Author's response to reviews

Title: The effectiveness and efficiency of diabetes screening in Ontario, Canada: A population-based cohort study.

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Author's response to reviews: see over
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Dear Editor,

Please find attached the revised manuscript, The effectiveness and efficiency of diabetes screening in Ontario, Canada: A population-based cohort study. This cover letter outlines the revisions made to the manuscript to respond to the referees’ and the editorial team’s feedback on the original manuscript.

I hope that you will find these revisions to be to your satisfaction. Please let me know if there are further modifications that will be required, in order for this manuscript to be considered for publication in your journal.

Sincerely,

Sarah Wilson

Response to the BioMed Central Editorial Team

Context information has now been included within the background section of the abstract (page 2 of the manuscript).

The manuscript has been reviewed and modified as required, to ensure that the revised manuscript conforms to the journal style requirements.

Response to Referees Comments

Reviewer 1: Ambady Ramachandran

Reviewer’s report

1. The reviewer found the reading of the paper rather tough as there was [too] much data for one paper. The paper may be divided into two parts, one on methodology and the other on the outcomes.

Response

This is a thoughtful suggestion on the part of the reviewer. Since the time of the original manuscript’s submission, a detailed manuscript outlining the methodology to develop and validate the DPort risk algorithm has been accepted for publication (Manuel, D.G, Burchill, C., Stukel, T.A. A population based risk algorithm for the development of diabetes: Development...
and validation of the Diabetes Population Risk Tool (DPORT). *Journal of Epidemiology and Community Health*. 2010. In Press.). This new citation (numbered 26) has now been included in the references of the manuscript. In the text of the revised manuscript the following sentence has been included to refer readers to this separate publication for more detailed information about the derivation of diabetes risk using this tool (under the subheading of baseline variables of interest, page 6):

“A separate publication describes the development and validation of this population-level risk algorithm in greater detail [26].”

**Minor Comments**

2. Methods: give reasons for excluding Indian Reserves etc.

**Response**

As stated on page 4 of the manuscript, the data source for the study was the Canadian Community Health Survey (CCHS), a national population health survey that is administered by Statistics Canada. For its sampling frame, the CCHS uses the area frame of the Labour Force Survey which covers the civilian, non-institutionalized population of Canada but does exclude persons living on reserves and other Aboriginal settlements in the provinces, full-time members of the Canadian Armed Forces and the institutionalized population. These groups together represent an exclusion of less than 2% of the Canadian population aged 15 and over (1). The exclusion of Canadian First Nations from population health surveys is a limitation of the data source but it is not unique to the CCHS and unfortunately applies to other population health surveys administered in Canada. Therefore, other surveys have been developed to assess the health of Canada’s First Nations people, including the Aboriginal People’s Survey (2), and the First Nations Regional Longitudinal Health Survey (3). The following sentence has been added to the methods section (subheading: cohort definition on page 4) to address the reviewer’s concerns:

“The CCHS uses the area frame of the Labour Force Survey [22] for sampling which excludes persons living on reserves and other Aboriginal settlements in the provinces, full-time members of the Canadian Armed Forces and the institutionalized population.”
3. A flow chart showing selection criteria and procedures is required

Response

Given the large number of figures and tables that are already present in the manuscript (a total of six) and the fact that the exclusion criteria are clearly listed in the text of the manuscript (on page 4) we would prefer not to include this information as an additional figure.

4. Mention the variables included for the risk assessment

Response

The following sentence has been added to the methods section, under the subheading of Baseline variables of interest (page 6):

“The predictive factors included in the DPoRT algorithm are BMI, age, ethnicity, hypertension, immigrant status, smoking, education status and heart disease [25,26].”

References


Reviewer 2: Maria Alice Souza de Oliveira Dode

Major Compulsory Revisions

a) The question posed by the authors is well defined at the end of the introduction. But during the method section, it is not clear if the efficiency of screening is the absolute number of individuals tested with a SBG over the five year study divided by the number of incident
diabetes cases, that accrued during the same period, or if it was only the ratio between the individual that fulfill the CDA guidelines divided by the number of incident diabetes cases. The results shows that 80% of women and 66% of men had a blood glucose test within 5 years, and the NNS is 22 among men and 14 among women. These results shows that are something that is no clear in the methods section.

Response

In this study we used the term ‘number needed to screen’ (NNS) to represent the efficiency of screening. The definition for NNS is the absolute number of individuals tested with a SBG over the five years of study, divided by the number of incident diabetes cases that accrue over the same five year time period. The number of individuals who are screened in accordance with the CDA guidelines is not used to calculate the efficiency of screening. The way in which we calculated efficiency is described on page 6 under the subheading of “measures of efficiency and population effectiveness of diabetes screening” and is unchanged:

“To compute ‘number needed to screen’ the number of individuals tested with a SBG over the five year study period was divided by the number of incident diabetes cases that accrued during the same period (NNS=number of individuals tested with at least one SBG test over 5 years/the number of individuals with new diabetes diagnoses over 5 years).”

The results that Dr de Oliveira Dode quotes are correct. Over the five years of study 80% of women and 66% of men underwent a SBG and the NNS is 22 among men and 14 among women. Using Table 2, the NNS for women is calculated by dividing column C (number tested with a SBG over 5 years) by column D (the number of incident cases of diabetes). For women, the NNS calculation is 2,569,124/180,747 which equals 14.2. The NNS calculation for men (column H/column I) is 3,250,814 individuals tested/149,850 incident cases of diabetes, which equals a NNS of 21.7, or 22.

The utility of having all the data presented in Table 2 is further underscored by this query of Dr de Oliveira Dode as the complete presentation of data allows readers to determine the raw numbers that are used to derive the estimates for screening efficiency and screening effectiveness that are presented in the manuscript.

Minor Essential Revisions

b) At page 8, fourth line “Figures 1 and 2 depict the relationship between SBG testing and the ten year risk “ The correct is “five year risk”

Response
Thank you for detecting this typographical error. The text has been changed to the following (page 9, first new paragraph):

“Figures 1 and 2 depict the relationship between SBG testing and the five-year risk of diabetes for men and women”.

**Discretionary Revisions**

c) The table 2 is too long, to summarize it, is necessary. Maybe it could be withdrawal since the necessary information is on the text.

**Response**

We agree that Table 2 contains a lot of information. However, we believe that the information contained within the Table is of interest to the readers of this paper and important to include to allow the reader to understand the basis for the calculations. This point is underscored by the fact that the third reviewer has requested that information contained within Table 2 be further expanded within the text of the manuscript.

**Reviewer 3: Edward Gregg**

**General comment**

Specific ways that this paper could be improved include the following:

1. A minor point. The 2nd and 3rd sentences of the introduction seem a bit out of place. Although they are true, it’s not quite clear how they relate to this specific analyses.

**Response**

The second and third sentences of the introduction describe what is currently known about the epidemiologic burden of ‘undiagnosed’ diabetes, and outline the fact that the traditional data sources for estimates of undiagnosed cases come from resource-intensive population-based health surveys which include physiological measures. These points were raised in the introduction to provide both context and contrast with our statements in the discussion (second new paragraph, page 13):

“Most of what is currently known about the prevalence of undiagnosed diabetes (screening effectiveness) comes from data collected as part of cross-sectional population health surveys which compare biological markers, such as blood glucose testing, with self-reported health states including diabetes. Here we demonstrate that surveillance of ‘undiagnosed’ diabetes can be accomplished with the use of longitudinal population-based administrative health data that include information on testing and diabetes diagnoses.”
2. Page 4, last sentence. The use of the term “anonymised” is not quite clear here. Does this mean that the data from administrative data specific to the individual are linked to the health surveys. Or alternatively, is the health survey sample simply linked to the aggregate administrative data for those that are in the health survey?

Response

Through unique encrypted health card numbers, individual-level data from the provincial health insurance plan can be linked to individual respondents of the CCHS who reside in Ontario, and their CCHS data. The use of ‘anonymised’ in this context refers to the fact that this is done using the unique encrypted health card number and without the use of other identifying data (such as name). To remove this potential source of confusion for the reader, the word ‘anonymised’ has been removed from the text. The modified text now reads as follows (Methods, subheading Data Sources, page 5):

“After our cohort was created using the CCHS survey database, data for each individual were linked to administrative health databases that include records for all individuals eligible for health services under the government-funded Ontario Health Insurance Plan (OHIP), using unique encrypted health card numbers. Individual-level data from each Ontario CCHS respondent in the cohort was deterministically linked to individual-level information on health services accessed through OHIP and to other administrative health databases.”

3. Page 5, 1st paragraph. How was diabetes status defined using the Ontario database.

Response

Further information regarding the Ontario Diabetes Database has been included in the text of the manuscript. The text under the subheading of Data sources now includes the following information about the ODD (page 5):

“The diabetes status of respondents was established by linking individuals to the Ontario Diabetes Database (ODD), which contains all patients said to have physician-diagnosed diabetes identified since 1991 and their date of diagnosis on the basis of administrative health data. An individual is said to have physician-diagnosed diabetes if at least one of the following criteria are met: (i) hospital admission with a diabetes diagnosis; (ii) a physician services claim with a diabetes diagnosis followed within 24 months by either a further physician service claim or a hospital admission with a diabetes diagnosis. A hospital record with a diagnosis or pregnancy care or delivery close to a diabetic record (e.g. 90 days before and 120 days after the diabetes record date) is considered to relate to gestational diabetes and is not included in the ODD. The ODD has been validated against primary-care records and demonstrated to be accurate for determining the incidence and prevalence of diabetes (sensitivity 86%, specificity 97%) [23,24].”
4. What proportion of all diabetes testing may be expected to be conducted and coded as a “SBG” test?

Response

The following text has been included in the manuscript to give more information about diabetes testing in the province of Ontario (subheading Survival analysis, pages 6-7):

“We have previously demonstrated that the SBG is the most common laboratory test used to identify diabetes in Ontario, representing 87% of all diabetes-related laboratory tests (among SBG, HbA1c, and oral glucose tolerance tests) undergone by individuals without a pre-existing physician-diagnosis of diabetes in the year 2005 [19]. We have also previously demonstrated that oral glucose tolerance tests are rarely used in Ontario with fewer than 2500 tests ordered in the year 2005 among an adult population size exceeding 9 million [19].”

5. Page 6, last paragraph to page 7, 1st paragraph. The approach to define undiagnosed diabetes is confusing. Could the authors give a bit more clarification of how this is derived and how it has been validated? What sources and magnitude of error is expected around this manner of estimating undiagnosed diabetes?

Response

The concept of undiagnosed diabetes in our manuscript describes the number of individuals who would be diagnosed if the screening efficiency observed in our cohort (as described by the NNS) was manifested in the un-tested population. In other words, had all the individuals who did not receive a test actually receive one, we would expect a certain number of diabetes cases that would be detected based on what we know about the efficiency of the screening test in our population. This method and its assumptions have been clearly outlined in our methods and discussion. The number of individuals with undiagnosed diabetes at the end of the study period is derived from the number of individuals not tested over the five years of study, divided by the NNS. NNS is determined by dividing the number of individuals tested over the study period by the number of incident diabetes cases accrued over the same time period. We arrived at this method for determining an estimate of the number of ‘undiagnosed’ diabetes after numerous conversations on how we could estimate the burden of undiagnosed diabetes, in the absence of data from a population health survey utilizing physiological measures. The main sources of error for our estimates of undiagnosed diabetes stem from limitations related to our NNS calculations, which have been discussed extensively throughout the manuscript.

This concept for calculating the burden of undiagnosed cases of diabetes has not been validated to date because the gold standard for ‘undiagnosed diabetes’, which would be the inclusion of serum blood glucose measurements in the context of a representative population survey, is not yet available in Canada. However, the Canadian Health Measures Survey, the first population health survey in Canada utilizing physical measures in more than 30 years has recently been completed and it includes fasting blood glucose measurements that have been conducted at the
population-level. We plan to use the findings of that survey once the data become available to validate our methodologic constructs. We believe our estimates using the methods outlined in the manuscript are reasonable and note in our discussion that our estimates of undiagnosed diabetes derived from our methods are consistent with national estimates of undiagnosed diabetes that have been derived from other countries’ population health surveys that have utilized physiologic measures.

6. The Figures need considerably more notation as part of the legends, such that the reader can interpret them without digging back through the methods section. For example, what is the decile of risk based on? Figure 1 just states “decile of 5-year diabetes risk” whereas Figure 2 states “estimated by DPoRT”. Are they both estimated by DPoRT?

Response

Thank you to the Referee for this suggestion. Both Figures use DPoRT to determine the five-year diabetes risk. The figure legends have been changed. The new x axis for both figures is: “Decile of 5-year diabetes risk, estimated using the Diabetes Population Risk Tool (DPoRT)”. The y axis for both figures has been changed from diabetes incidence (%) to: “Observed diabetes incidence (%)”.

7. Perhaps more importantly, the results section neglects to present some of the basic information that will be of greatest interest to the reader. (Some of this information is in the appendices, but would need synthesis and description to integrate into the paper)

These questions include:

a. What is the 5 year incidence among people who are not tested initially? I realize this may not be possible to know if the incidence measure depends upon the same variable as the testing variable. But we can’t really discern this from the methods at present.

b. What is the relationship between frequency of testing and subsequent risk?

Response

These are two very interesting questions that the Referee has posed. Unfortunately, due to the methodology of this particular study, which employed a survival analysis where respondents where followed only up until the date of their first serum blood glucose test or diabetes diagnosis (or up until death or loss of OHIP eligibility), we are unable to answer these thoughtful questions. However, these are important questions and we have included these as both limitations and directions for future analyses in the text of the manuscript (Discussion, page 15):
“Finally, the survival analysis methodology employed in this study involved following individuals until the date of respondents’ first diabetes laboratory test or diabetes diagnosis. However, this limited our ability to examine the relationship between the frequency of testing and future diabetes risk. This is an important area for future investigations.”

c. How does the NNS vary according to sub-groups? Page 8 describes this to some degree, but it would be nice to see more thorough presentation of this.

Response

Greater discussion was included in the manuscript of the text to elaborate further on the NNS estimates for different sub-groups. The following text has been added to the manuscript (Results, subheading Efficiency of Diabetes Testing, page 9-10):

“Table 2 displays the variation in the NNS estimates both within and between different sub-groups. For example, there was little difference in the NNS estimates for some subgroups such as urban residence as evidenced by a NNS of 14 for urban and a NNS of 15 for non-urban men; ethnicity with an observed NNS of 21 for white women and a NNS of 23 for women of non-white ethnicity; and similar NNS estimates for self-reported immigrant and non-immigrant status, within each gender. In contrast, there were other subgroups where the differences in NNS were more apparent within the subgroup such as BMI, self-reported hypertension, self-reported heart disease and the summary variable indicating whether the CDA would recommend testing. For example, the NNS estimate for men recommended to be screened by the CDA is 12, in contrast to a NNS of 81 for men not recommended to be screened in accordance with the CDA guidelines.”

8. Finally, the discussion would benefit from a bit more comment on the implications for screening and testing policies. Among whom should we be screening and testing more, and among whom less? Presumably the NNS is affected by the specificity of the test and by the prevalence in the population. There could be more comment here on how these factors influence (or don’t influence the study findings).

Response

Thank you for this suggestion. The following two paragraphs have been added to the discussion section (on pages 11 and 12 of the manuscript):

“Despite high levels of screening and a publicly funded health care system with universal access, an estimated 28% of all diabetes in the province of Ontario remains undiagnosed. This compares similarly with the results of the most recent NHANES surveys in the United States
where the percentage of undiagnosed diabetes was found to be 30.1% in the 1999-2002 survey [4] and 34.6% in the 1988-1994 survey [5]. In Ontario, men are more likely to be undiagnosed than women. This reflects both a lower rate of testing and a higher incidence of diabetes in men relative to women. Barriers to undergoing diabetes testing can be presumed to operate at the level of the individual, clinic and the health system. In our multivariate analysis we found that men with low incomes and women who did not self-report income were significantly less likely to under SBG testing, after controlling for other variables, including BMI. These findings suggest that not only is low income status a risk factor diabetes [28], but it appears also to be a risk factor for having undiagnosed diabetes, even in a system with universal access to publicly funded health care services. This suggests that a strategy beyond the dissemination of clinical practice guidelines for diabetes testing is required to address undiagnosed diabetes in low income populations.

The analyses presented here have several implications for diabetes screening. This study shows that, in general, clinicians’ screening behaviour increases in proportion to the risk of diabetes, with increasing proportions of individuals tested with increasing 5-year risk of diabetes. However, at the extremes of risk there appears to be a mis-match between screening and diabetes risk. Low-risk individuals, in particular women, undergo a disproportionate amount of screening in relation to their low-risk status resulting in large estimates for the NNS, while the screening rates of higher-risk individuals could be increased further, in order to further reduce the burden of undiagnosed diabetes. This finding could be a reflection of a healthy user effect. However, it is important to note that our methodology for the conceptualization of efficiency, NNS, may be over-estimated in lower risk individuals and be under-estimated in higher-risk individuals owing to the fact that the ODD is used for a determination of diabetes status and is likely to have a greater false positive rate associated with low risk individuals due to the lower prevalence of diabetes.”