labs and not any outpatient laboratory testing facilities. This means that the HbA1c data we have are incomplete and missing for approximately half our population. We also felt that HbA1c data may be missing in a way that could introduce additional systemic bias. For that reason, we have chosen not to present the data and it is highlighted as a limitation.

[2] Diabetes duration, presence of other diabetes complications, and medications such as Metformin use in pregnancy would also have been important features to assess since they affect pregnancy and neonatal outcomes.
We agree that these are important factors. As this is population-based data, we do not have reliable estimates of diabetes duration or other diabetes complications. Unfortunately, metformin use was not collected in this dataset. We completely agree that these are drawbacks of our dataset and have added these to the limitations section as follows:

"While we matched our type 2 diabetes and non-type 2 diabetes cohorts for important factors such as maternal age, we were unable to adjust for potential confounders not captured by our data such as maternal obesity, smoking status, or medication use". (page 13 lines 21-26). We have also mentioned metformin in the discussion of infant size as follows: "Additional research is needed to identify potential modifiable risk factors for large-for-gestational-age neonates such as above target glycemic control, metformin use, maternal weight and excess gestational weight gain in First Nation and all other women with type 2 diabetes, and to improve optimal timing and mode of delivery." Page 12 lines 45-54

[3] It may have been important to include and stratify ethnicities of women in the Other Manitoban category to better understand the comparative higher perinatal outcomes in Type 2 diabetes for First Nations women.
We agree that this may have been beneficial. Unfortunately, the Manitoba Centre for Health Policy does not collect detailed ethnicity data, so this could not be included. Additionally, since the primary research question was surrounding outcomes in First Nation women living in Manitoba, and not an examination of ethnicities, we feel that this would be outside the scope of our study.

[4] The matching process only accounted for a few variables. Were other baseline variables not available in the dataset? It would be important to include diabetes severity (HbA1C), BMI, diabetes duration, medications, other past medical history, and other pregnancy comorbidities (e.g.: hypertension, obesity) to account for confounding.
We completely agree. The intent this study was to begin to address the Truth and Reconciliation Commission of Canada's Call to Action #19, which calls on governments and research institutions to identify "gaps in health incomes between Aboriginal and non-Aboriginal communities". This approach was necessary to ensure that the results are interpreted within the proper context and to support planning and appropriate allocation of resources. For this reason, we did not adjust for potential confounding factors but rather report the differences in maternal and neonatal outcomes as they exist. As this is a population-based study, we lacked detailed clinic data as suggested by the reviewer, so we are unable to include these varaibles. As such, this is a limitation of our current study. Nonetheless, the differences noted between First Nation and all other Manitobans are important and striking however, this study is unable to identify the causes of the differences we identified.

[5] It was not clear how confounding was assessed beyond matching on only 4 variables. The authors did not present baseline standardized differences between the comparison groups.
Outside of matching, confounding was not assessed and is a limitation of this study.

Minor comments:

[1] "In both First Nation and all other Manitoban offspring, risk of preterm delivery, early preterm delivery, large-for-gestational-age infant, birth trauma, admission to neonatal intensive care unit, and congenital anomalies was higher with type 2 diabetes compared to diabetes free matches." – Unclear why this was assessed and mentioned in the results section as comparing outcomes between Type 2 diabetes and no diabetes was not the objective of the study and these results are already well established.

Thank you for this question. We agree, that it is well-established and is not a novel study finding. We report this as it was analysed and its consistency with the available literature supports the robustness of the current dataset.

[2] The study does not add new findings or novel methods about the higher risk of perinatal outcomes for mother and infant among First Nations women with diabetes compared to other women.
We agree that this has been reported in women with pre-existing diabetes. However, to our knowledge, the current available Canadian literature reports on pre-existing diabetes in First Nation populations and not type 2 diabetes specifically. As type 1 and type 2 diabetes have very different outcome profiles, we feel that this does add important information to the current literature.

[3] The authors did not state how missing data was handled in the Methods section. Did they conduct any analyses to account for missingness?
Thank you for this query. We did not do any analyses to account for missingness. Those with missing data were excluded from the analysis.

References

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3. Kallas-Koeman M, Khandwala F, Donovan LE. Rate of Preconception Care in Women with Type 2 Diabetes Still Lags behind that of Women with Type 1 Diabetes. Canadian Journal of Diabetes. 2012;36(4):170-4.
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8. Althouse AD. Adjust for Multiple Comparisons? It's Not That Simple. Ann Thorac Surg. 2016;101(5):1644-5.