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Title: The bidirectional relationship between depression and diabetes and the effect of immigration status: a retrospective cohort study using the Canadian Longitudinal Study on Aging
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Reviewer 1: Miss Vanessa Brunetti
Institution: McGill University, Montréal, Que.
General comments (author response in bold)

1. Please rephrase the sentence “Beyond screening … with diabetes” starting on line 87.
We changed “Beyond screening” to ‘in addition’ (p. 6)

2. The statement that delayed depression diagnosis may lead to complications is misleading, as diabetes is not a known complication of depression.
We have modified the wording to
Conversely, immigrants with depression may also be at high risk of diabetes because of complex social determinants of health (6, 27-29) and delayed depression diagnosis and treatment (30-34); although antidepressant use may also increase diabetes risk (35, 36). (p. 6)

3. The authors should specify that they are referring to type 2 diabetes in this paper.
Please see our response to the Editor’s point 4. We did not differentiate diabetes by type.

Methods

4. Is there reason to believe that the patients who were excluded due to missing immigration status may be different from the ones that were included? How many people were excluded due to missing immigration status information?
Only 3 individuals were excluded because of missing information on immigration status. We have included the numbers of those excluded because of missing information on immigration status, diabetes or depression at baseline in Figure 1. Please see our response to the Editor’s point 15. (Figure 1)

5. The authors should explain the rationale behind the inclusion of interaction terms: why do they think the effect of depression on the incidence of diabetes would be modified by immigration status, rather than simply confounded by it?
Our aim was to study the bidirectional diabetes/depression relationship among immigrant. This relationship was studied in the general population, but not in immigrants and for the reasons we provided in the introduction, we believe that immigrant could be different from non-immigrants in terms of risk of diabetes and risk of depression and their related adverse events. However, we do not believe that the effect will change direction (interaction) in immigrants. Nonetheless, adding the interaction term with immigrant allowed us to assess the effect modification of immigration status on the bidirectional relationship as presented in Tables 2 and 4. We have added this comment in the statistical analysis section:
To assess the effect modification by immigration status, interaction terms for diabetes and immigration status and depression and immigration status were included in the models for Cohort1 and Cohort2, respectively (p. 9)

6. How was immigration status measured? Are only first-generation immigrants considered or second generation immigrants as well?
Technically, only first generation immigrants were considered even though most of them lived in Canada for more than 40 years. It has been clarified in the text:
CLSA defined immigrants using the two questions "In what country were you born?", "In what year did you first come to Canada to live?" (11) (p. 7)

7. Would it be possible to expand on the sample weights provided by CLSA that are used in the regression?
Results:
As per the CLSA, basic design weights, which are proportional to the reciprocals of the individual inclusion probabilities, were computed by CLSA. They were then re-calibrated to the sum of the targeted (eligible) Canadian population using the Canadian Community Health Survey-Healthy Aging databases. Analytic weights are proportional to the inflation weights but rescaled to sum to the sample size within each province, so that their mean value is 1 within each province. Provinces with larger populations will tend to have much higher inflation weights compared to smaller provinces The observations from those strata would tend to dominate the statistical analysis. With analytic weights point estimators will remain the same, but they are more efficient if the model is correctly specified. The CLSA provided the basic design weights and the analytical weights. The basic design weights were proportional to the reciprocals of the individual inclusion probabilities and were calibrated to the sum of the targeted (eligible) Canadian population using the Canadian Community Health Survey-Healthy Aging database (37). Analytic weights are proportional to the inflation weights but rescaled to sum to the sample size within each province (26). Details are provided in the CLSA website (26).
This explanation is now summarized in the statistical section as follows:
To make the estimates generalizable to the Canadian population, we used the CLSA analytical sample weights and geographic strata information in the regression analyses (25, 26). Results were expressed in odds ratios (OR) and 95% confidence intervals (CI). (p. 9)

8. Would it be possible to run a sensitivity analysis including only those patients that were determined to have diabetes using HbA1c values? This would be to ensure that results are similar and that self-reported diabetes is a reliable measure.
Interpretation:
Baseline diabetes was defined using HbA1c, treatment, and self-reported being diagnosed by a health-care professional with diabetes. For, the outcome, we had defined it using self-reported diagnosis. We have included a sensitivity analysis of only those who have self-reported diabetes (without HbA1c) at baseline. The results were similar. HbA1c may be normal in a person reporting diabetes because of treatment. Therefore, HbA1c is not reliable among those who reported diabetes. It was used in our study to detect those who self-reported not having diabetes, but had elevated A1c (undiagnosed diabetes). These were only 59 (around 2%) from the overall number of diabetics (3,255) at baseline.
We added in the statistical analysis section
In sensitivity analyses, we defined baseline diabetes by the self-reported physician diagnosis solely and repeated the analyses

and in the results section:
***Results of both sensitivity analyses were similar to those of the main analyses (Appendix Table 2 and Tables 5-6)*.** (pp. 10 and 12)

9. As the authors mention, the time since immigration may play a key role in the association between diabetes and depression. Immigrants who have been in Canada for many years hopefully do not suffer from the stressors as much as immigrants who have immigrated in Canada more recently.
We have included the time since migration in all the tables and the text. Time since arrival to Canada was not found to be a significant risk factor in the logistic regression models, perhaps because most immigrants in the CLSA database have been in Canada for over 40 years. We included in strengths and limitations the following:
***Also, around 87% and 63% of immigrants in our cohort have been in Canada for over 20 years and over 40 years respectively (Table 1). Therefore, generalizability of our results to recently arrived immigrants should be done with caution*.** (pp. 8 and 14, Tables 1 and 4)

10. The interpretation is well written and help explain the results. However, it is unclear to me what intervention can come out from this study. What changes (regarding policy, healthcare, etc.) do the authors propose, in light of the results of this study? What is the impact of this study?
As mentioned in question 9, we believe that before suggesting policy changes, we need to investigate this question among newly arrived immigrants in both the short- (3-5 years) and long terms (5-10 years) following their arrival. In the conclusion, we have suggested the following:
***Future studies should investigate the bidirectional diabetes/depression relationship in recently-arrived immigrants*.** (p. 15)

11. Can the authors expand on the meta-analysis that is mentioned on line 248. What types of studies were included in this meta-analysis?
The meta-analysis included cohort, cross-sectional and case-control studies providing OR and 95%CI, or enough data to calculate these. Studies were conducted worldwide and showed moderate statistical heterogeneity for the diabetes/depression relationship (18) We have clarified it in the text as follows:
***The meta-analysis included cohort, cross-sectional and case-control studies that considered both prevalent and incident diabetes, contrary to our study that considered only incident diabetes*.** (p. 13)

Reviewer 2: Dr. Mamata Pandey
Institution: Saskatchewan Health Authority, Saskatoon, Sask.
General comments (author response in bold)

1. *Please clarify and address the following points*
Introduction Line 108 Acculturative stress, stigma, discrimination social and economic disadvantage …. etc. vulnerability to both diabetes and depression?
Immigrants experience complex events and psychosocial trauma at a higher level than the general population that can affect the psychological well-being of those with diabetes. We have provided references to define these terms and have included an example in the revised manuscript:

Immigrants may be particularly vulnerable to the development of diabetes and depression (2-5), due to factors associated with resettlement, such as acculturation, social and economic challenges and stress (38-46).
And
For example, studies have reported that South Asian immigrants are generally healthy upon arrival but rapidly develop diabetes after immigration (6, 7). (p. 6)

2. A stronger case needs to be made on why is it important to know whether there is a bidirectional relationship between diabetes and depression. How does immigration fit in the equation? To consider immigration status as being a factor it is important to highlight the relationship between immigration and diabetes and immigration and depression. Please provide more information with references.
Our aim was to study the bidirectional diabetes/depression relationship among immigrant. This relationship was previously studied in the general population, but not in immigrants and for the reasons we provided in the introduction, we believe that immigrant could be different from non-immigrants in terms of risk of diabetes and risk of depression and their related adverse events.
We have clarified it further. In the first paragraph, we have indicated that surveillance of diabetes and depression are particularly relevant among immigrant by adding the term 'among immigrant' in the sentence:
"*ongoing surveillance for diabetes may be relevant in the context of depression and ongoing surveillance for depression may be justified with diabetes, particularly among immigrants*" and have provided references and an example supporting why the study of the bidirectional relationship between diabetes and depression is particularly relevant in immigrants as follows:
Immigrants may be particularly vulnerable to the development of diabetes and depression (2-5), due to factors associated with resettlement, such as acculturation, social and economic challenges and stress (38-46).
and
For example, studies have reported that South Asian immigrants are generally healthy upon arrival but rapidly develop diabetes after immigration. **(6, 7).**
We have added this comment in the statistical analysis section:
To assess the effect modification by immigration status, interaction terms for diabetes and immigration status and depression and immigration status were included in the models for Cohort1 and Cohort2, respectively. (pp. 6 and 9)

Methods

3. Was there any difference in the demographic variables between Cohort 1 and Cohort 2 please address this.
The two cohorts are inherently different because of the inclusion and exclusion criteria. Cohort 2 has a younger, mostly female and lower income population because we excluded all those who had diabetes at baseline to look at diabetes incidence. While, for Cohort 1, we included those with diabetes and those without diabetes, but excluded those with depression at baseline. Therefore, Cohort 1 is older and has more comorbidities. However, our study was not interested in comparing results between Cohort 1 and Cohort 2. (pp. 9, 10)

4. Please discuss the outcomes in a stepwise manner starting with the interaction that you would like to highlight the most. For example over all diabetes at base line was

associated with increased risk of depression at 3 years follow up. Overall depression at baseline was associated with increased risk of diabetes at 3 years follow up. Non-immigrants diagnosed with diabetes are more likely at a risk of developing depression at 3 years follow up. Immigration status does not interact with risk of diabetes for those diagnosed with depression at baseline.
There is need to discuss whether a difference between immigrants and non-immigrants are expected in reference to a diagnosis of diabetes or depression. Discuss this in reference to the previous studies.
We have edited throughout. This section now reads:
Overall, diabetes at baseline was associated with increased risk of depression at 3-year follow up and depression at baseline was associated with increased risk of diabetes at 3-year follow up. In general, immigration status did not modify these risks in either direction. Specifically, while depression was associated with 39% increased odds of diabetes among non-immigrants and 60% increase among immigrants, the overlapping 95% CIs did not suggest a conclusive modifying effect by immigration status. Moreover, while diabetes at baseline was associated with 27% increased odds of depression among non-immigrants and a non- significant increase by 12% among immigrants, an effect modification by immigration status could not be concluded.
And
Differences in the bidirectional diabetes/depression relationship by immigration status was expected because of the complex social determinants of health and stressors that immigrants are exposed to (32) and that have been potentially associated with low-grade inflammation (47-49).To the best of our knowledge, our study is the first to assess the bidirectional diabetes/depression relationship by immigration status. We also did not find any published study that looked at the one-directional association between diabetes and depression by immigration status. The lack of effect modification in the diabetes/depression bidirectional effect found in our study may perhaps be explained by the resilience of immigrants in their dynamic process of positive adaptation (50, 51). (pp. 14, 15)

Results

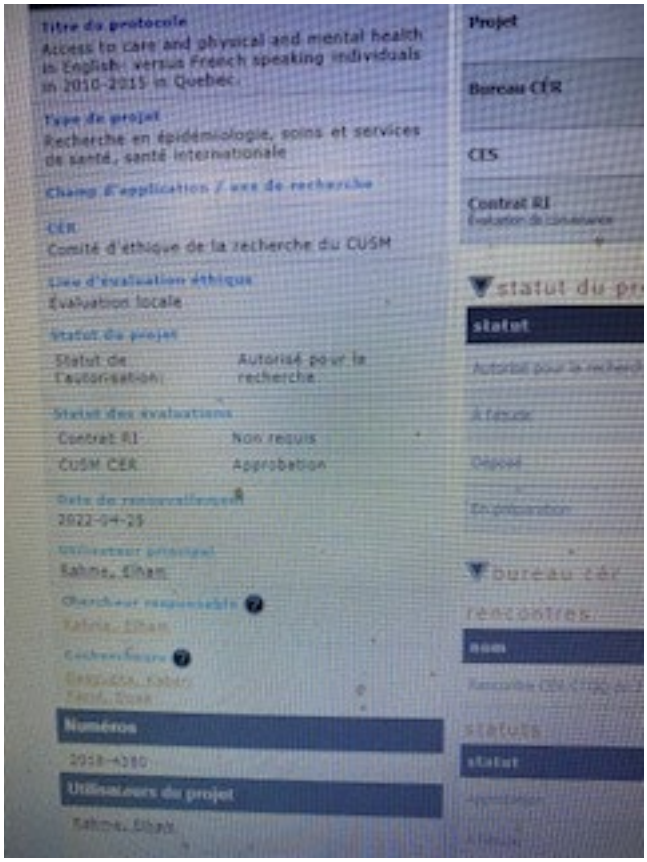
6. Was there any difference in the demographic variables between Cohort 1 and Cohort 2 please address this.
Differences between the two cohorts were expected, but not specifically assessed. As explained in point 3 above.

7. Lines 219-221 are very confusing. Is it obvious if the outcome variable is whether or not one develops diabetes at 3 years follow up, then at baselines they should not have diabetes. The same logic works when depression is the outcome. So the sentence should be “overall irrespective of immigration status those who had diabetes at baselines were 18% more likely than those without diabetes to have depression at 3 years. The same should be true for those with depression at baseline.
The text has been modified according to suggestion. Now it reads:
Overall, diabetes at baseline was associated with increased risk of depression at 3-year follow up and depression at baseline was associated with increased risk of diabetes at 3-year follow up. In general, immigration status did not modify these risks in either direction. Specifically, while depression was associated with 39% increased odds of diabetes among non-immigrants and 60% increase among

immigrants, the overlapping 95% CI did not suggest a conclusive modifying effect by immigration status. Moreover, while diabetes at baseline was associated with 27% increased odds of depression among non-immigrants and a non- significant increase by 12% among immigrants, a modification effect by immigration status could not be concluded. (p. 12)

8. A sentence or two about the significance of the study for clinicians and patients. Page 21 of 41 Figure 1: Line 15-18 is confusing. Cohort 1 and 2 should be distinguished based on the outcome variable that was being examined.
We have added the following to the Discussion:
Among individuals over 45 years of age, regardless of immigration status, clinicians are encouraged to screen for depression in those with diabetes and to screen for diabetes in those with depression for early detection that may prevent complications. These recommendations are also supported by the Canadian Collaboration for Immigrant and Refugee Health clinical guidelines (28). In addition, among individuals in this age group, those with diabetes are encouraged to speak to their physician about their feelings and mood changes and those with depression are encouraged to speak to their physicians about getting tested for diabetes.
The cohorts have been distinguished using subheadings. (pp. 10, 11, 16)

Ethics correspondence



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